Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-17]

  Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[18-35] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[26,27,30] Given the paucity of clinical experience and long-term safety data, the 2013 European League against Rheumatism guidelines recommend that tofacitinib should primarily be used when biological treatment has failed.[18] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[36]

Table 1. Current Medications Available in the Therapeutic Class[1-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥six years)	Prefilled syringe: 125 mg/mL Single use vial: 250 mg	-
Adalimumab (Humira®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥four years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (adults only); ulcerative colitis (adults only); plaque psoriasis (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL	-
Anakinra (Kineret®)	rheumatoid arthritis (adults); cryopyrin-associated periodic syndromes – neonatal-onset multisystem inflammatory disease (no age restriction)	Prefilled syringe: 100 mg/0.67 mL	-
Canakinumab (Ilaris®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells	Vial: 180 mg (150	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	syndrome; juvenile idiopathic arthritis	mg/mL)	
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis (age ≥2 years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®, Simponi Aria®)	rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL, 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial*: 50 mg/4 mL	-
Infliximab (Remicade®)	Crohn's disease (age ≥6 years); ulcerative colitis (age ≥6 years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only), plaque psoriasis (adults only)	Single use vial: 100 mg	-
Rilonacept (Arcalyst®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years); juvenile idiopathic arthritis (age ≥12 years)	Vial: 220 mg (80 mg/mL)	-
Secukinumab (Cosentyx®)	Plaque Psoriasis (adults only)	Prefilled pen, syringe: 150 mg/mL Vial: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ 2 years) ; systemic juvenile idiopathic arthritis (age ≥ 2 years); rheumatoid arthritis (adults only);	Prefilled syringe*: 162 mg/0.9 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	
Tofacitinib (Xeljanz®)	Rheumatoid arthritis (adults only)	Tablet: 5 mg	-
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Single use vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[41-137]
- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[69]
- The safety and efficacy of secukinumab was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,76-78]
- To date, the majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results. In one trial in rheumatoid arthritis patients who were either intolerant or were not candidates for methotrexate treatment, significantly greater improvements were observed in patients treated with tocilizumab compared to adalimumab.[118] In another trial in rheumatoid arthritis patients with inadequate response to methotrexate, similar responses were observed in patients treated with abatacept and adalimumab.[119,120] The inclusion of adalimumab arm in one phase 3 trial of tofacitinib allowed establishing relative safety and efficacy of tofacitinib; however, formal noninferiority comparison was not performed.[121] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.

- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease, the only agent FDA-approved for this indication. The approval was based on the results of a single trial demonstrating sustained improvements in affected patients over 60 months.[135]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[18-35]
  - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
  - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[26,27,30] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary. In general, no one agent is preferred over another; however, given the paucity of clinical experience and long-term safety data, the use of tofacitinib for rheumatoid arthritis is recommended primarily after biological treatment has failed.[18]

- Other Key Facts:
  - None of the immunomodulators included in this review are available generically.
  - Dosing frequency and route of administration vary between products.
    - Tofacitinib is formulated as an oral tablet dosed twice daily.
    - Abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab (vial), and vedolizumab
      - Each is infused over 30 minutes, with the exception of infliximab which is infused over two hours.
    - Anakinra is administered subcutaneously, but requires more frequent (daily) administration.
  - Intravenous formulation of golimumab and subcutaneous formulation of tocilizumab are only indicated in the treatment of rheumatoid arthritis.
  - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

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Therapeutic Class Review
Immunomodulators

Overview/Summary

This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 2. These agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi®, Simponi ARIA®), and infliximab (Remicade®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-17]

The interleukins (ILs) that are targeted by immunomodulator agents are IL-1 (1α and/or 1β), IL-6, IL-12, IL-17A, or IL-23. IL-1 plays an important role in the inflammatory process as a proinflammatory mediator along with TNF-α. IL-1 is also associated with cartilage breakdown as well as stimulation of bone resorption. Anakinra is a recombinant, non-glycosylated form of the naturally occurring human interleukin-1 receptor antagonist (IL-1Ra) and blocks the effect of both IL-1α and IL-1β at its receptor.[1,16] Canakinumab is a human monoclonal antibody against IL-1β. Binding of canakinumab to IL-1β blocks the interaction with IL-1 receptors.[2] Rilonacept binds IL-1β, acting as a decoy receptor, thus preventing IL-1β from binding with cell surface receptors, inhibiting the inflammatory pathway. Rilonacept also binds IL-1α and IL-1Ra but with reduced affinity.[3] IL-6 is a chemical messenger that has been associated with the inflammatory process as well as other diverse processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. Tocilizumab is a humanized monoclonal antibody that competes with IL-6 for binding to IL-6 receptor which can be found in the serum or membrane-bound.[4] IL-17A stimulates keratinocytes to secrete proinflammatory chemokines and other proinflammatory cells as part of the normal inflammatory and immune response. Secukinumab is a human IgG1 monoclonal antibody that selectively binds to IL-17A, which prevents its binding to the IL-17A receptor.[5] IL-12 influences CD4+ T cells to develop into CD4+ T helper-1 (Th1) while IL-23 influences CD4+ T cells to develop into IL-17 producing CD4+ T cells (Th17). Both Th1 and Th17 produce additional proinflammatory cytokines to help mediate cellular immunity, along with other functions. Ustekinumab is a human IgG monoclonal antibody that specifically binds to the p40 protein subunit which is part of both IL-12 and IL-23 with high affinity, disrupting signal transduction and reducing the formation of proinflammatory Th1 and Th17 cells.[6]

TNF-α is another proinflammatory mediator that is released by lymphocytes. Working together with IL-1 and other cytokines and growth factors, they induce certain gene expression and protein synthesis.[17] Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind to both membrane-bound TNF-α and soluble TNF-α, preventing its binding to the TNF receptors. Certolizumab pegol, an antibody-binding fragment modified with polyethylene glycol (pegylated), acts in a similar fashion. Similar to the other TNF-α antagonists, certolizumab pegol binds to membrane bound and soluble TNF-α preventing its binding to the TNF receptor. Neither of these drugs have affinity for TNF-β, which utilizes that same receptor.[7-11] Etanercept is a fusion protein that that contains the ligand binding site of the p75 TNF receptor. As etanercept mimics the TNF receptor, it has affinity for and binds both TNF-α and TNF-β, etanercept. These agents have been found to be similar with respect to adverse events and interacting medications.[12]

Abatacept is the only T-cell activation inhibitor in the immunomodulator class of drugs. Abatacept binds to CD80 and CD86 preventing CD28 activation, which is required for the costimulatory signal necessary for full activation of the T-cell.[13] Tofacitinib is an oral janus kinase inhibitor. It is a synthetic chemical compound that interferes with specific signal-transduction pathways. Through its broad effect on multiple cytokine pathways, tofacitinib may reduce tissue inflammation and joint damage in rheumatoid arthritis.[14] Vedolizumab is a humanized monoclonal antibody that binds to the α4β7 integrin and blocks the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and inhibits the migration of memory T-cells across endothelium into inflamed gastrointestinal parenchymal tissue. The interaction of α4β7 integrin with MAdCAM-1 is thought to be an important contributor to the chronic inflammation associated with ulcerative colitis and Crohn's disease.[15]

Dosing and administration varies both by drug and by dosage form. While the majority of these agents are subcutaneous injections, several are formulated as an intravenous (IV) injection and one, tofacitinib is an oral tablet. Tofacitinib is taken twice daily. The IV injections include abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab (vial), and vedolizumab. Each is infused over 30 minutes, with the exception of infliximab which is infused over two hours. Most injectables require infrequent dosing, ranging from one to 12 weeks. Anakinra however, is the only injectable immunomodulator that requires daily dosing. The majority of these agents have not been studied in renal or hepatic dysfunction. Anakinra and tofacitinib require renal dose adjustment for creatinine clearances less than 30 mL or 40 mL, respectively. Additionally, tofacitinib requires a dose adjustment in patients with moderate hepatic dysfunction, however, it has not been studied in patients with severe hepatic dysfunction and no dosing recommendations are available. The safety and efficacy of these agents is varies based on drug and indication. Anakinra, canakinumab and rilonacept are FDA-approved for the treatment of Cryopyrin-Associated Periodic Syndromes. Anakinra does not have a minimum age associated with its use while canakinumab is approved for use in children aged four or older and rilonacept is approved for use in children 12 to 17 years old. Safety and efficacy in pediatric patients to treat juvenile idiopathic arthritis has been established for abatacept (age six or older), adalimumab (two to 17), canakinumab (two or older), etanercept (two or older), and tocilizumab (two or older). Additionally, infliximab has been FDA-approved for ulcerative colitis and Crohn's disease in pediatric patients aged six or older.[1-15]

Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[18-35] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[26,27,30] Given the paucity of clinical experience and long-term safety data, the 2013 European League against Rheumatism guidelines recommend that tofacitinib should primarily be used when biological treatment has failed.[18] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[36]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Abatacept (Orencia®)	T-cell activation inhibitor	-
Adalimumab (Humira®)	TNFα antagonist	-
Anakinra (Kineret®)	IL-1 antagonist	-
Canakinumab (Ilaris®)	IL-1β antagonist	-
Certolizumab pegol(Cimzia®)	TNFα antagonist	-
Etanercept (Enbrel®)	TNFα antagonist	-
Golimumab (Simponi®, Simponi Aria®)	TNFα antagonist	-
Infliximab (Remicade®)	TNFα antagonist	-
Rilonacept (Arcalyst®)	IL-1β antagonist*	

Generic Name (Trade name)	Medication Class	Generic Availability
Secukinumab (Cosentyx®)	IL-17A antagonist	-
Tocilizumab (Actemra®)	IL-6 antagonist	-
Tofacitinib (Xeljanz®)	Janus kinase inhibitor	-
Ustekinumab (Stelara®)	IL-12 and IL-23 antagonist	-
Vedolizumab (Entyvio®)	α4-β7 Integrin receptor antagonist	-

*Also has affinity for IL-1α and IL-1Ra, but to a lesser extent than IL-1β
IL=interleukin, TNF=tumor necrosis factor

Indications

Table 2. Food and Drug Administration Approved Indications[1-15]

Indications	Abatacept	Adalimumab	Anakinra	Canakinumab	Certolizumab	Etanercept	Golimumab††	Infliximab	Rilonacept	Secukinumab	Tocilizumab	Tofacitinib	Ustekinumab	Vedolizumab
Ankylosing Spondylitis		a			a	a	a	a						
CAPS: FCAS, MWS				a					a					
CAPS: NOMID			a											
Crohn's Disease		a †			a ¶			a ¶						a ##
JIA	a *	a		a		a					a ‖‖			
Plaque Psoriasis		a ‡				a #		a §§		a #			a #	
Psoriatic Arthritis		a *			a	a **	a	a					a	
Rheumatoid Arthritis	a *	a *	a *‖		a	a	a ‡‡	a ‡‡			a ‖	a ¶¶		
Ulcerative Colitis		a §					a §	a ¶						a ##

CAPS=Cryopyrin-Associated Periodic Syndromes, FCAS= Familial Cold Autoinflammatory Syndrome, JIA=juvenile Idiopathic Arthritis, MWS=Muckle-Wells Syndrome, NOMID=Neonatal-Onset Multisystem Inflammatory Disease
*Alone or in combination with disease modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor inhibitors.
†In patients who have had an inadequate response to conventional therapy and if they have also lost response to or are intolerant of infliximab.
‡In patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
§In patients who had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine.
‖In patients who have failed one or more DMARDs.
¶In patients who have had an inadequate response to conventional therapy.
#In patients who are not candidates for systemic therapy or phototherapy.
**May be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
††Golimumab (Simponi Aria®) is only indicated in the treated of rheumatoid arthritis.
‡‡In combination with methotrexate.
§§In patients with chronic severe disease who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
‖‖Indicated in the treatment of both active polyarticular and systemic juvenile idiopathic arthritis.
¶¶ In patients who have had an inadequate response or intolerance to methotrexate; may be used as monotherapy or in combination with methotrexate or other DMARDs.
In adult patients who have had an inadequate response with, lost response to or were intolerant to a tumor necrosis factor blocker or immunomodulator; or who had an inadequate response with, were intolerant to or demonstrated dependence on corticosteroids.

As a class, the immunomodulators are used off-label for a wide-variety of autoimmune diseases. Anti-tumor necrosis factor (TNF) agents are under investigation for the treatment of Behcet's disease, non-infectious ocular inflammation, pyoderma gangrenosum, and hidradenitis suppurativa.[37] Tofacitinib is currently being studied for the treatment of psoriatic arthritis, ulcerative colitis, and plaque psoriasis.[38]

Pharmacokinetics

Table 3. Pharmacokinetics[1-15,39,40]

Generic Name	Bioavailability (%)	Time to Peak Concentration	Elimination Half-Life
Abatacept	100 (intravenous); 78.6 (subcutaneous)	Not reported	13.0 to 14.3 days
Adalimumab	64	131±56 hours	10 to 18 days
Anakinra	95	3 to 7 hours	4 to 6 hours
Canakinumab	66	2 to 7 days	26 days
Certolizumab	80	54 to 171 hours	14 days
Etanercept	58	69±34 hours	102±30 hours
Golimumab	100 (intravenous); 53 (subcutaneous)	48 to 144 hours (subcutaneous)	14 days
Infliximab	100	Not reported	8 to 10 days
Rilonacept	Not reported	Not reported	Not reported
Secukinumab	555 to 77	Not reported	22 to 31 days
Tocilizumab	100 (intravenous); 80 (subcutaneous)	Not reported	11 to 23 days
Tofacitinib	74%	0.5 to 1.0 hour	3 hours
Ustekinumab	Not reported	7.0 to 13.5 days	14.9 to 45.6 days
Vedolizumab	Not reported	Not reported	25 days

Clinical Trials

Clinical studies evaluating the safety and efficacy of the immunomodulators in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[41-137]

The FDA-approval of adalimumab for the treatment of ankylosing spondylitis (AS) was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients in the adalimumab group achieved an improvement of at least 20% in Assessment in Spondyloarthritis International Society (ASAS), the primary endpoint, compared to placebo (58 vs 21%; P<0.001). An improvement of at least 50% in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients at week 12 (P<0.001). This response was sustained through week 24, with 42% of patients in the adalimumab group achieving at least 50% improvement in BASDAI score compared to 15% in the placebo group (P<0.001).[41]

The FDA-approval of certolizumab pegol for the treatment of AS was based on one randomized, double-blind, placebo-controlled study (N=325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab pegol 200 mg every two weeks and certolizumab pegol 400 mg every four weeks compared to placebo at 12 weeks (57.7 and 63.6% vs 38.3%; P=0.004 and P<0.001, respectively). The difference in ASAS 20 response was sustained through week 24 in both certolizumab pegol treatment groups. Improvements in BASDAI scores were greater in patients treated with certolizumab pegol 200 mg every two weeks and certolizumab pegol 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001) and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively.[42]

The efficacy of etanercept in patients with AS was established in two double-blind, randomized, placebo-controlled trials. Patients treated with etanercept experienced a significantly greater response to treatment compared to placebo (P<0.001).[43] A greater proportion of patients achieved an ASAS 20 response compared to placebo (P<0.001).[44] In an open-label extension study evaluating the long-term safety and efficacy of etanercept in patients with AS, the most common adverse events were injection site reactions, headache and diarrhea after 192 weeks of treatment. A total of 71% of patients were ASAS 20

responders at week 96 and 81% of patients were responders at week 192. The ASAS5/6 response rates were 61% at week 96 and 60% at week 144 and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance.[45] Etanercept and sulfasalazine were compared in a multicenter, randomized, double-blind trial in adult patients with active AS who had failed treatment with nonsteroidal antiinflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept achieved the primary outcome of ASAS 20 at week 16 compared to patients treated with sulfasalazine (P<0.0001). Similarly, a significantly greater proportion of patients achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (P<0.0001 for both).[46]

The FDA-approval of subcutaneous formulation of golimumab for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least three months (N=356). Golimumab with or without a disease modifying antirheumatic drug (DMARD) was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14.[47] The efficacy of infliximab in the treatment of AS was demonstrated in 12- and 24-week double-blind placebo-controlled trials. A significantly greater proportion of patients achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (P<0.0001).[48] At 24 weeks, a significantly greater proportion of patients in the infliximab group achieved ASAS 20 compared to patients in the placebo group (P<0.001).[49]

In a meta-analysis of randomized controlled trials of patients with AS, treatments with tumor necrosis factor (TNF) antagonists, adalimumab, etanercept, golimumab, and infliximab, was more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% confidence interval [CI], 1.91 to 2.56) and 24 weeks of treatment (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab was associated with the highest likelihood of achieving ASAS 20 response at week 12, though it did not significantly differ from other agents. While treatment with infliximab was associated with the highest likelihood of achieving ASAS 20 response at week 24, this was based on few studies and the confidence interval was large.[50]

In a systematic review of patients with Crohn's disease who had failed a trial with infliximab, the administration of adalimumab was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to four years of treatment.[51] Shao et al performed a meta-analysis evaluating certolizumab pegol use over 12 to 26 weeks for the treatment of Crohn's disease. The results demonstrated that certolizumab pegol was associated with an increased rate of induction of clinical response (relative risk [RR], 1.36; P=0.004) and remission (RR, 1.95; P<0.0001) compared to placebo; however, risk of infection was higher with certolizumab pegol use.[54] In a trial evaluating infliximab for induction of remission, significantly greater proportion of patients achieved remission at four weeks with infliximab compared to placebo (P<0.005).[55] In a trial by Present et al, significantly greater proportion of patients treated with infliximab 5 mg/kg and 10 mg/kg experienced a reduction of at least 50% in the number of fistulas compared to patients treated with placebo (P=0.002 and P=0.02, respectively).[56] In an open-label trial evaluating the use of infliximab in pediatric Crohn's patients, 88.4% responded to the initial induction regimen and 58.6% were in clinical remission at week 10.[57] Treatment with adalimumab, certolizumab, and infliximab was associated with a higher likelihood of achieving clinical response (RR, 2.69; P<0.00001; RR, 1.74; P<0.0001 and RR, 1.66; P=0.0046, respectively) and maintaining clinical remission (RR, 1.68; P=0.000072 for certolizumab pegol and RR, 2.50; P=0.000019 for infliximab; adalimumab, data not reported) compared to placebo in patients with Crohn's disease. Adalimumab and infliximab also had a steroid-sparing effect.[59]

The FDA-approval of vedolizumab for the treatment of Crohn's disease was based on two Phase III randomized, placebo controlled trials, GEMINI-2 and GEMINI-3, which compared vedolizumab 300 mg intravenously (IV) at weeks 0 and 2 (induction phase) followed by 300 mg IV every four or eight weeks (maintenance phase; GEMINI-2) or vedolizumab 300 mg IV at weeks 0, 2 and 6 (GEMINI-3).[60,61] In the GEMINI-2 trial, a significantly greater proportion of patients treated with vedolizumab achieved clinical remission at weeks 6 and 52 compared to placebo. In addition, at week 52, a significantly greater

proportion of patients treated with vedolizumab achieved a ≥100-point decrease in Crohn's disease activity index (CDAI-100) compared to the placebo group.[60]

Similarly, in GEMINI-3, a greater proportion of patients in the overall study population were in clinical remission at week six compared to placebo and CDAI-100 at week six was achieved in a greater proportion of patients treated with vedolizumab. In patients who had previously failed treatment with a TNF antagonist, there was no significant difference in the proportion of patients in clinical remission at week six between the vedolizumab and placebo groups.[61]

In a trial by Ruperto et al in pediatric patients (six to 17 years of age) with juvenile idiopathic arthritis, patients treated with placebo experienced significantly more disease flares compared to patients treated with abatacept (P=0.0003). The time to flare was significantly different, favoring abatacept (P=0.0002).[62] Adalimumab was studied in a group of patients (four to 17 years of age) with active juvenile rheumatoid arthritis who had previously received treatment with NSAIDs. Patients were stratified according to methotrexate (MTX) use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. At 16 weeks, 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30. Among those not receiving MTX, flares occurred in 43% of patients receiving adalimumab and 71% receiving placebo (P=0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment.[60] In a trial involving 69 pediatric patients with active polyarticular juvenile rheumatoid arthritis despite treatment with NSAIDs and MTX, etanercept was associated with a significant reduction in flares compared to placebo (28 vs 81%; P=0.003).[64] Ninety-four percent of patients who remained in an open-label four-year extension met juvenile rheumatoid arthritis 30% definition of improvement; while C-reactive protein levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious adverse events related to etanercept therapy after four years.[65] The approval of tocilizumab for systemic juvenile idiopathic arthritis was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active systemic juvenile idiopathic arthritis and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85 vs 24%; P<0.0001).[67] The approval of tocilizumab for polyarticular juvenile idiopathic arthritis was based on a randomized, placebo-controlled trial (N=166). Children age two to 17 years of age with active polyarticular juvenile idiopathic arthritis who failed MTX were included in the study. The primary endpoint was juvenile idiopathic arthritis ACR 30 flare at week 40. At week 40, tocilizumab treated patients experienced significantly fewer flares at week 40 compared to patients treated with placebo (25.6 vs 48.1%; P<0.0024).[68]

The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. The first study was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short term efficacy of canakinumab in 84 patients randomized to receive a single subcutaneous dose of 4 mg/kg canakinumab or placebo. At day 15, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study was a randomized, double-blind, placebo-controlled, withdrawal study of flare prevention in patients who were taking canakinumab and a glucocorticoid broken into two parts. One hundred seventy-seven patients were enrolled in the study and received 4 mg/kg canakinumab subcutaneously every four weeks in part one and 100 of these patients continued into part two to receive either canakinumab 4 mg/kg or placebo subcutaneously every 4 weeks. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids. There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI, 0.17 to 0.75).[69]

In a randomized, double-blind, double-dummy trial, adalimumab was compared to MTX and placebo in patients with moderate to severe psoriasis despite treatment with topical agents. The primary outcome, the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks, was achieved by significantly greater proportion of patients in the adalimumab group compared to patients in the MTX (P<0.001) and placebo (P<0.001) groups.[71] In the PHOENIX 1 and PHOENIX 2 studies, more than 2,200 patients with moderate to severe psoriasis were randomized to receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter.[72,73] In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (≥75% improvement in psoriasis area and severity at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (P<0.0001 for both). PASI 75 response was better maintained to at least one year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (P<0.0001).[72] In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compare to patients receiving placebo (P<0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every eight weeks. More partial responders at week 28 who received 90 mg every eight weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no response to changes in dosing intensity in partial responders treated with 45 mg. Adverse events were similar between groups.[69] In a study comparing etanercept and ustekinumab, a greater proportion of psoriasis patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7 vs 0.7% of all ustekinumab patients).[74] In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe psoriasis, adalimumab use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (P<0.00001) while etanercept 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (P<0.00001 for both strengths vs placebo). The infliximab group had the greatest response with a risk difference of 77% compared to the placebo group (P<0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab.[75]

The safety and efficacy of secukinumab was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. All patients were 18 years of age or older with a diagnosis of moderate-to-severe plaque psoriasis who had a minimum body surface area involvement of 10% who did not respond to phototherapy, topical therapy, systemic therapy or a combination of those therapies. Collectively, 2,403 patients were randomized (secukinumab 300 mg [N=691], secukinumab 150 mg [N=692], placebo [N=694], and etanercept [N=323]). In all trials, the endpoints were the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline to week 12 and treatment success (clear or almost clear) on the Investigator's Global Assessment modified 2011 (IGA). [5,76-78]

The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). The proportion of patients who achieved an IGA mod 2011 score of 0 or 1 was statistically significantly greater in the secukinumab 300 mg group (65.3%, 62.5%, 69.0%, 73.3%) and secukinumab 150 mg group (51.2%, 51.1%, 52.5%, 53.3%) compared with placebo (2.4%, 2.8%, 0%, 0%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (62.5 and 51.1) had a higher proportion

of patients that achieved PASI 75 compared with etanercept (27.2%; P<0.001 for both secukinumab comparisons).[5,76-78]

In two trials, psoriatic arthritis patients receiving adalimumab 40 mg every other week achieved an ACR 20 at a higher rate compared to placebo. Thirty-nine percent of patients in the active treatment group compared to 16% in the placebo group achieved this endpoint by week 12 (P=0.012) in a trial by Genovese et al (N=100), while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (P<0.001).[79,80] Adalimumab use was associated with an improvement in structural damage, as measured by the Modified Total Sharp Score (mTSS), compared to those receiving placebo (-0.2 vs 1.0; P<0.001).[80] The FDA-approval of certolizumab pegol for psoriatic arthritis was based on the results of a randomized, double-blind, placebo-controlled trial (RAPID-PsA) in adult patients with active psoriatic arthritis despite DMARD therapy. A greater proportion of patients treated with certolizumab pegol 200 mg every two weeks (58.0%) and certolizumab pegol 400 mg every four weeks (51.9%) achieved an ACR 20 response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons).[81,82] In a 12-week trial in adult patients with psoriatic arthritis despite NSAID therapy, 87% of etanercept treated patients met psoriatic arthritis response criteria, compared to 23% of those on placebo (P<0.0001). A PASI 75 improvement and ACR 20 response was detected in 26 and 73% of etanercept-treated patients compared to 0 (P=0.0154) and 13% (P<0.0001) of placebo-treated patients.[83] In a second trial, the mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75, compared to 3% of placebo patients (P=0.001). Furthermore, health assessment questionnaire scores were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).[77] The FDA-approval of subcutaneous formulation of golimumab for psoriatic arthritis was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active psoriatic arthritis despite NSAID or DMARD therapy (N=405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy.[85] In a trial by Antoni et al, more infliximab treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (P<0.001).[87] The FDA-approval of ustekinumab for psoriatic arthritis was based on the results of two randomized, double-blind, placebo-controlled trials in adult patients with active psoriatic arthritis despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In the PSUMMIT 1 (N=615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; P<0.0001 for both comparisons); responses were maintained at week 52. The results of the PSUMMIT 2 trial (N=315) have not yet been published.[88]

The approval of the subcutaneous formulation of abatacept was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous formulation. The trial enrolled patients with rheumatoid arthritis that had an inadequate response to MTX. The proportion of patients achieving ACR 20 was not significantly different between the groups.[90] The RAPID-1 and RAPID-2 studies compared certolizumab pegol in combination with MTX to placebo plus MTX in adults with active rheumatoid arthritis despite MTX therapy.[94,95] A significantly greater proportion of patients on certolizumab pegol 400 mg plus MTX at weeks zero, two, and four then 200 mg or 400 mg every two weeks attained ACR 20, ACR 50 and ACR 70 responses after 24 weeks compared to patients treated with placebo and MTX (P≤0.01). The response rates were sustained with active treatment over 52 weeks.[94] The mTSS' were significantly lower with certolizumab pegol in combination with MTX compared to MTX in combination with placebo.[94,95] Fleischmann et al evaluated certolizumab pegol monotherapy compared to placebo in patients with active disease who had failed at least one prior DMARD trial. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; P<0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab pegol therapy.[96]

The FDA-approval of subcutaneous formulation of golimumab for rheumatoid arthritis was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients with moderate to severe active disease. A greater percentage of patients from all three trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 compared to patients treated with MTX alone.[99-101] Moreover, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI).[100,101] The FDA-approval of intravenous formulation of golimumab for rheumatoid arthritis was based on one multicenter, randomized, double-blind, controlled trial in 592 patients with moderate to severe active disease. In this trial, significantly higher proportion of patients achieved an ACR 20 response in the golimumab group compared to placebo, when both were added to background MTX therapy.[103]

The efficacy and safety of tocilizumab was assessed in five randomized, double-blind, multicenter studies in patients ages 18 years and older with active rheumatoid arthritis. Patients had rheumatoid arthritis diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was administered every four weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate adverse events were reported, occurring in similar frequencies in all study groups. The most common adverse events in all studies were infections and gastrointestinal symptoms.[104-107,110] AMBITION evaluated the safety and efficacy of tocilizumab monotherapy compared to MTX in patients with active rheumatoid arthritis for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy compared to MTX monotherapy produced greater improvements in rheumatoid arthritis signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. In addition, more patients treated with tocilizumab achieved remission at week 24 compared to patients treated with MTX.[104] The 24-week ADACTA trial in RA patients intolerant to methotrexate treatment found significantly greater improvements in DAS 28 scores and ACR core set measures in patients treated with tocilizumab compared to adalimumab.[118]

In the LITHE study, 1,196 patients with moderate to severe rheumatoid arthritis who had an inadequate response to MTX were randomized to receive 4 mg/kg of tocilizumab, 8 mg/kg of tocilizumab or placebo every four weeks in addition to background MTX. At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the Disease Activity Score using 28 joint counts (DAS28 score <2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001).[107] OPTION evaluated tocilizumab in 623 patients with moderate to severely active rheumatoid arthritis. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo intravenously every four weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with <20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. An ACR 20 was seen in significantly more patients receiving tocilizumab compared to those receiving placebo at week 24 (P<0.001). Moreover, a significantly higher proportion of patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 (P<0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg).[105] In the TOWARD study, investigators examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active rheumatoid arthritis. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response compared to patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60 vs 30%; P value

not reported).[106] In the RADIATE trial, investigators evaluated the safety and efficacy of tocilizumab in patients with rheumatoid arthritis refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg weekly) for 24 weeks. ACR 20 responses and safety endpoints were assessed. The results demonstrated that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of rheumatoid arthritis in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with adalimumab and infliximab, irrespective of the type or number of failed TNF antagonists.[109]

A Cochrane review examined abatacept for the treatment of rheumatoid arthritis. ACR 50 response was not significantly different at three months, but was significantly higher in the abatacept group at six and 12 months compared to placebo (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70.[104] The safety and efficacy of adalimumab for the treatment of rheumatoid arthritis was assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses at six months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious.[112] A Cochrane review was performed to compare anakinra to placebo in adult patients with rheumatoid arthritis. Significant improvement in both primary (ACR 20, 38 vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in adverse events noted with anakinra use was the rate of injection site reactions (71 vs 28% for placebo).[113] In another Cochrane review, etanercept was compared to MTX or placebo in adult patients with rheumatoid arthritis and 64% of individuals on etanercept 25 mg twice-weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo after six months of treatment (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39 and 15% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. Etanercept 10 mg twice-weekly was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.50; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose.[114] A meta-analysis by Wiens et al evaluated the efficacy of infliximab in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03).[116] Nixon et al performed a meta-analysis of randomized controlled trials including adalimumab, anakinra, etanercept, and infliximab with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.50; $P<0.05$).[117]

Treatment with abatacept was compared to treatment with adalimumab, both added to MTX, in a randomized controlled trial (N=646) of RA patients with inadequate response to MTC. After 12 months, the proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%).[119] ACR 20 responses were similar between the two groups following two years of treatment.[120]

ORAL Solo (N=611) was a six-month monotherapy phase 3 trial in which patients with moderate to severe active RA who had an inadequate response or adverse reaction to a DMARD (nonbiologic or biologic) received tofacitinib 5 mg or 10 mg twice daily or placebo. Compared to placebo at month three, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons) and Disease Activity Score for 28-joint counts based on the erythrocyte sedimentation rate (DAS28-4[ESR])<2.6 (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively). The reductions from baseline in HAQ-DI scores at month three were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.50 and -0.57 vs -0.19; P<0.001 for both comparisons).[121]

ORAL Standard (N=717) was a 12-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. At six months, ACR20 was achieved in 51.5 and 52.6% of patients treated with tofacitinib 5 mg and 10 mg, 47.2% of patients in the adalimumab group and 28.3% of placebo patients (P<0.001 for all comparisons to placebo). At six months, the DAS28-4(ESR) <2.6 was reached in 6.2% (P≤0.05) and 12.5% (P≤0.001) of patients treated with tofacitinib 5 mg and 10 mg, 6.7% (P≤0.05) of adalimumab group compared to 1.1% of patients in the placebo group. At month three, the reductions from baseline in HAQ-DI scores were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.55 and -0.61 vs 0.24; P≤0.001 for both comparisons) and adalimumab compared to placebo (-0.49 vs 0.24; P≤0.001).[122]

ORAL Step (N=399) was a six-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to at least one TNF-blocking agent received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Compared to placebo at month three, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (41.7 and 48.1 vs 24.4%; P<0.0024 and P<0.0001, respectively) and DAS28-4(ESR)<2.6 (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively). At month three, the reductions from baseline in HAQ-DI scores were significantly greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons).[123]

ORAL Scan (N=797) is an ongoing two-year phase 3 trial with a planned analysis at one year in which patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Compared to placebo at month six, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (51.5 and 61.8 vs 25.3%; P<0.0001 for both comparisons), achieved reductions in radiographic progression as demonstrated by mTSS (0.12 and 0.06 vs 0.47; P=0.0792 and P≤0.05, respectively), and had DAS28-4(ESR) <2.6 (7.2 and 16.0 vs 1.6%; P value not reported for the first comparison and P<0.0001 for the second comparison). At month three, the reductions from baseline in HAQ-DI scores were greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.40 and -0.54 vs -0.15; P value not reported for the first comparison and P<0.0001 for the second comparison).[124]

ORAL Sync (N=792) was a 12-month phase 3 trial in which patients with moderate to severe active RA who had an inadequate response to a nonbiologic DMARD received tofacitinib 5 mg or 10 mg twice daily or placebo added to DMARD. Compared to placebo at month six, greater proportions of patients treated with tofacitinib 5 mg and 10 mg achieved ACR20 response (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons) and had DAS28-4(ESR) <2.6 (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). At month three, the reductions from baseline in HAQ-DI scores were greater with tofacitinib 5 mg and 10 mg compared to placebo (-0.44 and -0.53 vs -0.16; P<0.001 for both comparisons).[125]

Two meta-analyses conducted by He at al and Berhan et al, respectively, confirmed greater efficacy of tofacitinib compared to placebo in RA patients for the primary endpoints of ACR20 and ACR50 response rates, and improvements in HAQ-DI score, all of which reached statistical significance for tofacitinib dosages ≥5 mg.[126,127]

Infliximab demonstrated effectiveness in ulcerative colitis in two trials. Studies ACT 1 and ACT 2 evaluated infliximab compared to placebo for this indication. In both trials, clinical response at week eight was significantly higher in patients treated with infliximab 5 mg/kg or 10 mg/kg compared to placebo (all P<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies.[128] A randomized, open-label trail evaluated infliximab as different dosing intervals for the treatment of pediatric ulcerative colitis. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%).[129]

The FDA-approval of adalimumab for the inducing and sustaining clinical remission of patients with active ulcerative colitis was based on the results of two placebo-controlled studies. In both studies adalimumab initially dosed at 160 mg, then 80 mg at week 2 and 40 mg every other week thereafter showed significant improvements in proportion of patients that were in remission after 8 weeks of treatment (P<0.05 in each study).[130,131] Patients also demonstrated significant decreases compared to placebo (P<0.05 in each study) in rectal bleeding, stool frequency and physician global assessment scores. In the study by Sandborn et al, remission observed by week 8 was sustained out to 52 weeks in 8.5% of the patients as did mucosal healing in 18.5% of patients (P<0.05 for all). In this study, it was noted that larger proportion of patients were also able to discontinue corticosteroid use at week 52 (13.3%) vs placebo (5.7%) and achieve remission (P=0.035).[131] It was noted that a treatment arm in the Reinisch et al trial that utilized a lower dose of adalimumab (initial dose 80 mg, then 40 mg every other week thereafter) did not show significant improvements in remission rates, clinical response or symptom improvement when compared to placebo.[130]

The FDA-approval of subcutaneous formulation of golimumab for the treatment of moderately to severely active ulcerative colitis was based on the results of two multicenter, randomized, double-blind, placebo-controlled clinical trials (PURSUIT-SC and PURSUIT-M).[132,133] PURSUIT-SC study included a phase 2 dose-finding and phase 3 dose-confirmation trials. In phase 2 trial, patients were randomized to placebo or one of four golimumab treatment groups: 400 mg at week zero and 200 mg at week two (400 mg/200 mg), 200 mg at week zero and 100 mg at week two (200 mg/100 mg), or 100 mg at week zero and 50 mg at week two (100 mg/50 mg). In phase 3 trial, 774 patients were randomized to placebo or to one of two golimumab treatment groups: 400 mg at week zero and 200 mg at week two or 200 mg at week zero and 100 mg at week two. In phase 2 trial, changes from baseline in Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group; P=0.038, P=0.332 and P=0.038, respectively). In phase 3 trial, the proportion of patients with clinical response at week six was greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons). Rates of clinical remission, mucosal healing and mean changes in Inflammatory Bowel Disease Questionnaire scores were significantly greater in both golimumab groups than the placebo group. [132] PURSUIT-M was a randomized-withdrawal maintenance trial that evaluated 464 patients who achieved clinical response with golimumab induction. Patients were randomized to receive golimumab 50 mg, golimumab 100 mg or placebo every four weeks. The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Rates of clinical remission at both weeks 30 and 54 were significantly greater in the golimumab 100 mg group than the placebo (27.8 vs 15.6%; P=0.004); however, the differences in the rates of mucosal healing and corticosteroid-free clinical remission were not statistically significant between both golimumab groups and placebo.[133]

The FDA-approval of vedolizumab for the treatment of ulcerative colitis was based on one Phase III randomized, placebo-controlled trial, GEMINI-1, which evaluated the safety and efficacy of vedolizumab 300 mg IV at weeks 0 and 2 followed by 300 mg IV every four or eight weeks compared to placebo. In the double-blind cohort, a significantly greater proportion of patients treated with vedolizumab achieved clinical response at week six compared to placebo (47.1 vs 25.5%; 95% CI, 11.6 to 31.7; P<0.001). In the open-label vedolizumab cohort, 44.3% of patients achieved a clinical response and 19.2% achieved clinical remission. In the maintenance phase, a significantly greater proportion of patients treated with vedolizumab every four or eight weeks achieved clinical remission at week 52 compared to placebo (44.8 and 41.8% vs 15.9% respectively; 95% CI, 14.9 to 37.2; P<0.001).[134]

Neonatal-onset multisystem inflammatory disease (NOMID) is a rare autoinflammatory disorder that presents around birth with systemic inflammation and rash and may develop with severe organ manifestations involving the eyes, ears, bones and central nervous system. Progressive cognitive impairment and physical disability is a consequence of the organ damage with mortality rates estimated at up to 20% before adulthood. Anakinra recently became the first and only FDA-approved treatment for patients with NOMID. The approval was the result of a single trial in 43 NOMID patients over 60 months that demonstrated sustained improvements in patients' diary scores, physician global scores of disease activity, patient/parent pain scores, and inflammatory markers (all P<0.001 at 36 and 60 months). In addition, most patients showed stable or improved hearing as well as stable visual acuity and peripheral vision.[135]

FDA-approval of canakinumab for the treatment of CAPS was based on a single study. This study was a 48-week, three-part, randomized, double-blind, placebo-controlled. In part-1 of the study all 35 patients received a single 150 mg dose of canakinumab. Those with a complete response in part-1 were enrolled into part-2 and were randomly assigned to either 150 mg of canakinumab every eight weeks or placebo. After the completion of part-2 all patients entered into the third part of the study where they received at least two more doses of canakinumab. In part-1 of the study 34 of the 35 patients (97%) had a complete response canakinumab. Of the 15 patients who continued to receive canakinumab in part-2, all remained in remission. In contrast, disease flare ups occurred in 13 of the 16 patients (81%) in the placebo group, (P<0.001). By the end of the third part of the study, 30 of the 31 patients (97%) who had entered the final phase had no or minimal disease activity, with the remaining having only mild disease activity.[136]

The safety and efficacy of rilonacept for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts conducted sequentially in the same patients with Familial Cold Autoinflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS). Part-1 was a six-week, randomized, double-blind, parallel-group period comparing rilonacept 160 mg weekly after an initial loading dose of 320 mg to placebo. Part-2 followed immediately after part-1 and consisted of a 9-week, patient-blind period during which all patients received rilonacept 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on rilonacept 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with rilonacept 160 mg weekly. There was a statically significant difference in least square mean difference for symptom scores in part-1 and part-2. Scores for part-1 were -2.4 and -0.5 for rilonacept and placebo respectively (95% CI, -2.4 to -1.3; no P value reported) and 0.9 to 0.1 for part-2 (95% CI, -1.3 to -0.4; no P value reported).[3]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ankylosing Spondylitis				
van der Heijde et al[41] Adalimumab 40 mg every other week vs placebo Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of AS based on the modified New York criteria with active disease BASDAI score ≥4, a total back pain score ≥4 by VAS (VAS, 0 to 10 cm) or a duration of morning stiffness ≥1 hour	N=315 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, and ASAS partial remission	Primary: An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (P<0.001). Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52 vs 18%; P<0.001). Adalimumab, compared to placebo, resulted in a significant improvement in other measures of disease activity such as a 50% improvement in BASDAI at week 12 (45 vs 16%; P<0.001) which was sustained through week 24 (42 vs 15%; P<0.001). ASAS 5/6 and ASAS 40 responses were attained in 49 vs 13% and 40 vs 13% of adalimumab vs placebo patients at week 12 (P<0.001) and 45 vs 12% and 39 vs 13% at week 24 (P<0.001), respectively. Partial remission was achieved in 21 vs 4% at week 12 and 22 vs 6% at week 24 in the adalimumab and placebo groups, respectively (P<0.001).
Landewe et al[42] (RAPID-axSpA) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg)	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of AS based on the ASAS criteria, with active disease BASDAI score ≥4, spinal pain ≥4, CRP>7.9 mg/L and/or sacroiliitis on MRI, chronic back pain ≥3 months, inadequate	N=325 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, change from baseline in BASFI, BASDAI, and BASMI linear at week 12 and 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (57.7%) and CZP 400 mg every four weeks (63.6%) achieved ASAS 20 response at week 12 compared to placebo (38.3%; P=0.004 and P<0.001, respectively). Secondary: The difference in ASAS 20 response was sustained through week 24 in both CZP treatment groups (P<0.001). Improvements in BASFI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.0 and -2.0 vs -0.5; P<0.001) and at 24 weeks (-2.2 and -2.2 vs -0.4; P<0.001 for both comparisons), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Patients receiving placebo who did not achieve an ASAS 20 response at weeks 14 and 16 were randomized to active treatment at week 16. Concurrent DMARDs (SSZ and MTX) were allowed.	response or intolerance to ≥1 NSAID or ≥2 weeks each for ≥2 NSAIDs in the last ≥30 days			Improvements in BASDAI scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-2.8 and -2.8 vs -1.2; P<0.001) and at 24 weeks (-3.1 and -3.0 vs -1.1; P<0.001 for both comparisons), respectively. Improvements in BASMI linear scores from baseline were greater in patients treated with CZP 200 mg every two weeks and CZP 400 mg every four weeks compared to placebo at 12 weeks (-0.6 and -0.5 vs -0.1; P<0.001 and P<0.05, respectively) and at 24 weeks (-0.5 and -0.5 vs -0.1; P<0.001 for both comparisons), respectively.
Gorman et al[43] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs, NSAIDs, and oral corticosteroids.	DB, RCT Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments	N=40 4 months	Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, and joint swelling Secondary: Physician's global assessment of disease activity, measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels,	Primary: A response to treatment was detected in 80% of individuals receiving etanercept as opposed to 30% of individuals receiving placebo (P=0.004). Primary endpoints were reported as follows for the etanercept and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 vs 60.0±65.0 minutes (P<0.001); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (P<0.001); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (P=0.17); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (P<0.001); and the BASFI scores (0=none to 10=severe limitations), 2.2±2.1 vs 3.1±3.0 (P<0.001). Secondary: Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to those taking placebo including, physician's global assessment of disease activity (23.0±10.6; P<0.001), chest expansion (3.5±1.9 vs 2.9±1.7 cm; P=0.006), Modified Newcastle Enthesis Index, which is a measure of 17 enthesis on a four point pain scale (0.0±3.0 vs 1.5±8.0; P=0.001), ESR level (8.5±12.8 vs 16.5±18.7 mm/hour; P<0.001) and CRP level (0.7±1.1 vs 2.0±2.8 mg/dL; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and adverse events	Injection site reactions and minor infections were the most commonly reported adverse events. The incidence in overall adverse events or specific events did not differ significantly.
Calin et al[44] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).	DB, MC, RCT Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=84 12 weeks	Primary: ASAS 20 response Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI, acute phase reactants, spinal mobility tests, and safety	Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (P<0.001). Secondary: The etanercept group was associated with the higher rates of ASAS 50 and 70 responses (48.9 and 24.4%) compared to placebo (10.3 and 10.3%) at week 12. However, only the differences in ASAS 50 response reached statistical significance at this assessment point (P<0.001). ASAS 70 response was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; P<0.05). The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3 vs 15.9% (P=0.003); nocturnal and total pain, 43.1 vs 6.2% (P=0.000); patient's global assessment, 37.0 vs 12.6% (P=0.11); functional impairment (BASFI), 35.4 vs 3.4% (P=0.000); BASDAI composite score, 43.6 vs 13.6% (P=0.001); and BASDAI fatigue score, 42.6 vs -4.9% (P=0.000). Injection site reactions occurred more frequently with etanercept compared to placebo (33 vs 15%; P<0.05).
Davis et al[45] Etanercept 25 mg twice weekly until week 72, then 50 mg once weekly Stable doses of corticosteroids and NSAIDs were required 2 weeks prior to enrollment; stable doses of HCQ,	ES, OL Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=257 Up to 192 weeks	Primary: Safety (adverse events, serious adverse events, infections, serious infections, and death) and efficacy (ASAS 20 response, ASAS 5/6	Primary: After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported. For etanercept treatment the exposure adjusted serious event rate/patient year was 0.08, the exposure adjusted infection rate/patient year was 1.10, and the exposure adjusted serious infection rate/patient year was 0.02. Injection site reactions were reported in 22.2% of patients, which lead to the withdrawal of 0.4% of patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MTX, or SSZ were required if deemed necessary.			response, and partial remission rates) Secondary: Not reported	A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% of patients were considered responders at week 192. ASAS 5/6 response rates were 61% at week 96 and 60% at week 144. Partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance. Secondary: Not reported
Braun et al[46] ASCEND Etanercept 50 mg once weekly vs SSZ titrated to 3 g daily in divided doses	DB, MC, RCT Patients ≥18 years of age with active AS (diagnosed according to modified New York criteria) who failed treatment with ≥1 NSAID taken for ≥3 months at the maximum recommended dose and were determined to be candidates for SSZ therapy by the investigators	N=566 16 weeks	Primary: Proportion of patients achieving ASAS 20 response at week 16 Secondary: Proportion of patients achieving ASAS 20 response at weeks two, four, eight and 12; proportion of patients achieving ASAS 40 response and ASAS 5/6 response at all time points	Primary: At week 16, significantly greater proportion of patients in the etanercept group achieved ASAS 20 response compared to the SSZ group (75.9 vs 52.9%; P<0.0001). Secondary: Significantly greater proportion of patients in the etanercept group achieved ASAS 20 response at week two compared to patients in the SSZ group; this difference was maintained throughout the time points (P<0.0001 for all). Significantly greater proportion of patients in the etanercept group achieved ASAS 40 and ASAS 5/6 responses compared to patients in the SSZ group at all time points (P<0.0001 for all). At week 16, a greater proportion of patients achieved ASAS 40 and ASAS 5/6 responses in the etanercept group compared to the SSZ group (59.8 vs 32.6%; P<0.0001 and 45.5 vs 21.2%; P<0.0001, respectively). The rates of adverse events and serious adverse events were similar between the two groups.
Inman et al[47] Golimumab 50 mg once	DB, MC, PC, RCT Patients ≥18 years	N=356 24 weeks	Primary: ASAS 20 response at week	Primary: Treatment with golimumab with or without a DMARD, compared to placebo with or without a DMARD, resulted in a significant improvement in signs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who were on stable doses of HCQ, MTX, NSAID, oral corticosteroid and/or SSZ were permitted in the study.	of age with a diagnosis of AS and no evidence of active TB and/or no evidence of latent TB on screening		14 Secondary: Not reported	and symptoms as demonstrated by ASAS 20 response at week 14 (59 vs 22%; P≤0.001). All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group compared to the placebo group at week 14. Secondary: Not reported
Braun et al[48] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs placebo Concurrent use of NSAIDs not exceeding the baseline dose was allowed.	DB, MC, PC, RCT Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score ≥4 and spinal pain score ≥4	N=70 12 weeks	Primary: Improvement from baseline in BASDAI by 50% at week 12 Secondary: Improvement from baseline in spinal pain, BASFI, BASMI, SF-36, CRP, and ESR	Primary: A greater proportion of patients achieved a 50% improvement in BASDAI at week 12 in the infliximab group (53%; 95% CI, 37 to 69) compared to the placebo group (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until week 12 (P<0.0001). Secondary: At week 12, the infliximab group had a significant mean improvement from baseline in spinal pain (P<0.0001), BASFI (P<0.0023), BASMI (P<0.0001), CRP (P<0.0001), and ESR (P<0.0001); while there was no significant difference in the placebo group. At 12 weeks, there were significant improvements from baseline in the physical component and mental component of the SF-36 in the infliximab group (P<0.0001); however, only the improvement in the physical component was significantly greater compared to the placebo group (P<0.0001). A greater proportion of patients reported infections in the infliximab group (51%) compared to the placebo group (35%; difference, 16%; 95% CI, -7 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				40; P=0.227). A greater proportion of patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to the placebo group (3 vs 0; P=0.239).
van der Heijde et al[49] (ASSERT) Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18 vs placebo Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	MC, PC, RCT Adult patients (median age of 40) with AS based on the modified New York criteria for at least three months with a BASDAI score ≥4, spinal pain assessment score ≥4 on a VAS and a normal chest radiograph within three months, and negative TB screening	N=279 24 weeks	Primary: Proportion of patients with ASAS 20 at week 24 Secondary: ASAS 40 response, ASAS partial remission, ASAS 5/6, disease activity (BASDAI, night pain, patient's global assessment and CRP), physical function (BASFI), range of motion (BASMI), other musculoskeletal assessments (swollen joint count and degree of tenderness) and quality of life (SF-36)	Primary: After 24 weeks, significantly greater proportion of patients were ASAS 20 responders in the infliximab group (61.2%) compared to the placebo group (19.2%; P<0.001). The difference was significant at week two and continued to week 24. Secondary: Over the 24-week study period, significantly greater proportion of patients were ASAS 40 responders in the infliximab group compared to the placebo group (P<0.001). At 24 weeks 47% of patients were ASAS 40 responders in the infliximab group compared to 12% in the placebo group (P<0.001). Significantly greater proportion of patients treated with infliximab achieved ASAS 5/6 (49%) compared to placebo treated patients (8%; P<0.001). Significantly greater proportion of patients achieved a partial ASAS response in the infliximab group (22.4%) compared to the placebo group (1.3%; P<0.001). The median improvement in all measures of disease activity (BASDAI, night pain, patient's global assessment and CRP) was significantly greater in the infliximab treated patients compared to placebo treated patients (P<0.001). The patients in the infliximab group had a significantly greater median improvement in BASFI compared to patients in the placebo group (P<0.001). There was a significantly greater median improvement in BASMI in the infliximab group compared to the placebo group (P=0.019). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to the placebo treated patients (P=0.019). There was a significantly greater improvement in the physical component of the SF-36 in the infliximab group compared to the placebo group (P<0.001); there was no significant difference in the mental component (P=0.547). Compared to patients in the placebo group, a greater proportion of patients in the infliximab group experienced at least on adverse event (82.2 vs 72.0%), reported at least one infection (42.6 vs 36.0%) and had severe

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse reactions (3.5 vs 2.7%). Of the adverse events that occurred in at least 5% of patients in either group, the rates of pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.
Machado et al[50] Infliximab vs etanercept vs adalimumab vs golimumab vs certolizumab vs control Concurrent use of stable doses of other medications was allowed.	MA RCTs of patients with AS based on the modified New York criteria	N=2,820 (18 trials) 6 to 104 weeks	Primary: Proportion of patients with ASAS 20 at 12- or 14 weeks and at 30 weeks of follow-up Secondary: ASAS 40 response, ASAS 5/6, ASAS partial remission, BASDAI, BASDAI 50, BASFI, and BASMI, withdraws and safety outcomes at 12 or 14 weeks and 30 weeks of follow-up	Primary: Patients treated with TNF-blockers were more likely to achieve ASAS 20 response after 12 or 14 weeks (RR, 2.21; 95% CI, 1.91 to 2.56) and 24 weeks (RR, 2.68; 95% CI, 2.06 to 3.48) compared to controls. Treatment with golimumab was associated with the highest RR for ASAS 20 response after 12 or 14 weeks (RR, 2.74; 95% CI, 1.78 to 4.22), followed by adalimumab (RR, 2.33; 95% CI, 1.45 to 3.74), etanercept (RR, 2.13; 95% CI, 1.75 to 2.58), and infliximab (RR, 1.82; 95% CI, 1.16 to 2.58) compared to controls. Treatment with infliximab was associated with the highest RR for ASAS 20 response after 24 weeks (RR, 3.18; 95% CI, 1.99 to 5.08), followed by etanercept (RR, 2.53; 95% CI, 1.80 to 3.57) and adalimumab (RR, 2.15; 95% CI, 0.96 to 4.83) compared to controls. Secondary: Patients treated with TNF-blockers were more likely to achieve ASAS 40 response after 12 or 14 weeks (RR, 2.77; 95% CI, 2.05 to 3.75) and 24 weeks (RR, 3.32; 95% CI, 2.44 to 4.51) compared to controls. Patients treated with TNF-blockers were more likely to achieve ASAS 5/6 response after 12 or 14 weeks (RR, 3.52; 95% CI, 2.17 to 5.71) and 24 weeks (RR, 4.25; 95% CI, 2.80 to 6.46) compared to controls. Patients treated with TNF-blockers were more likely to achieve partial remission after 12 or 14 weeks (RR, 4.79; 95% CI, 2.46 to 9.34) and 24 weeks (RR, 4.43; 95% CI, 2.62 to 7.49) compared to controls. Patients treated with TNF-blockers achieved greater improvements in the disease activity (BASDAI) after 12 weeks (mean difference, -1.64; 95% CI, -2.06 to -1.22) and after 30 weeks (mean difference, -1.79; 95% CI, -2.27 to 1.31) compared to controls.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients treated with TNF-blockers were more likely to achieve BASDAI 50 response at 12 or 14 weeks (RR, 2.87; 95% CI, 2.23 to 3.69) and at 24 weeks (RR, 3.39; 95% CI, 2.46 to 4.67) compared to controls. Patients treated with TNF-blockers achieved greater improvements in physical function (BASFI) at 12 weeks (mean difference, -1.39; 95% CI, -1.59 to -1.19) and at 24 weeks (mean difference, -1.52; 95% CI, -1.72 to -1.31) compared to controls. Patients treated with TNF-blockers achieved greater improvements in vertebral mobility (BASMI) at 12 weeks (mean difference, -0.53; 95% CI, -0.72 to -0.35) and at 24 weeks (mean difference, -0.60; 95% CI, -0.87 to -0.33) compared to controls. Meta-analysis of safety outcomes and withdraws did not indicate statistically significant differences between treatment and control groups after 12 or 30 weeks (P value not reported).
Crohn's Disease				
Ma et al[51] Adalimumab	SR OL and RCT cohort studies of patients with CD who had either lost response, were intolerant or refractory to infliximab	N=1,810 (15 trials) 8 weeks to 4 years	Primary: Short-term and long-term efficacy Secondary: Adverse events	Primary: Short-term clinical response or remission was evaluated in nine trials. Forty-one to 83% of patients achieved a clinical response at four weeks, while 12 to 67% of participants attained clinical remission. Long-term remission rates ranged from 31 to 82% at six months and 19 to 68% at one year. Secondary: Serious adverse events were reported in 0 to 19% of patients and included sepsis, cellulitis, and fungal pneumonia.
Lofberg et al[52] (CARE) Adalimumab 160 mg at week zero, followed by 80 mg at week two, followed by 40 mg every other	MC, OL Patients 18 to 75 years of age with a radiologic or endoscopic diagnosis of CD for	N=945 20 weeks	Primary: Remission rates, proportion of patients free of EIM at week 20 Secondary:	Primary: The proportion of patients in remission who received adalimumab was 43% at week four (95% CI, 40 to 46) and increased to 52% (95% CI, 49 to 55) at week 20. There was a significantly higher remission rate at week 20 among adalimumab-treated patients who were also infliximab naïve compared to patients exposed to infliximab (62 vs 42; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week At week 12 or later, patients who experienced a disease flare or did not respond to treatment could increase the adalimumab dose to 40 mg weekly.	≥4 months and a HBI >7 points at screening		Fistula healing, remission rates based on concomitant therapies and adverse events	A shorter disease duration (less than two years and between two and five years) was associated with higher rates of clinical remission at week four compared to a disease duration longer than five years (50, 52, and 38%, respectively; P<0.001); however the remission rates at 20 weeks were not significantly different (58, 56, and 50%, respectively; P=0.136). Overall, 53% of patients had at least one EIM at baseline, compared to 30% at week 20. Of these, 79% had resolution of at least one EIM and 51% were free of EIM signs and symptoms following 20 weeks of adalimumab treatment. The EIM resolution rates were similar across adalimumab-treated patients regardless of prior infliximab use (P=0.100) and prior infliximab response and those who discontinued treatment for other reasons (P=0.625). Secondary: Complete fistula healing occurred in 26% of patients at week 20. Fistula closure rates were numerically higher in the infliximab-naïve group at week 20 (33%) compared to the infliximab-experienced group (22%); however, the difference was not significant (P=0.275). Fistula healing rates were similar in nonresponders to infliximab compared to those who discontinued infliximab for other reasons (19 vs 23%; P=0.973). Of patients taking corticosteroids at baseline, 37% were able to discontinue them by week 20; Eleven percent and 14% of patients achieved a steroid-free remission at weeks 12 and 20, respectively. Seven percent of patients taking immunosuppressants at baseline were able to discontinue them at week 20. There were similar rates of clinical remission at week 20 between patients taking and not taking steroids at baseline (52% in both groups; P=0.976). By week 20, the rates of clinical remission were 55 and 49%, respectively, in patients who were and were not taking immunosuppressants at baseline (P=0.052). Adverse events occurred in 80% of patients and 11% of patients who

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				discontinued treatment due to adverse events. Serious adverse events were reported in 19% of patients. The adverse events profiles were similar among patients who were exposed to infliximab previously and those who were treatment naïve. The most common adverse event categories were "gastrointestinal disorders" and "CD'' indicating a worsening of patient's underlying disease.
Watanabe et al[53] (Induction study) Adalimumab 160 mg at week zero, followed by 80 mg at week two (ADA 160/80 group) vs adalimumab 80 mg at week zero, followed by 40 mg at week two (ADA 80/40 group) vs placebo (Maintenance study) adalimumab 40 mg every other week vs placebo Patients achieving a Clinical Response 70 (decrease from baseline in	2 DB, MC, PC, RCT Patients 15 to 75 years of age, with moderate to severely active CD, CDAI score 220 to 450 for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation	N=90 (induction) N=83 (maintenance) 56 weeks (4 weeks induction study and 52 week maintenance study)	Primary: Induction study Proportion of patients in clinical remission (CDAI <150) at week four Maintenance Clinical remission (CDAI <150) at week 52 Secondary: Induction study Proportion of patients in clinical remission at week two and with CR-100 or CR-70 (CDAI decrease ≥100 or ≥70) at week four, changes from baseline in CDAI and IOIBD at week two and week four and changes in SF-36 MCS and PCS,	Primary: Induction A greater proportion of patients treated with ADA 160/80 and ADA 80/40 achieved a clinical remission by week four compared to placebo (33 and 18 vs 12%, respectively; P value not reported). Maintenance By week 52, a significantly greater proportion of patients treated with adalimumab 40 mg achieved a clinical remission compared to placebo (P<0.05). Secondary: Induction At week two, clinical remission rates were higher with ADA 160/80 and ADA 80/40 compared to placebo (18 and 15 vs 4%, respectively; P value not reported). At week four, significantly greater proportion of patients receiving ADA 160/80 or ADA 80/40 experienced a CR-100 (50 and 46 vs 17%, respectively; P<0.05 for both) compared to placebo. At week four, significantly greater proportion of patients receiving ADA 160/80 experienced a CR-70 (70 vs 30%; P=0.0062); however, the improvement with the ADA 80/40 was not statistically significant. The changes in CDAI from baseline to week two and four, respectively, were, -75.9 and -101.3 in the ADA 160/80 group, -74.4 and -81.3 in the ADA 80/40 group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from baseline to week two and week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
CDAI ≥70 points at week four) entered the blinded maintenance trial.			and IBDQ scores in each treatment group at week four Maintenance Proportion of patients in clinical remission, (CDAI decrease ≥100 or ≥70) every four weeks, changes from baseline of the induction to week 52 in CDAI, IOIBD, SF-36 MCS and PCS scores, and IBDQ	four, respectively, were -1.2 and -1.5 in the ADA 160/80 group, -0.7 and -0.8 in the ADA 80/40 group, and -0.4 and -0.5 in the placebo group. ADA 160/80 or ADA 80/40 significantly improved SF-36 MCS from baseline to week four compared to placebo. (6.2 and 5.5 vs -1.6, respectively; P<0.05 for both). There were no statistically significant differences in SF-36 PCS and IBDQ between patients receiving ADA 160/80 compared to patients receiving placebo. Maintenance Adalimumab therapy was more effective compared to placebo at each of the four-week evaluations throughout the 52-week trial compared to placebo with regard to CR-100 (P≤0.05) and CR-70 (P≤0.01). Adalimumab was more effective compared to placebo with regard to maintaining clinical remission at weeks eight, 36, 36, 40, 48 and 52 (P<0.05). The mean changes in CDAI from baseline of the induction trial to week zero and week 52, respectively, were -147.7 and -83.7 in the adalimumab-treated patients and -139.0 and -9.1 in the placebo-treated patients. The mean changes in IOIBD from baseline to week zero and week 52, respectively, were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively. Adalimumab 40 mg was associated with statistically significant improvements in SF-36 MCS and IBDQ compared to placebo at eight weeks (12.0 vs 2.0; P=0.03 and 34.8 vs 8.3; P=0.05, respectively); however, the changes were not significantly different at 52 weeks.
Shao et al[54] Certolizumab vs placebo	MA DB, RCTs in patients with moderate to severe CD	N=1,040 (3 trials) 12 to 26 weeks	Primary: Clinical response (a decrease ≥100 points from baseline in CDAI score) and clinical remission (CDAI score	Primary: Certolizumab was associated with an increased rate of induction of clinical response (RR, 1.36; 95% CI, 1.10 to 1.68; P=0.004) and remission (RR, 1.95; 95% CI, 1.41 to 2.70; P<0.0001) compared to placebo. Secondary: Only infection was reported more frequently with certolizumab compared to placebo (60.6 vs 40.7%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			≤150 points) at week four Secondary: Safety	
Targan et al[55] Infliximab 5 mg/kg vs infliximab 10 mg/kg vs infliximab 20 mg/kg vs placebo	DB, MC, PC, RCT Adult patients with CD for six months with CDAI scores 220 to 400 and previously receiving mesalamine (for ≥8 weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for ≥8 weeks and a stable dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)	N=108 12 weeks	Primary: Decrease from baseline in CDAI ≥70 points at four weeks without a change in concomitant medications Secondary: Not reported	Primary: At week four, the primary endpoint was reached in 81, 50, 64 and 17% in the 5 mg/kg, 10 mg/kg, 20 mg/kg and placebo groups, respectively. The overall response of the infliximab groups was significantly higher (65%) compared to the placebo group (P<0.001). At week two, 61% of the infliximab treated patients had a response compared to 17% of the placebo treated patients (P<0.001). A greater proportion of patients was in remission (CDAI score <150) in the infliximab group at two weeks (27%) compared to the placebo group (4%; P=0.06). At week four, 33% of the infliximab treated patients were in remission compared to 4% of the placebo treated patients (P<0.005). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo treated patients (12%; P=0.008); however, the remission rate was not significantly different at 12 weeks (24 vs 8%; P=0.31). Secondary: Not reported
Present et al[56] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs infliximab 10 mg/kg at weeks 0, 2 and 6	DB, MC, PC, RCT Patients 18 to 65 years of age with ≥1 confirmed draining abdominal or perianal fistulas of ≥3 months as a complication of CD	N=94 18 weeks	Primary: Reduction ≥50% from baseline in number of draining fistulas at two or more consecutive study visits Secondary:	Primary: There were significantly greater response rates in the infliximab 5 (68%) and 10 mg/kg (56%) groups compared to the placebo group (26%; P=0.002 and P=0.02, respectively). The response rates were not significantly different between the two infliximab groups. Secondary: A greater proportion of patients in the infliximab 5 (55%) and 10 mg/kg (38%) groups had complete response compared to the placebo group (13%; P=0.001 and P=0.04, respectively). In the infliximab group, the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Proportion of patients with a complete response (absence of any draining fistula at two consecutive visits), length of time to beginning of response, and duration of response	median time to the onset of response was two weeks compared to six weeks in the placebo group. The duration of response was approximately three months in patients that reached the primary endpoint. The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.
Hyams et al[57] (REACH) Infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 8 weeks at weeks 14, 22, 30, 38 and 36 or every 12 weeks at weeks 18, 30 and 42 vs infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 12 weeks at weeks 18, 30 and 42	OL, MC, RCT Patients 6 to 17 years of age with a PCDAI >30 at baseline and who initiated immunomodulator therapy (azathioprine, mercaptopurine or MTX) ≥8 weeks before screening and at stable dose for two weeks	N=112 46 weeks	Primary: Clinical response at week 10 (decrease from baseline to week 10 in PCDAI ≥15 points and total PCDAI no more than 30) Secondary: Maintenance of clinical response and remission (PCDAI ≤10)	Primary: At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9). Secondary: At week 10, 58.6% of patients were in clinical remission (95% CI, 49.8 to 68.0). At week 54, 63.4 and 55.8% of patients treated with infliximab every eight weeks achieved clinical response and clinical remission, respectively, compared to 33.3 and 23.5% of patients treated with infliximab every 12 weeks (P=0.002 and P<0.001, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all P<0.001). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all P<0.001). Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.
Van Assche et al[58] (SWITCH) Adalimumab 80 mg at	OL, PRO, RCT Patients ≥18 years with luminal CD	N=73 54 weeks	Primary: Proportion of patients in the adalimumab	Primary: There was a statistically significant increase in the preference of adalimumab over infliximab for patients who changed from infliximab to adalimumab therapy at all evaluation points (P<0.05), except week 56

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week zero and 40 mg every other week Patients not randomized to adalimumab continued prior infliximab at 5 mg/kg at their regularly scheduled interval. Patients with a disease flare were able to intensify treatment as follows: adalimumab 40 mg every week and in the infliximab group, a decrease of the dosing interval with two-week decrements.	treated with infliximab maintenance therapy started for ≥6 months with a complete clinical response (PGA assessment of signs and symptoms, but the CDAI at baseline <200) with stable infliximab dosing intervals of ≥6 weeks		group preferring adalimumab over infliximab and proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or who had to stop the assigned anti-TNF agent Secondary: Proportion of patients with an injection- or infusion-related reaction and proportion of patients with an increase in the CDAI of >100 above baseline and IBDQ	(P=0.08). Dose intensification or early treatment termination occurred significantly more frequently over 54 weeks in patients switched to adalimumab (47%) compared to those who continued infliximab (16%; P=0.003). Significantly more patients initiating adalimumab therapy discontinued therapy due to loss of response or intolerance compared those who continued infliximab therapy (28 vs 2%; P<0.01). Of note, the patient who discontinued infliximab was successfully treated with adalimumab and eight of the 10 patients who stopped adalimumab treatment returned to infliximab therapy. The reasons for early discontinuation of treatment were loss of tolerance in six of 10 patients on adalimumab and in the one patient receiving infliximab. Four other patients in the adalimumab group stopped for loss of efficacy. Refractory eczema with fatigue or arthralgias (n=2), general malaise and diarrhea following injections (n=2) and fatigue plus inability to comply with injections (n=2) led to adalimumab intolerance and an infusion reaction to infliximab intolerance. Secondary: There was no difference in the change from baseline in CDAI at time of early termination in the adalimumab group (184 vs 78; P=0.10). Dose intensification occurred in 27.7% of patients in the adalimumab group, three of which later stopped adalimumab for loss of response, and in and 13.5% of patients in the infliximab group (P=0.20). The median time to dose intensification was not significantly different between the adalimumab and infliximab treatment arms (24 vs 32 weeks; P=0.64). An increase in CDAI ≥100 points was observed in 18.9% of patients in the infliximab group and in 27.7% of patients in the adalimumab group while on the initially assigned treatment. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial.

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Behm et al[59] Adalimumab, certolizumab, or infliximab vs placebo	SR RCTs including patients ≥18 years of age with CD who had a clinical response or clinical remission with a TNF-α blocker, or patients with CD in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocker or placebo	N=3,586 (9 trials) Duration varied	Primary: Clinical remission, clinical response, and steroid-sparing effects Secondary: Not reported	Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; P<0.00001), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported). Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; P=0.000072) and clinical response (RR, 1.74; 95% CI, 1.41 to 2.13; P<0.00001) compared to placebo. Infliximab was more effective than placebo at maintaining fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; P=0.012), clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; P=0.000019), clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; P=0.0046, and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; P=0.014). Secondary: Not reported
Sandborn et al[60] (GEMINI-2) Vedolizumab 300 mg intravenous at weeks 0 and 2 (induction) followed by vedolizumab 300 mg intravenous every four or eight weeks (maintenance) vs placebo Stable doses of oral prednisone (≤30 mg/day)	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with Crohn's disease for ≥3 months, a score of 220 to 450 on the CDAI and one of the following: a CRP >2.87 mg/mL, colonoscopy showing ≥3 large ulcers of ≥10 aphthous ulcers or fecal calprotectin >250 µg/g stool plus	N=1,115 52 weeks	Primary: Induction Clinical remission (CDAI ≤150), CDAI-100 response at week six Maintenance Clinical remission at week 52 Secondary: Induction Mean change in CRP from baseline to week	Primary: Induction In the double-blind cohort, a greater proportion of patients treated with vedolizumab achieved clinical remission at week six (14.5 vs 6.8%; P=0.02). A numerically greater proportion of patients treated with vedolizumab achieved a CDAI-100 response (31.4 vs 25.7%; P=0.23). Among the patients included in the open-label vedolizumab cohort, 17.7% achieved a clinical remission and 34.4% had a CDAI-100 response at week six. Maintenance At week 52, 39% of patients receiving vedolizumab every eight weeks and 36.4% of patients receiving vedolizumab every four weeks were in clinical remission, compared to 21.6% of patients in the placebo group (P<0.001 and P=0.004, respectively).

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or budesonide (≤9 mg/day), immunosuppressive agents, mesalamine and antibiotics were permitted.	evidence of ulcers on CT or MRE, small-bowel radiography or capsule endoscopy. All patients had no response or unacceptable side effects from one of more of the following: glucocorticoids, immunosuppressive agents or TNF antagonists.		six Maintenance CDAI-100 response, glucocorticoid-free remission, durable clinical remission (defined as clinical remission at ≥80% of study visits, including final visit) at week 52	Secondary: Induction In the double-blind cohort, the mean changes in CRP levels from baseline to week six were similar for both the vedolizumab and placebo groups. Maintenance At week 52, a significantly greater proportion of patients receiving vedolizumab achieved a CDAI-100 response and glucocorticoid-free remission compared to placebo; however, the proportion of patients with a durable clinical remission was not significantly different between vedolizumab and placebo.
Sands et al.[61]† (GEMINI-3) Vedolizumab 300 mg intravenous at weeks 0, 2 and 6 vs placebo	DB, MC, PC, RCT Patients 18 to 80 years of age with moderately to severely active CD (CDAI score of 220 to 400 points within seven days before enrollment and one of the following: a screening CRP level >2.87 mg/mL, a colonoscopy within past four months that documented ulcerations or a fecal calprotectin level >250 µg/g stool during screening with	N=416 10 weeks	Primary: Proportion of patients in clinical remission at week six Secondary: Proportions of patients in the overall and TNF antagonist failure populations in remission at week 10, proportions of patients in the overall and TNF antagonist failure populations with remission at both week 6 and 10	Primary: For the TNF antagonist failure population, there was no statistically significant difference in the proportion of patients in clinical remission at week six between the vedolizumab and placebo groups (15.2 vs 12.2%; P=0.433). Secondary: For the TNF antagonist failure population, a greater proportion of patients treated with vedolizumab were in clinical remission at week 10 (26.6 vs 12.1%; P=0.001; RR, 2.2; 95% CI, 1.3 to 3.6). Furthermore, a greater proportion of vedolizumab-treated patients also had a CDAI-100 response at week six (39.2 vs 22.3%; P=0.001; RR, 1.8; 95% CI, 1.2 to 2.5) and at week 10 (46.8 vs 24.8%; P<0.0001; RR, 1.9; 95% CI, 1.4 to 2.6). The between-group difference in remission rates at weeks 6 and 10 was no statistically significant (12.0 vs 8.3%; P=0.276; RR, 1.4; 95% CI, 0.7 to 2.8). For the overall population, a greater proportion of patients treated with vedolizumab were in clinical remission at week 6 (19.1 vs 12.1%; P=0.048; RR, 1.6; 95% CI, 1.0 to 2.5). Furthermore, a greater proportion of the overall population was in remission at week 10 with vedolizumab compared to placebo (28.7 vs 13.0%; P<0.0001; RR, 2.2; 95% CI, 1.4 to 3.3). The

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	features of active CD supported by small bowel imaging) with known involvement of the ileum and/or colon at ≥3 months prior to enrollment. All patients had experienced an inadequate response, loss of response or intolerance to TNF antagonists, immunosuppressives or corticosteroids within previous five years.		and the proportion of patients in the TNF antagonist failure population with a CDAI-100 response at week six	between-group difference in remission rates at weeks 6 and 10 was statistically significant (15.3 vs 8.2%; P=0.025; RR, 1.9; 95% CI, 1.1 to 3.2). In the overall population, a greater proportion of patients in the vedolizumab group achieved a CDAI-100 response at week six (39.2 vs 22.7%; P=0.0002; RR, 1.7; 95% CI, 1.5 to 2.6) and at week 10 (47.8 vs 24.2%; P<0.0001; RR, 2.0; 95% CI, 1.5 to 2.6).
Juvenile Idiopathic/Rheumatoid Arthritis				
Ruperto et al[62] Abatacept 10 mg/kg every 28 days vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 6 to 17 years of age with JIA with at least 5 active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=122 (RCT); 190 (OL lead in period) 6 months (4-month OL lead in)	Primary: Time to flare Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables, and assessment of safety and tolerability	Primary: In the placebo group, the median time to flare was six months; however, insufficient events occurred in the abatacept group to assess median time to flare (P=0.0002). Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to the abatacept group (53 vs 12%; P=0.0003). The HR for patients in the abatacept group to experience a flare compared to the placebo group was 0.31 (95% CI, 0.16 to 0.59). After six months or at the time of first flare, 82% of the abatacept group and 69% of the placebo group improved by ≥30% as measured by ACR (P=0.1712), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (P=0.0071), 53% of the abatacept group and 31% of the placebo group improved by ≥70% as measured by

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				ACR and 40% of the abatacept group and 16% of the placebo group improved by ≥90% as measured by ACR. In the abatacept group, 30% had inactive disease compared to 11% in the placebo group (P=0.0195). Adverse events were similar between the groups.
Lovell et al[63] Adalimumab 24 mg/m^2 (maximum of 40 mg) every other week with or without MTX vs placebo Patients were stratified according to MTX use and received OL adalimumab 24 mg/m^2 (maximum of 40 mg) every other week for 16 weeks. The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.	DB, MC, OL, RCT Patients 4 to 17 years of age with active JRA who had previously received treatment with NSAIDs	N=171 48 weeks	Primary: Rate of disease flare in patients not receiving MTX Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety	Primary: Among patients not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (P=0.03). In patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (P=0.02). Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63 vs 38% (P=0.03), 63 vs 35% (P=0.03), 63 vs 27% (P=0.002) and 42 vs 27% (P=0.17) in the adalimumab and placebo groups, respectively. In patients not receiving MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were reported in 57 vs 32% (P=0.06), 53 vs 32% (P=0.10), 47 vs 29% (P=0.16) and 30 vs 18% (P=0.28) in the adalimumab and placebo groups, respectively. The most frequently noted adverse events were mild to moderate in nature and included infections and injection site reactions. There were seven cases of serious infection reported with adalimumab use.
Lovell et al[64] Etanercept 0.4 mg/kg twice weekly vs placebo	DB, MC, OL, RCT Patients 4 to 17 years of age with active polyarticular JRA despite treatment with NSAIDs and MTX	N=69 7 months	Primary: Rate of disease flare Secondary: Median time to flare, safety	Primary: Seventy-four percent (51/69) of patients demonstrated improvement and were included in the DB part of the trial. The rate of disease flare was significantly higher in the placebo group compared to the etanercept group (81 vs 28%; P=0.003). Secondary: The median time to flare was reported as 116 days in the active treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received etanercept 0.4 mg/kg twice weekly for up to 3 months in the OL part of the study; the patients whose condition improved were then randomly assigned to either etanercept or placebo. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	≥10 mg/m^2/week			arm compared to 28 days with placebo (P<0.001). During the OL segment of the study the adverse events most often reported included injection-site reaction, upper respiratory tract infections, headache, rhinitis and gastrointestinal side effects. There were no differences noted between groups during the latter part of the study.
Lovell et al[65] Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly Intra-articular and soft-tissue injections of corticosteroids were permitted after 12 continuous weeks of etanercept. MTX could be added to treatment after one year. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or	Ongoing ES, MC, OL by Lovell et al[22] (updated efficacy and safety results from the study)	N=58 Median of 4 years	Primary: JRA 30% DOI Secondary: JRA 50% DOI, JRA 70% DOI, an articular severity score (0 to 926), assessment of pain (Likert scale, 0 to 10), CRP levels, safety	Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI. Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively. At four years, the median CRP level was lowered to 0.1 mg/dL from 3.4 mg/dL at baseline, the median articular severity score was decreased to 18 from 88 at baseline, and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline. Duration of morning stiffness was only assessed through one year and was reported as 5 minutes at month 12 (from 53 minutes at baseline). After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/ patient year.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
equivalent) were allowed.				
Horneff et al[66] Etanercept 0.4 mg/kg twice weekly Combination treatment with MTX or oral corticosteroids was permitted.	MC, OL Patients 4 to 17 years of age with active idiopathic juvenile arthritis despite treatment with MTX	N=322 Up to 48 months, median of 12 months	Primary: Change in indices of disease activity, 30, 50, and 70% improvement in idiopathic juvenile arthritis Secondary: Safety	Primary: At 12 months, the mean number of tender joints, swollen joints, and joints with limited range of movement were reduced to 1.7 (SD, 3.5), 2.6 (SD, 4.7), and 7.1 (SD, 8.9) from a baseline of 9.1 (SD, 9.5), 8.4 (SD, 9.0), and 11.8 (SD,11.8), respectively. The duration of morning stiffness was decreased to 7 (SD, 23) minutes from 45 (SD, 65) minutes and CHAQ scores (on a scale of 0=best to 3=worst) were decreased to 0.4 (SD, 0.6) from 1.0 (SD, 0.8). Patient's and PGA scores (on a scale of 0=best to 100=worst) were reduced to 16 (SD, 18) and 20 (SD, 23) from 56 (SD, 27) and 67 (SD, 25), respectively. At last report (30 months) a 30, 50, and 70% improvement was noted in approximately 60, 48, and 28% of patients remaining on etanercept, respectively. Significant improvements in all indices of disease activity were detected at all points of time (months one, three, six, 12, 18, 24, and 30; P<0.0001 with the exception of swollen joint count at 30 months; P<0.0005 and duration of morning stiffness; P<0.001). Secondary: There were 20 reports of infection or infection related events. Discontinuation of treatment was reported in 53 patients, of which 11 cases were secondary to adverse events.
De Benedetti et al[67] TENDER (abstract) Tocilizumab 8 mg/kg every 2 weeks for patients ≥30 kg or 12 mg/kg every 2 weeks for patients <30 kg vs placebo	PC, RCT Patients 2 to 17 years of age with active systemic JIA for ≥6 months with an inadequate response to NSAIDs and corticosteroids	N=112 12 weeks	Primary: Proportion of patients with JRA ACR 30 response plus absence of fever at week 12 Secondary: Not reported	Primary: At week 12, significantly greater proportion of patients treated with tocilizumab achieved JRA 30 response plus absence of fever (85%) compared to patients treated with placebo (24%; P<0.0001). Significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 50, JRA ACR 70, and JRA ACR 90 responses compared to patients in the placebo group (P<0.0001). Secondary: Not reported
Brunner et al[68] CHERISH (abstract)	DB, PC, RCT (OL lead in period)	N=166 24 weeks	Primary: Proportion of patients with JIA	Primary: Tocilizumab treated patients experienced significantly fewer JIA ACR 30 flare at week 40 compared to patients treated with placebo (25.6 vs 48.1%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tocilizumab 8 mg/kg every 4 weeks for patients ≥30 kg vs 8 mg/kg every 4 weeks for patients <30 kg vs 10 mg/kg every 4 weeks for patients <30 kg vs placebo	Patients 2 to 17 years of age with active polyarticular JIA for ≥6 months who failed MTX		ACR 30 flare relative to week 16 Secondary: Proportion of patients with JIA ACR 30, ACR 50, and ACR 70 responses	P<0.0024). Secondary: At week 40, significantly greater proportion of patients in the tocilizumab group achieved JRA ACR 30 (74.4 vs 54.3%; P=0.0084), JRA ACR 50 (73.2 vs 51.9%; P=0.0050), and JRA ACR 70 (64.6 vs 42.0%; P=0.0032) response compared to patients in the placebo group. The degree of improvement was lower for these endpoints in the tocilizumab 8 mg/kg (<30 kg body weight) group compared to the other two tocilizumab groups (10 mg/kg for patients weighing <30 kg and 8 mg/kg for patients weighing ≥30 kg).
Ruperto et al[69] Trial 1 Canakinumab 4 mg/kg (max 300 mg) for one dose Trial 2 canakinumab 4 mg/kg (max 300 mg) SC every four weeks and glucocorticoid dose tapered Both trials: prednisone 1	Trial 1: DB, PC, RCT Patients 2 to 19 years of age with a diagnosis of systemic juvenile idiopathic arthritis, including active systemic features and arthritis. Trial 2: OL followed by DB, PC, RCT Patients who had a fever response after	Trial 1: N=84 29 days Trial 2: N=177 12 to 32 weeks	Primary: Trial 1: Proportion of patients ACR 30 response at day 15. Trial 2: ACR 50 response, corticosteroid dose tapering and time to flare Secondary; Not reported	Primary: Trial 1: At day 15 of Trial 1, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR 30 response, which was sustained at day 29 (P<0.001). Trial 2: At the end of the open-label phase of Trial 2, after a median of 113 days and a median of four injections of canakinumab, 128 of 175 patients (73%) had at least an adapted JIA ACR 50 response, and 55 of 176 (31%) had inactive disease. A total of 100 of 177 patients (56%) underwent glucocorticoid tapering, had at least an adapted JIA ACR 30 response, and were eligible to undergo randomization in the withdrawal phase of Trial 2. In the withdrawal phase, the median time to flare was 236 days (95% CI, 141 to 449) in the placebo group; the median was not observable in the canakinumab group, since less than 50% of the patients had a flare

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/kg, stable NSAID doses and methotrexate ≤20 mg/m^2 per week were allowed.	three days in Trial 1 or who had a response at day 15 in Trial 1.			(P=0.003 by the log-rank test). A total of 39 patients in the canakinumab group (74%, according to the Kaplan–Meier estimate) had no flare, as compared with 24 in the placebo group (25%, according to the Kaplan–Meier estimate), with a significant relative risk reduction of 64% with regard to flare. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids. Secondary; Not reported.
Psoriasis				
Bagel et al[70] Etanercept 50 mg twice-weekly for 12 weeks followed by etanercept 50 mg weekly plus placebo weekly for 12 additional weeks (Group A) vs placebo twice-weekly for 12 weeks followed by etanercept 50 mg twice-weekly for 12 additional weeks (Group B) Patients discontinued the use of background therapies.	DB, MC, PC, RCT Patients ≥18 years of age with stable moderate-to-severe plaque psoriasis covering ≥10% of BSA for ≥6 months and PASI scores ≥10 and ≥30% of SSA affected, with PSSI scores ≥15	N=124 24 weeks	Primary: Percentage change in PSSI score at week 12 Secondary: Percentage change in the PSSI score at week 24 for Group B patients, the proportion of patients achieving PSSI 75 improvement at week 12, patient satisfaction with treatment at week 12, and safety	Primary: At week 12, Group A experienced a significantly greater mean improvement in PSSI score compared to Group B (86.8 vs 20.4%; P<0.001) with significant improvements as early as week four of treatment. Secondary: At week 24, both Group A and Group B experienced improvements in PSSI scores from baseline (90.6 vs 79.1%, respectively; P value not reported). A significantly greater proportion of patients in Group A compared to Group B experienced a PSSI 75 at week 12 (86 vs 11%; P<0.0001). Significantly more etanercept-treated patients were either satisfied or very satisfied at week 12 compared to placebo (P<0.0001). At week 24, after etanercept treatment, Group B patients' satisfaction increased significantly over their first 12 weeks on placebo (P<0.0001). More than two thirds of Group A patients continued to be satisfied or very satisfied at week 24. The rates of adverse events were comparable between groups, both at week 12 (etanercept vs placebo) and week 24 (etanercept 50 mg twice-weekly vs once-weekly). No serious adverse events were reported at week 12; however, by week 24, three patients had reported serious events. The most commonly reported adverse events were upper respiratory tract

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				infection, injection site reactions, headache, sinus congestion, cough, and ear infection.
Saurat et al[71] (CHAMPION) Adalimumab 80 mg at week 0, then 40 mg every other week from week 1 through week 15 vs MTX 7.5 mg at week 0, then increased to 10 mg weekly at week 2, then increase to 15 mg weekly at week 4; at week 8, patients not achieving PASI 50 had the dose of MTX increased to 15 mg weekly; at week 12, patients not achieving PASI 50 at week 12 and 8 had the dose of MTX increased to 25 mg weekly vs placebo	DB, DD, MC, RCT Patients ≥18 years of age with moderate to severe psoriasis (>10% of BSA and PASI ≥10), plaque psoriasis for >1 year, stable plaque psoriasis for >2 months, that are candidates for systemic therapy of phototherapy, with plaque psoriasis despite treatment with topical agents and treatment naïve to TNF-antagonists and MTX	N=271 16 weeks	Primary: Proportion of patients achieving PASI 75 at week 16 relative to baseline Secondary: Proportion of patients achieving PASI 50, PASI 90, PASI 100, and PGA	Primary: At 16 weeks, significantly more patients in the adalimumab group (79.6%) achieved PASI 75 compared to the MTX group (35.5%; RD, 43.7%; 95% CI, 30.8 to 56.7; P<0.001) and placebo group (18.9%; RD, 60.5%; 95% CI, 44.5 to 76.6; P<0.001). The difference in treatment groups was seen starting at two weeks for adalimumab vs MTX (P<0.05) and at four weeks for adalimumab vs placebo (P<0.001). Secondary: At week 16, PASI 100 was achieved in significantly more patients in the adalimumab group (16.7%) compared to the MTX group (7.3%; P<0.04) and the placebo group (1.9%; P<0.001).Significantly more patients achieved PASI 50, PASI 90 and a PGA of clear or minimal in the adalimumab group compared to the MTX and placebo groups (P<0.001 for all). Rates of reported infectious adverse events were not significantly different between the groups (P value not reported). Total adverse events and serious adverse events were similar.
Leonardi et al[72] (PHOENIX-1) Ustekinumab 45 mg vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of plaque psoriasis for ≥6	N=766 ≤76 weeks	Primary: Proportion of patients achieving PASI 75 at week 12 Secondary:	Primary: Significantly more patients in both the 45 and 90 mg ustekinumab groups achieved the primary endpoint of PASI 75 at week 12 than did those in the placebo group (difference in response rate, 63.9%; 95% CI, 57.8 to 70.1; P<0.0001 and 63.3%; 95% CI, 57.1 to 69.4; P<0.0001 for 45 and 90 mg vs placebo, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ustekinumab 90 mg vs placebo Each group received a subcutaneous injection at week 0, 4, and then every 12 weeks thereafter.	months, candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement		Not reported	The onset of efficacy was rapid, with higher proportions of ustekinumab-treated patients achieving at least 50% improvement from baseline in PASI 50 by week two (P=0.0008 for 45 mg and P=0.0005 for 90 mg vs placebo) and PASI 75 by week four (P<0.0001 for each comparison vs placebo). Maximum efficacy was observed at week 24 in the 45 and 90 mg groups (PASI 75 response, 76.1% in 45 mg group and 85.0% in 90 mg group). Among patients re-randomized at week 40, maintenance of PASI 75 was better in patients receiving maintenance therapy than in patients withdrawn from therapy through at least one year (P<0.0001), The median percentage improvement in PASI remained stable to at least week 76. Secondary: Not reported
Papp et al[73] (PHOENIX-2) Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received an injection at week 0, 4, and then every 12 weeks thereafter. Partial responders at week 28 were re-randomized to continue dosing every 12	DB, MC, PC, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	N=1,230 ≤52 weeks	Primary: Proportion of PASI 75 responders at week 12 Secondary: Proportion of patients with a physician's global assessment score of cleared or minimal at week 12, change in dermatology life quality index, the number of visits with PASI 75 response between weeks 40 and 52	Primary: Significantly more patients in both ustekinumab groups achieved PASI 75 at week 12 than did patients in the placebo group (difference in response rate, 63.1%; 95% CI, 58.2 to 68.0; P<0.0001 and 72.0%; 95% CI, 67.5 to 76.5; P<0.0001 for 45 and 90 mg vs placebo, respectively). Secondary: A greater proportion of patients in each ustekinumab group achieved a physician's global assessment of psoriasis of cleared or minimal at week 12 than did those in the placebo group (difference in response rate, 63.1%; 95% CI, 58.1 to 68.1; P<0.0001 for 45 mg vs placebo and 68.6%; 95% CI, 63.9 to 73.4; P<0.0001 for 90 mg vs placebo). Median changes in dermatology life quality index were greater in the ustekinumab groups than in the placebo group (mean of differences vs placebo, -8.0; 95% CI, -8.0 to -7.0; P<0.0001 for 45 mg and -9.0; 95% CI, -9.0 to -8.0; P<0.0001 for 90 mg vs placebo). A total of 22.7% of patients in the 45 mg group and 15.8% of patients in the 90 mg group were partial responders at week 28. Compared to patients responding to dosing every 12 weeks, partial responders tended to have

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks or escalate to dosing every 8 weeks.				higher bodyweight, more marked or severe disease as measured by physician's global assessment, and a higher incidence of PsA. Among the re-randomized partial responders, dosing intensification did not result in greater efficacy compared to continuing treatment every 12 weeks, as assessed by the number of visits between weeks 40 and 52 (four visits) at which patients achieved PASI 75 response (mean, 1.75 visits in the every eight week group and 1.56 in the every 12 week group; P=0.468). There was a lack of response to intensified dosing in the individuals receiving 45 mg, both in terms of number of visits at which patients achieved PASI 75 response (mean, 1.13 vs 1.54 visits; P=0.210), and in terms of PASI 75 rates over time. This is in contrast to patients receiving intensified 90 mg dosing, which resulted in a greater number of visits with PASI 75 response (mean, 2.63 vs 1.58 visits; P=0.014) and higher PASI 75 response rate (68.8% of patients with dosing every eight weeks vs 33.3% of patients with dosing every 12 weeks; difference in response rate, 35.4%; 95% CI, 12.7 to 58.1 at week 52 for dosing every eight weeks vs dosing every 12 weeks; P=0.004).
Griffiths et al[74] Etanercept 50 mg twice weekly vs ustekinumab 45 mg at weeks 0 and 4 vs ustekinumab 90 mg at weeks 0 and 4 Patients without a response to etanercept at	MC, PG, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA involvement, and	N=903 12 weeks	Primary: PASI 75 at week 12 Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group (73.8%) than in the etanercept group (56.8%; P=0.01 vs ustekinumab 45 mg; P<0.001 vs ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; P<0.001 for each comparison vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (P<0.001, for each comparison vs etanercept).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab			Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Schmitt et al[75] Adalimumab, cyclosporine, efalizumab*, etanercept, or infliximab vs placebo	MA RCTs in patients with moderate to severe psoriasis	16 trials Duration varied	Primary: PASI 75 Secondary: Tolerability	Primary: Compared to placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; P<0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; P<0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; P<0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48; P<0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35; P<0.00001) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; P<0.00001). Secondary: Average monthly rates of serious adverse events were 0.5% with adalimumab, 2.3% with cyclosporine, 1.2% with efalizumab, 0.6% with etanercept 50 mg twice weekly and 1.1% with infliximab. This outcome was not reported in with etanercept 25 mg twice weekly. Withdrawals due to adverse events occurred on average in 0.3% of adalimumab-treated patients, 16.1% of cyclosporine-treated patients, 1.2% of efalizumab-treated patients, 0.5% of patients on the lower dose of etanercept and 0.4% of patients on the higher dose of etanercept and 1.3% of infliximab-treated individuals/month.
Langley et al[76] ERASURE and FIXTURE ERASURE:	DB, DD, MC, PC, PG, RCT (FIXTURE also AC)	N=2,044 (ERASURE: 737 FIXTURE:	Primary: Proportion of patients that had a PASI75 and a	Primary: ERASURE A greater proportion of patients who received secukinumab 300 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
secukinumab 300 mg vs secukinumab 150 mg vs placebo FIXTURE: secukinumab 300 mg vs secukinumab 150 mg vs etanercept vs placebo All drugs were dosed once weekly at baseline and at weeks one, two and three, then every four weeks starting from week four.	Patients 18 years of age or older with moderate-to-severe plaque psoriasis for at least six months and poorly controlled with topical treatments, phototherapy, systemic therapy or a combination of those therapies, score ≥12 on the PASI scale, 3 or 4 on the modified investigator global assessment, and 10% or more involvement in body surface area	1,306) 52 weeks	score of 0 or 1 in the investigator's global assessment at week 12. Secondary: PASI90 at week 12, maintenance of PASI75 and a 0 or 1 response on the investigator's global assessment from week 12 to week 52, and PASI100 at week 12, , improvement in DLQI, improvement in pain/itching/ scaling	(200/245 [81.6%]) and secukinumab 150 mg (174/243 [71.6%]) had a PASI75 response at week 12 compared to placebo (11/246 [4.5%]; P<0.001 for both comparisons). Additionally, a greater proportion of patients who received secukinumab 300 mg (160/245 [65.3%]) and secukinumab 150 mg (125/244 [51.2%]) had a response of 0 or 1 on the modified investigator's global assessment at week 12 compared to placebo (6/246 [2.4%]; P<0.001 for both comparisons). FIXTURE The proportion of patients who had a PASI75 response at week 12 was 77.1% (249/323), 67.0% (219/327), 44.0% (142/323), and 4.9% (16/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who achieved PASI75 at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo). The proportion of patients who had a 0 or 1 response on the modified investigator's global assessment at week 12 was 62.5% (202/323), 51.1% (167/327), 27.2% (88/323), and 2.8% (9/324) for secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo respectively. Both secukinumab 300 mg and 150 mg had a statistically significant greater proportion of patient who had a 0 or 1 response on the modified investigator's global assessment at week 12 compared with etanercept and placebo (P<0.001 for each secukinumab dose when compared to either etanercept or placebo). Secondary: ERASURE A greater proportion of patients who received secukinumab 300 mg (145/245 [59.2%]) and secukinumab 150 mg (95/243 [39.1%]) had a PASI90 response at week 12 compared to placebo (3/246 [1.2%]; P<0.001

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				for both comparisons). PASI75 was maintained from week 12 to 52 for 80.5% (161/200) and 72.4% (126/174) of patients in the secukinumab 300 mg and 150 mg groups respectively. A 0 or 1 response on the modified investigator's global assessment was maintained from week 12 to 52 for 74.4% (119/160) and 59.2% (74/125) of patients in the secukinumab 300 mg and 150 mg groups respectively. PASI100 at week 12 was reached by 28.6%, 12.8% and 0.8% of patients in the secukinumab 300 mg, secukinumab 150 mg, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to placebo (P<0.001 for both comparisons). Patients in both secukinumab groups reported significant improvements in DLQI, itching, pain and scaling by week 12 compared to etanercept and placebo groups (P values not reported). FIXTURE A greater proportion of patients who received secukinumab 300 mg (175/323 [54.2%]) and secukinumab 150 mg (137/327 [41.9%]) had a PASI90 response at week 12 compared to placebo (5/324 [1.5%]; P<0.001 for both comparisons). Additionally both secukinumab groups had a significantly higher proportion of patients that achieved PASI90 at week 12 compared with the etanercept group (67/323 [20.7%]; P<0.001 for both comparisons). PASI75 was maintained from week 12 to 52 for 84.3% (210/249), 82.2% (180/219), and 72.5% (103/142) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained PASI75 from week 12 to 52 (P<0.001 and P=0.009 for the 300 mg and 150 mg dose respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A 0 or 1 response on the modified investigator's global assessment was maintained from week 12 to 52 for 79.7% (161/202), 67.7% (113/167), and 56.8% (50/88) of patients in the secukinumab 300 mg, secukinumab 150 mg, and etanercept groups respectively. When compared to etanercept, both secukinumab 300 mg and secukinumab 150 mg had a statistically significant greater proportion of patients that maintained 0 or 1 response on the modified investigator's global assessment from week 12 to 52 (P<0.001 and P=0.002 for the 300 mg and 150 mg dose respectively). PASI100 at week 12 was reached by 24.1%, 14.4%, 4.3% and 0% of patients in the secukinumab 300 mg, secukinumab 150 mg, etanercept, and placebo groups respectively. There was a statistically significant greater proportion of patients who achieved PASI100 in both the secukinumab groups compared to etanercept (P<0.001 for both comparisons). There was no comparison done with placebo as no patients achieved PASI100 at week 12. Patients in both secukinumab groups reported significant improvements in DLQI, itching, pain and scaling by week 12 compared to placebo groups (P values not reported).
Blauvelt et al[77] FEATURE Secukinumab 300 mg once weekly at baseline and at weeks one, two and three, then every four weeks starting from week four vs secukinumab 150 mg once weekly at baseline and at weeks one, two and	DB, MC, PC, PG, RCT Patients ≥ 18 years of age with a diagnosis of moderate-to-severe plaque psoriasis for ≥ 6 months disease (PASI score ≥ 12 at baseline, 2011 modified investigator's global assessment score ≥ 3, and body surface	N=177 12 weeks	Primary: Proportion of patients who achieved PASI75 at week 12 and an IGA mod 2011 score of 0 or 1 at week 12 Secondary: Usability of the prefilled syringe, PASI 75/90/100 and IGA mod 2011 0/1	Primary: Treatment with secukinumab 300 and 150 mg resulted in 75.9% and 69.5% of patients, respectively, achieving a PASI75 response at week 12. No patients in the placebo group achieved a PASI75 at week 12 (P<0.001 for all comparisons to placebo). Treatment with secukinumab 300 and 150 mg resulted in 69.0% and 52.5%, respectively, achieving an IGA mod 2011 0/1 response at week one2. No patients in the placebo group achieved an IGA mod 2011 0/1 response at week 12 (P<0.0001 for all comparisons to placebo). Secondary: PASI90 rates at week 12 were found to be 60.3% and 45.8% for secukinumab 300 and 150 mg respectively, compared with 0% for placebo (P<0.0001 for all comparisons to placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
three, then every four weeks starting from week four vs placebo	area involvement ≥ 10%); and disease inadequately controlled by topical treatments, phototherapy or previous systemic therapy		responses over time	A PASI100 response was achieved by 43·1% of patients treated with secukinumab 300 mg (P<0.0001 compared to placebo), by 8.5% treated with secukinumab 150 mg (P=0.057), and by 0% of placebo patients. For all PASI and IGA mod 2011 0/1 responses, higher response rates were seen with the 300-mg dose compared with the 150-mg dose through 12 weeks. Secukinumab exhibited a rapid onset of efficacy; a 50% decrease in mean PASI from baseline was achieved by week three with secukinumab 300 mg and by week four with 150 mg. For usability, SIAQ scores for all three domains common to the pre- and post- modules were high from baseline to week 12 in all groups. For the total cohort, the mean domain score (0 to10) on self-assessment of feelings about self-injection was 7.87 for the baseline pre- module and 8.70 for the week 12 post- module; on self-confidence, 7.09 and 8.23, respectively; on satisfaction with self-injection, 6.83 and 8.35, respectively. The scores for all patients on the domains exclusive to the post- modules assessing pain and reaction during and after injections (entire cohort, 9.56 to 9.68 out of 10 [with 10 indicating absence of pain/reaction]), ease of use (8.02 to 8.18 of 10) and self-image (9.03 to 9.09 of 10), were very high through 12 weeks in all treatment groups.
Paul et al[78] JUNCTURE Secukinumab 300 mg once weekly at baseline and at weeks one, two and three, then every four weeks starting from week four vs secukinumab 150 mg	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of moderate-to-severe plaque psoriasis for ≥ 6 months disease (PASI score ≥ 12 at baseline, 2011 modified investigator's global assessment score ≥	N=182 12 weeks	Primary: Proportion of patients who achieved PASI75 at week 12 achieved an IGA mod 2011 score of 0 or 1 at week 12 Secondary: Usability of the prefilled syringe, PASI 75/90/100	Primary: Treatment with secukinumab 300 and 150 mg resulted in 86.7% and 71.7% of patients, respectively, achieving a PASI75 response at week 12 with 3.3% of patients in the placebo group achieving a PASI75 at week 12 (P<0.001 for all comparisons to placebo). Treatment with secukinumab 300 and 150 mg resulted in 73.3% and 53.3%, respectively, achieving an IGA mod 2011 0/1 response, at week 12 with 0% of patients achieving an IGA mod 2011 0/1 score at week 12 (P<0.001 for all comparisons to placebo). Secondary: PASI90 response was achieved 55.0% of patients in the secukinumab 300

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once weekly at baseline and at weeks one, two and three, then every four weeks starting from week four vs placebo	3, and body surface area involvement ≥ 10%); and disease inadequately controlled by topical treatments, phototherapy or previous systemic therapy		and IGA mod 2011 0/1 responses over time	mg group, 40.0% in the secukinumab 150 mg group and 0% in the placebo group (P<0.0001 for all comparisons to placebo). Total skin clearance (PASI100 response) was greater with secukinumab treatment (300 mg, 26.7%; 150 mg, 16.7%) than placebo (0%) (No P value reported). Patient rating of autoinjector acceptability was assessed by the SIAQ. Subject-reported scores on the three domains common to the SIAQ pre- and post- modules (feeling about self-injections, self-confidence, satisfaction with self-injection) were high from the baseline pre- module to the week 12 post- module in all groups (no P values reported).
Psoriatic Arthritis				
Genovese et al[79] Adalimumab 40 mg every other week vs placebo Patients who completed a 12 week blinded phase could elect to receive OL therapy.	DB, MC, RCT Patients with moderately to severely active PsA with an inadequate response to DMARD therapy	N=100 24 weeks	Primary: ACR 20 response at week 12 Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic lesions, and quality of life	Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (P=0.012). Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25 and 14%, respectively) compared to patients on placebo at week 12 (2 and 0%, respectively; P=0.001 for ACR 50 and P=0.013 for ACR 70). A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (P=0.007). At week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; P≤0.001) and disability were statistically significantly improved with adalimumab. Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (P=0.027), bodily pain (P=0.007), general health (P=0.017) and mental health (P=0.009). OL adalimumab provided continued improvement for adalimumab patients

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				and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 and 57%, respectively, observed at week 24. Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%). Adalimumab use was not associated with serious infections.
Mease et al[80] Adalimumab 40 mg every other week vs placebo Stable doses of MTX were allowed and corticosteroid or DMARD rescue therapy was permitted in patients without at least a 20% reduction in swollen and tender joints by week 12.	DB, MC, PG, RCT Patients ≥18 years of age with moderately to severely active PsA with active psoriatic skin lesions or a documented history of psoriasis and a history of inadequate response to NSAIDs	N=315 24 weeks	Primary: ACR 20 response at 12 weeks, change in mTSS at week 24 Secondary: ACR 20 response at 24 weeks, ACR 50 and ACR 70 response at weeks 12 and 24, measures of joint disease, disability, quality of life, and severity of skin disease in patients with psoriasis involving at least 3% of BSA	Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared to 14% of the placebo-treated patients (P<0.001). The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (P<0.001). Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (P<0.001). An ACR 50 response was detected in 36% of adalimumab-treated individuals at 12 weeks and 39% of adalimumab-treated individuals at week 24 compared to 4 and 6% of those on placebo, respectively (P<0.001 for both outcomes). An ACR 70 response was found in 20% in the adalimumab arm and 1% in the placebo arm at 12 weeks and 23 and 1% at 24 weeks (P<0.001). PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26 and 23% on placebo, respectively (P value not reported). Among the 69 adalimumab treated patients evaluated with the PASI, 59% achieved a PASI 75 improvement response at 24 weeks, compared to 1% of placebo-treated patients (P<0.001). Disability and quality of life measures were also significantly improved with

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				adalimumab treatment compared to placebo treatment (P<0.001 for changes in both HAQ-DI and SF-36 PCS scores at weeks 12 and 24). Changes in SF-36 MCS scores were not statistically significant between groups at both week 12 (P=0.708) and week 24 (P=0.288). The rates of overall and serious adverse events were similar among groups.
Mease et al[81] and van der Heijde et al[82] (RAPID-PsA) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks (CZP 400 mg) vs placebo Concurrent MTX (up to 25 mg/week), SSZ (up to 3 g/day), leflunomide (up to 20 mg/day) at stable doses or oral corticosteroids (≤10 mg/day prednisone or equivalent) were allowed.	DB, MC, PC, RCT Patients ≥18 years of age with adult-onset active PsA for ≥6 months despite treatment with ≥1 DMARD	N=409 24 weeks	Primary: ACR 20 response at week 12, change from baseline in mTSS at week 24 Secondary: ACR 20 at week 24, HAQ-DI at week 24, PASI 75 (in patients with least 3% body surface area psoriatic skin involvement) at week 24, and change from baseline in mTSS at week 24	Primary: A greater proportion of patients treated with CZP 200 mg every two weeks (58.0%) and CZP 400 mg every four weeks (51.9%) achieved an ACR 20 response at week 12 compared to placebo (24.3%; P<0.001 for both comparisons). Secondary: A greater proportion of patients treated with CZP 200 mg every two weeks (63.8%) and CZP 400 mg every four weeks (56.3%) achieved an ACR 20 response at week 24 compared to placebo (23.5%; P<0.001 for both comparisons). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with CZP compared to placebo (combined CZP groups: -0.50 vs -0.19; P<0.001). In patients with least 3% body surface area psoriatic skin involvement at baseline, a greater proportion of patients treated with CZP 200 mg every two weeks (62.2%) and CZP 400 mg every four weeks (60.5%) achieved PASI 75 at week 24 compared to placebo (15.1%; P<0.001 for both comparisons). Prespecified imputation analysis led to an estimated mean mTSS change from baseline that was not statistically different between CZP and placebo groups (combined CZP groups: 18.3 vs 28.9; P≥0.05). Post hoc analysis using the median mTSS of the entire population to impute missing values in patients with fewer than two analyzable mTSS suggested that patients treated with CZP had reduced radiographic progression compared to placebo patients (combined CZP groups: 0.06 vs 0.28; P=0.007).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mease et al[83] Etanercept 25 mg twice weekly vs placebo Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.	DB, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=60 12 weeks	Primary: PsARC, PASI 75 at 12 weeks Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI 75, and improvement in target psoriasis lesions	Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared to 23% of placebo-controlled patients (P<0.0001). PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (P=0.0154). Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared to 13% of placebo-treated patients (P<0.0001), while approximately 48 and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (P=0.0001 for ACR 50; P value not reported for ACR 70). Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in PASI, compared to none of the placebo-treated patients (P=0.0154). Median target lesion improvements were 50 and 0%, for etanercept and placebo, respectively (P=0.0004). There were no significant differences detected in the rate of adverse events between groups.
Mease et al[84] Etanercept 25 mg twice weekly vs placebo Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week	DB, MC, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=205 72 weeks	Primary: ACR 20 response Secondary: ACR 50 response, ACR 70 response, change in mTSS, PsARC, PASI 75, SF-36 Health Survey, HAQ, and safety	Primary: At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared to 15% of placebo patients (P<0.0001), and results were sustained at 24 and 48 weeks. Secondary: At 24 weeks, ACR 50 and ACR 70 responses were achieved in approximately 40 and 15% of etanercept patients and 5 and 1% of placebo patients, respectively (P values not reported). The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
extension. Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.				A PsARC response was achieved by 72 and 70% of etanercept patients at weeks 12 and 24, respectively vs 31 and 23% of placebo patients (P values not reported). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared to 3% of placebo patients (P=0.001). SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups. HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; P<0.0001). Injection site reactions occurred at a greater rate with etanercept than placebo (36 vs 9%; P<0.001).
Kavanaugh et al[85] Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who had used or were currently using MTX, an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were	MC, PC, RCT Patients ≥18 years of age with a diagnosis of PsA and active PsA despite current or previous DMARD or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening	N=405 24 weeks	Primary: ACR 20 response at week 14 Secondary: Not reported	Primary: Golimumab 50 mg with or without MTX compared to placebo with or without MTX, resulted in a significant improvement in signs and symptoms as demonstrated by ACR 20 response at week 14 (51 vs 9%; P<0.001). Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
enrolled.				
Antoni et al[86] Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 vs placebo	DB, MC, PC, PG, RCT Patients ≥18 year of age with active PsA for ≥6 months, inadequate response to current or previous DMARDs or NSAIDs, ≥1 qualifying lesion and negative serum RF	N=200 24 weeks	Primary: ACR 20 response at week 14 Secondary: PsARC, PASI 75, duration of morning stiffness, dactylitis in hands and feet, and presence or absence of enthesopathy in the feet and SF-36	Primary: At week 14, there was significantly more patients in the infliximab group that achieved an ACR 20 response (58%) compared to the placebo group (11%; P<0.001). This difference continued through week 24 (54 vs 16%; P<0.001). Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to the placebo group (27%; P<0.001) at week 14 and continued through week 24 (70 vs 32%; P<0.001). At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18 and 12%) compared to the placebo group (30 and 34%; P=0.025 and P<0.001, respectively). Fewer patients in the infliximab group had enthesopathy compared to the placebo group at week 14 (22 vs 34%; P=0.016) and week 24 (20 vs 37%; P=0.002). A significantly higher proportion of patients achieved PASI 75 in the infliximab group compared to the placebo group at weeks 14 and 24 (64 vs 2%; P<0.001 and 60 vs 1%; P<0.001, respectively). At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to the placebo group (both P<0.001). There was also significant improvement at week 24 in the physical and mental components of the SF-36 in the infliximab group compared to the placebo group (P<0.001 and P=0.047, respectively). Adverse events were similar between the groups. There were a higher proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to the placebo group (4 vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to the placebo group (1 vs 6%).

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Baranauskaite et al[87] (RESPOND) Infliximab 5 mg/kg infusions at weeks 0, 2, 6 and 14 plus MTX 15 mg/week vs MTX 15 mg/week The use of NSAIDs and oral steroids (maximum dose 10 mg/day of prednisone or equivalent) was allowed if the dose was stable within four weeks before screening and kept stable throughout the study.	MC, OL, PC, PRO Patients ≥18 years of age who were treatment naïve and had active psoriasis in combination with peripheral articular disease with ≥1 of the following for three or more months before screening: distal interphalangeal joint involvement; polyarticular arthritis in the absence of rheumatoid nodules; arthritis mutilans; or asymmetric peripheral arthritis	N=115 16 weeks	Primary: Proportion of patients achieving an ACR 20 response at week 16 Secondary: Proportions of patients with ACR 50 and ACR 70 responses, PASI 75 in patients whose baseline PASI was 2.5 or greater, EULAR response, DAS28 scores, number of digits with dactylitis, Maastricht AS enthesitis score, fatigue scores, and duration of morning stiffness and safety	Primary: In the ITT analysis, an ACR 20 response at week 16 was achieved by significantly more patients treated with infliximab plus MTX compared to patients treated with MTX alone (86.3 vs 66.7%; P=0.021). Secondary: The ACR 50 (72.5 vs 39.6%; P=0.0009) and ACR 70 (49.0 vs 18.8%; P=0.0015) response rates at week 16 were also significantly higher in the infliximab plus MTX group at 16 weeks compared to those receiving MTX alone. In patients with a PASI ≥2.5 or at baseline, a PASI 75 response at week 16 occurred in 97.1% of patients receiving infliximab plus MTX compared to 54.3% of patients receiving MTX alone (P<0.0001). By week 16, the mean reduction in PASI score was 93.3% for patients treated with infliximab plus MTX compared to 67.4% of patients treated with MTX alone (P=0.0029). The mean DAS28 at week 16 improved by 56.5% in the infliximab plus MTX patients compared to 29.7% of patients receiving MTX alone (P<0.0001). The EULAR response at week 16 was achieved in 98% of patients receiving infliximab plus MTX compared to 72.9% of those receiving MTX alone (P<0.0001). A median reduction of two digits with dactylitis was observed at week 16 in the patients treated with infliximab plus MTX, while no reduction was observed in the MTX monotherapy group (P=0.0006). Patients treated with infliximab plus MTX experienced a median reduction of two sites with enthesitis at week 16 compared to a reduction of one site in the MTX alone group (P=0.082). A significantly greater reduction from baseline in fatigue scores occurred in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the infliximab plus MTX group compared to the MTX monotherapy group at week 16 (70.8 vs 44.0%, respectively; P=0.0003). At week 16, the median change in the duration of morning stiffness was -0.92 hour with combination treatment vs -0.50 hour with MTX alone (P=0.0015). The incidence of adverse events was higher in patients receiving infliximab plus MTX compared to MTX alone. Most adverse events were mild or moderate in severity. One adverse event in each group was considered severe: increased transaminases in the infliximab plus MTX group and renal colic in the MTX-alone group. Treatment related adverse events were reported in 45.6% of the infliximab plus MTX group and 24.1% in the MTX alone group. The most frequent treatment-related adverse event involved hepatic enzyme increases.
McInnes et al[88] (PSUMMIT 1) Ustekinumab 45 mg at weeks 0, 4, and every 12 weeks vs ustekinumab 90 mg at weeks 0, 4, and every 12 weeks vs placebo Patients receiving placebo were switched to ustekinumab 45 mg at week 16 (if they did not	DB, MC, PC, RCT Patients ≥18 years of age with active PsA for ≥6 months despite treatment with DMARDs for ≥3 months or NSAIDs for ≥4 weeks, or both, or with intolerance to these treatments	N=615 52 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50, ACR 70, HAQ-DI, and PASI 75 at week 24	Primary: A greater proportion of patients treated with ustekinumab 45 mg (42.4%) and ustekinumab 90 mg (49.5%) achieved an ACR 20 response at week 24 compared to placebo (22.8%; P<0.0001 for both comparisons). Secondary: A greater proportion of patients treated with ustekinumab 45 mg (24.9%) and ustekinumab 90 mg (27.9%) achieved an ACR 50 response at week 24 compared to placebo (8.7%; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (12.2%) and ustekinumab 90 mg (14.2%) achieved an ACR 70 response at week 24 compared to placebo (2.4%; P=0.0001 and P<0.0001, respectively). At week 24, improvements in HAQ-DI scores from baseline were greater in patients treated with ustekinumab 45 mg (median change -0.25) and ustekinumab 90 mg (median change -0.25) compared to placebo (median change 0; P<0.0001 for both comparisons). A greater proportion of patients treated with ustekinumab 45 mg (57.2%) and ustekinumab 90 mg (62.4%) achieved PASI 75 at week 24 compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
have an improvement of at least 5% in tender and swollen joints) or at week 24 (if they had an improvement at week 16). Patients receiving ustekinumab 45 mg were switched to ustekinumab 90 mg if they did not have an improvement of least 5% in tender and swollen joints at week 16. The use of a DMARD or an NSAID was allowed if the dose was stable for three months and four weeks before the start of the study, respectively.				to placebo (11.0%; P<0.0001 for both comparisons).
Rheumatoid Arthritis				
Westhovens et al[89] Abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every four weeks plus MTX 15 mg/weekly vs placebo plus MTX 15 mg/weekly	DB, MC, PC, RCT Patients ≥18 years of age with RA for ≤2 years and ≥12 tender and 10 swollen joints, CRP ≥0.45 mg/dL, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet; patients were either MTX-	N=509 24 months	Primary: Remission rates (DAS28 <2.6) and structural damage at year one (Genant-modified Sharp scoring system maximum score of 290) Secondary: ACR 50 responses, MCR (ACR 70 maintained for >6	Primary: A significantly higher proportion of patients in the abatacept group achieved DAS28-defined remission compared to the placebo group after one year of treatment (41.4 vs 23.3%, respectively; P<0.001). The mean change in structural damage at year one, measured using the Genant-modified Sharp scoring system total scores, was significantly lower in patients treated with abatacept compared to patients treated with placebo (0.63 vs 1.06, respectively; P=0.040). Secondary: A higher proportion of patients treated with abatacept achieved an ACR 50 (57.4 vs 42.3%; P<0.001), ACR 70 (42.6 vs 27.3%; P<0.001) and ACR 90 (16.4 vs 6.7%; P=0.001) compared to patients treated with placebo after one year of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	naive or had previous exposure of 10 mg/week or less for three weeks or less, with none administered		consecutive months); DAS28 scores, erosion score (maximum possible 145) and joint-space narrowing score (JSN; maximum possible 145), physical function (improvement of >0.3 units from baseline in the; HAQ-DI), SF-36 scores, proportion of patients achieving ACR 70 and ACR 90 responses, and the proportion of patients without radiographic progression and safety	After one year of abatacept therapy, 27.3% of patients achieved an MCR (ACR 70 maintained for more than six consecutive months) compared to 11.9% of patients receiving placebo alone (P<0.001). Following one year of abatacept treatment, disease activity was significantly reduced compared to patients receiving placebo (-3.22 vs -2.49; P<0.001). Patients treated with abatacept achieved significantly greater improvements from baseline in total score and erosion score compared to patients randomized to the placebo group (P=0.040 and P=0.033, respectively). The changes from baseline in JSN scores were similar between the abatacept and placebo groups (P=0.246). The proportion of patients with no radiographic progression in the abatacept group at one year was 61.2% (95% CI, 55.0 to 67.3) compared to the group receiving placebo 52.9% (95% CI, 46.6 to 59.2), with an estimated difference of 8.3% (95% CI, 21.0 to 17.5). A significantly greater proportion of patients in the abatacept group compared to the placebo group experienced a change from baseline in HAQ-DI score ≥0.3 units following one year of therapy (71.9 vs 62.1%; P=0.024). Abatacept treatment was associated with statistically significant improvements in the mental and physical components of the SF-36 questionnaire compared to the placebo group (P<0.05 for both). The most frequently reported adverse events in the abatacept group were nausea, upper respiratory tract infection and headache. Six deaths were reported; two (0.8%) in the abatacept group and four (1.6%) in the placebo Of the two deaths in the abatacept group, one patient had pneumonia and severe gastrointestinal bleeding and the other had an acute myocardial infarction.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most frequent infections in patients treated with abatacept and placebo respectively, were upper respiratory tract infection in 26 (10.2%) and 26 (10.3%) patients, nasopharyngitis in 21 (8.2%) and 26 (10.3%) patients and influenza in 19 (7.4%) and 23 (9.1%) patients. Serious infections occurred in five (2.0%) abatacept-treated patients (pneumonia, gastroenteritis, cellulitis, pseudomonal lung infection and postoperative wound infection, one patient each) and five (2.0%) patients receiving placebo (pneumonia, three patients; gastroenteritis, one patient; and breast cellulitis and staphylococcal infection, both in the same patient). No patients in the abatacept group discontinued due to an infection. In the abatacept treatment group, autoimmune disorders were reported in six patients compared to five patients in the placebo group. Sixteen patients in the abatacept treatment group experienced infusion related reaction compared to five patients receiving placebo.
Genovese et al[90] Abatacept subcutaneous 125 mg days 1 and 8 then weekly (intravenous loading dose of ~10 mg/kg was also administered on day 1) vs abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every 4 weeks	DB, DD, MC, RCT Patients with RA (defined by ACR 1987 criteria) and functional class I, II and III (defined by ACR 1991 revised criteria) that had an inadequate response to ≥3 months of MTX therapy (≥15 mg/week), with ≥10 swollen joints, ≥12 tender joints and CRP ≥0.8 mg/dL	N=1,457 6 months	Primary: Proportion of patients achieving ACR 20 at six months Secondary: Proportion of patients achieving ACR 50 and ACR 70	Primary: The proportion of patients achieving ACR 20 with abatacept subcutaneous (76.0%; 95% CI, 72.9 to 79.2) and abatacept intravenous (75.8%; 95% CI, 72.6 to 79.0) was not significantly different (estimated between group difference, 0.3%; 95% CI, -4.2 to 4.8). Secondary: The proportion of patients achieving ACR 50 with abatacept subcutaneous and abatacept intravenous (51.5 vs 50.3%) was not significantly different. The proportion of patients achieving ACR 70 with abatacept subcutaneous and abatacept intravenous (26.4 vs 25.1%) was not significantly different. Adverse events were also similar between the groups.
Keystone et al[91] (ATTUNE) Abatacept 125 mg	OL Patients ≥18 years of age with active	N=128 12 months	Primary: Safety at three months	Primary: Up to month three, adverse events occurred in 39.8% of patients; no individual adverse events were reported in ≥5% of patients. One adverse event (musculoskeletal pain) led to discontinuation. Overall, 75.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
subcutaneously once weekly	RA previously refractory to either MTX or anti-TNFs who had received ≥4 years of intravenous abatacept in either of two previous RCTs		Secondary: Immunogenicity at three months, and efficacy at 12 months	patients experienced an adverse event during the cumulative period. After month three, 12 further adverse events were reported, of which three led to discontinuation (breast cancer, sarcoidosis and brain neoplasm). No deaths were reported in the study or during follow-up. Infections reported up to month three (more than one patient) included nasopharyngitis (n=4), urinary tract infection (n=3), bronchitis (n=2), gastroenteritis (n=2), sinusitis (n=2) and upper respiratory tract infection (n=2). No serious infections, malignancies or autoimmune events were reported during the first three months. Serious infections, malignancies or autoimmune events occurring after month three were as follows: one serious infection (pneumonia)), two malignancies (breast and uterine cancer) and two autoimmune events occurred (sarcoidosis and erythema nodosum). Secondary: Eight patients were seropositive based on ELISA through month three. Of these eight, six were already positive prior to enrolment. All seropositive patients continued treatment. Adverse events experienced by the seropositive patients were not consistent with immune-mediated toxicities, except for one patient who developed sarcoidosis and discontinued treatment. None of these patients had an abatacept-induced seropositive result based on the ECL assay. At baseline, mean DAS28 and HAQ-DI scores in the overall population were 3.39 and 0.94, respectively. Improvements in disease activity and physical function achieved during intravenous treatment were maintained through month 12 of subcutaneous treatment.
Haraoui et al[92] (CanACT) Adalimumab 40 mg subcutaneously every other week	MC, OL, PRO Patients ≥18 years of age with RA diagnosed according to the 1987 revised ACR	N=879 12 weeks	Primary: Mean change in DAS28 Secondary: Proportion of patients	Primary: Patients treated with adalimumab achieved significantly lower DAS28 scores at week 12 compared to baseline (4.2 vs 6.1; P<0.001). Secondary: Following 12 weeks of treatment with adalimumab, 15.3 and 28.9% of patients achieved clinical remission (DAS28 <2.6) and low-disease activity

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	criteria with active disease, (≥5 swollen joints (of 66 joints evaluated) and one of the following: positive RF, ≥1 joint erosions present on x-ray, or a HAQ-DI score ≥1 and an unsatisfactory responses or intolerance to prior antirheumatic therapies		achieving clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2) at week 12, proportion achieving EULAR-moderate and good response, ACR 20, ACR 50, and ACR 70) responses at weeks four, eight, and 12, mean changes in ACR core components [tender joint count, swollen joint count, ESR, physician and patient assessments, and HAQ-DI	(DAS28 <3.2), respectively (P values not reported). At week 12, 25.9% of patients treated with adalimumab were considered EULAR responders to treatment. The proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response at 12 weeks was 58.4, 30.6 and 12.7%, respectively (P values not reported). At week eight, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response was 52.2, 21.7 and 7.2%, respectively (P values not reported). At week four, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response, was 37.6, 10.6 and 2.4%, respectively (P values not reported). Patients treated with adalimumab experienced a decrease in the number of tender joints at week 12 compared to baseline (6.8 vs 19.9; P value not reported) and the number of swollen joints was reduced from 13.2 at baseline to 6.4 after 12 weeks (P value not reported). As measured on a VAS, patient's assessment of pain decreased from a 66.2 at baseline to 37.3 following adalimumab therapy. Patients' assessment of disease activity decreased from 65.1 at baseline to 37.4 at follow up. Similarly physician assessment of disease activity decreased from 63.6 at baseline to 29.0 (P values not reported). The mean HAQ-DI score improved by an average of 0.5 units from 1.5 at baseline to 1.0 after 12 weeks of adalimumab treatment. In addition, the ESR decreased from a mean of 30.3 mm/h at baseline to 20.0 mm/h at 12 weeks (P<0.001). Adverse events were reported in 43.4% of patients treated with adalimumab. Most adverse events were mild to moderate in intensity. The most commonly reported adverse events were injection site reactions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(9.9%), headache (5.2%), injection site erythema (3.5%), nausea (3%) and rash (2.8%). Of the treatment-emergent adverse events considered by the investigator to be related to study drug, injection site reaction and headache were the most frequently reported (≥5% of patients).
Keystone et al[93] Adalimumab 40 mg subcutaneous injection every other week vs placebo All patients received concurrent MTX therapy.	ES, OL Patients ≥18 years of age with RA (defined by ACR 1987 criteria) despite ≥3 months of MTX (12.5 to 25 mg/week), tender joint count ≥9 out of 68, swollen joint count ≥6 out of 66, CRP ≥1 mg/L, and positive for RF or at least one bony erosion	N=202 10 years	Primary: ACR 20, ACR 50, ACR 70, DAS28-CRP <3.2, clinical remission (DAS 28-CRP <2.6 or SDAI ≤3.3), SDAI, HAQ-DI score, and mTSS at 10 years Secondary: Not reported	Primary: At year 10, 64.2, 49.0, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively. Mean DAS28-CRP was 2.6, with 74.1% achieving DAS28-CRP <3.2 at year 10. The proportions of patients achieving DAS28-CRP and SDAI clinical remission states were 59.0 and 33.2%, respectively. From baseline to year 10, mean HAQ-DI was reduced by 50%, with 42.2% of patients achieving HAQ-DI <0.5 or normal functionality. Mean change from baseline to year 10 in mTSS was 2.8 units (annual progression rate of approximately 0.3 units/year), suggesting minimal radiographic progression over 10 years. Secondary: Not reported
Keystone et al[94] (RAPID 1) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria), for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=982 52 weeks	Primary: ACR 20 at 24 weeks, mean change from baseline in mTSS at 52 weeks Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI, ACR 20 at 52	Primary: A significantly greater number of ACR 20 responders at 24 weeks were found in the CZP 200 mg group (58.8%) and CZP 400 mg group (60.8%) compared to the placebo group (13.6%; P<0.001). There was no significant difference detected between the two CZP regimens. mTSS were significantly lower with CZP 200 mg (0.4 Sharp units) and 400 mg (0.2 Sharp units) vs placebo (2.8 Sharp units; P<0.001). Secondary: Active treatment was associated with reduced mTSS at 24 weeks compared to placebo (0.2 Sharp units for 200 and 400 mg vs 1.3 Sharp units for placebo; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.			weeks, ACR 50, and ACR 70 at 24 weeks	The HAQ-DI score at 52 weeks was -0.60 with CZP 200 mg, -0.63 with CZP 400 mg and -0.18 with placebo (P<0.001). ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (P<0.001 vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1 and 21.4%) and CZP 400 mg (39.9 and 20.6%) compared to placebo (7.6 and 3.0%; P<0.001) at week 24. Infections and infestations occurred in 56.4% of CZP 200 mg patients, 58.4% of CZP 400 mg patients and 56.9% of placebo patients with serious infections occurring in 5.3, 7.3 and 2.2% of CZP 200 mg, 400 mg and placebo patients, respectively. The most frequent adverse events reported included headache, hypertension and back pain.
Smolen et al[95] (RAPID 2) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria) for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=619 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, mTSS, SF-36 Health Survey and individual ACR core set variables, and safety	Primary: ACR 20 was attained by significantly more individuals receiving CZP 200 mg (57.3%) and CZP 400 mg (57.6%) compared to placebo (8.7%; P≤0.001). Secondary: ACR 50 and ACR 70 were achieved in a significantly greater number of patients in the CZP 200 mg group (32.5 and 15.9%, respectively) and CZP 400 mg group (33.1 and 10.6%, respectively) vs placebo (3.1 and 0.8%, respectively; P≤0.01). CZP 200 mg (0.2; 95% CI, -1.0 to 0.6) and CZP 400 mg (-0.4 mg; 95% CI, -0.7 to -0.1) were associated with a significantly lower change in mTSS than placebo (1.2; 95% CI, 0.5 to 2.0; P≤0.01 compared to CZP 200 mg; P≤0.001 compared to CZP 400 mg). Active treatment resulted in greater improvements in SF-36 scores vs placebo (P<0.001) and ACR core components vs placebo (P<0.001). Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of CZP 400 mg patients and 0% of placebo patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				Tuberculosis was reported in five patients receiving certolizumab.
Fleischmann et al[96] (FAST4WARD) Certolizumab 400 mg every 4 weeks vs placebo Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	DB, MC, RCT Patients 18 to 75 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥6 months, with active disease and failed at least one prior DMARD	N=220 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, and safety	Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; P<0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (22.7 vs 3.7%; P<0.001 and 5.5 vs 0%; P≤0.05, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; P<0.001). Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (P<0.001), arthritis pain (P≤0.05) and fatigue (P<0.001). Headache, nasopharyngitis, upper respiratory tract infections, diarrhea and sinusitis occurred in at least 5% of certolizumab patients. There were no reports of tuberculosis or opportunistic infections throughout the study.
Weinblatt et al[97] (REALISTIC) Certolizumab 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks vs	DB, MC, RCT Patients ≥18 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥3 months, with active	N=1063 12 weeks	Primary: ACR 20 at 12 weeks Secondary: ACR 50, ACR 70, DAS 28, and ACR component	Primary: ACR 20 achievement at 12 weeks was significantly higher with certolizumab (51.1%) than placebo (25.9%; P < 0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (26.6 vs 9.9%; P<0.001 and 13.0 vs 2.8%; P<0.001, respectively). A significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	disease and failed at least one prior DMARD		scores	improvement in all ACR components was also detected among patients on certolizumab vs placebo (P≤0.05). At 12 weeks, 81.1% of patients on certolizumab achieved a DAS28 improvement of at least 1.2 vs 56.5% with placebo (P<0.001). The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches. Injection and infusion-site reactions occurred in 5.8% of certolizumab patients and 1.0% placebo patients.
Tanaka et al[98] (GO-FORTH) Golimumab 50 mg once every four weeks and MTX (Group 3) vs golimumab 100 mg once every four weeks and MTX (Group 2) vs placebo and MTX (Group 1)	DB, MC, PC, RCT Patients 20 to 75 years of age with RA (diagnosed with ACR 1987criteria) with RA for ≥3 months and were receiving 6 to 8 mg/week oral MTX for RA for ≥3 months before study and active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/ baseline) and ≥2 of the following criteria at screening/ baseline: CRP >1.5 mg/dL, ESR by the Westergren method of >28 mm/hour, morning stiffness lasting ≥30 minute, radiographic evidence of bone	N=269 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: Proportion of patients achieving an ACR 50 and ACR 70 response, ACR-N Index of Improvement, DAS28(ESR) response DAS28(ESR) remission (score <2.6), HAQ-DI, and safety	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab 50 and 100 mg groups compared to the placebo group (74.7 and 72.1 vs 27.3%; P<0.0001). Secondary: Similarly, more patients in the golimumab 50 and 100 mg groups achieved an ACR 50 compared to the placebo group (43.0 and 37.9 vs 9.1%; P≤0.005). More patients receiving golimumab 50 or 100 mg achieved an ACR 70 compared to patients receiving placebo (22.1 and 13.8 vs 2.3%; P≤0.005). The ACR-N index of improvement was significantly higher in patients receiving golimumab 50 mg (30%) and golimumab 100 mg (25.85%) compared to placebo (20.00; P<0.001 for both). Significantly more patients in the golimumab 50 mg and 100 mg treatment groups achieved DAS28(ESR) scores for response to treatment compared to placebo (79.5 and 85.5 vs 37.6%; P<0.0001). A higher proportion of patients receiving golimumab 50 mg or 100 mg achieved DAS28(ESR) for remission compared to placebo at 14 weeks (31.4 and 18.4 vs 3.4%; P<0.0001). Patients randomized to golimumab 100 mg and 50 mg treatment groups experienced statistically significant improvements in HAQ-DI scores

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	erosion, or anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive			compared to placebo at 14 weeks (0.32 and 0.39 vs 0.07; P<0.0001). By week 16, 72.7, 75.6 and 78.2% of patients receiving placebo, golimumab 100 mg and 50 mg, respectively, had adverse events. Infections were the most common adverse event in the placebo (39.8%), golimumab 100 mg (38.4%) and golimumab 50 mg (33.3%) treatment groups at week 24. Serious adverse events were relatively uncommon through week 16, occurring in one patient (1.1%) in receiving placebo (intervertebral disc protrusion), one patient (1.2%) in the golimumab 100 mg group (ileus) and two patients receiving golimumab 50 mg (2.3%). By week 24, 11 (5.5%) of the 201 patients treated with golimumab 50 mg or 100 mg had discontinued golimumab due to the following adverse events: infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).
Emery et al[99] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	DB, PC, RCT MTX naïve patients ≥18 years of age with a diagnosis of active RA for ≥3 months and not previously treated with a TNF-blocker	N=637 24 weeks	Primary: ACR 50 response at week 24 Secondary: ACR 20, 70, 90 responses at week 24	Primary: The golimumab monotherapy group was not statistically different from the MTX monotherapy group in ACR response (P=0.053). However, post-hoc modified intent-to-treat analysis (excluding three untreated patients) of the ACR 50 response showed statistically significant difference between the two groups (P=0.049). Secondary: The combined golimumab and MTX groups had greater proportion of patients achieve an ACR 20 response at week 24 compared to placebo and MTX groups (P=0.028 for both groups). ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Keystone et al[100] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated with a TNF-blocker	N=444 24 weeks	Primary: ACR 20 response at week 14, change from baseline in HAQ at week 24 Secondary: ACR 50, 70, 90 responses and ACR-N EULAR response, remission according to DAS 28, and sustained remission (DAS 28 remission at week 14 and maintained through week 24)	Primary: At week 14, an ACR 20 response was achieved by 33.1% of placebo and MTX-treated patients, 44.4% of golimumab 100 mg and placebo-treated patients (P=0.059), 55.1% of golimumab 50 mg and MTX-treated patients (P=0.001), and 56.2% of golimumab 100 mg and MTX-treated patients (P<0.001). At week 24, the median improvements from baseline in the HAQ-DI scores were -0.13 (P=0.240), -0.38 (P=0.001), and -0.50 (P<0.001), respectively. Secondary: ACR 50 and ACR-N response was significant for all the groups except placebo and MTX; ACR 70 was significant for all the groups except the placebo and MTX and golimumab and placebo groups; ACR 90 was not significant for any of the groups. Greater proportion of patients in the golimumab and MTX groups achieved significant EULAR response. At week 24, clinical remission was achieved by 6.0% of placebo and MTX-treated patients, 12.0% (P=0.087) of golimumab 100 mg and placebo-treated patients, 20.2% (P=0.001) of golimumab 50 mg and MTX-treated patients, and 22.5% (P<0.001) of golimumab 100 mg and MTX-treated patients, respectively. Sustained remission was achieved by 0.8%, 6.3% (P=0.018), 10.2% (P=0.001), and 11.9% (P<0.001), respectively.
Smolen et al[101] (GO-AFTER) Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response at week 14, DAS 28 response at week 14, ACR 20 response at week 24, and improvement from	Primary: Golimumab 50 and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3 and 37.9 vs 18.1%, respectively; P<0.001). ACR 20 responders at week 14 among patients who discontinued previous TNF-blocker therapy due to lack of efficacy included 35.7 and 42.7% of patients in the golimumab 50 and 100 mg groups, respectively, compared to 17.7% of patients in the placebo group (P=0.006, golimumab 50 mg vs placebo; P<0.001, golimumab 100 mg vs placebo). Secondary: ACR 50 response at week 14 was significant for the golimumab-treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.			baseline in HAQ scores at week 24	groups compared to the placebo group. DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2 and 59.5 vs 30.3%, respectively; P<0.001). ACR 20 response at week 24 was significant for the golimumab-treated groups compared to the placebo group. At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.
Smolen et al[102] (GO-AFTER Extension) Golimumab 50 mg once every 4 weeks (Group 1) vs golimumab 50 mg once every 4 weeks. Dose could be increased to 100 mg if <20% improvement in both tender and swollen joint counts at week 16 of the original study occurred. (Group 2) vs golimumab 100 mg once every 4 weeks (Group 3)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=459 160 weeks	Primary: ACR 20 Secondary: ACR 50/70,DAS 28, SDAI, and HAQ score	Primary: At week 160, 62.7, 66.7 and 56.8% of patients achieved ACR20 response and 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Secondary: At week 160, 17.3, 14.8 and 23.5% of patients achieved ACR70 response Groups 1, 2 and 3, respectively. DAS 28 response for groups 1, 2 and 3, response was 71.8, 83.8 and 71.4%, respectively. Remission as measured by DAS 28 for groups 1, 2 and 3, response was 16.9, 12.5 and 21.5%, respectively. SDAI remission for groups 1, 2 and 3, response was 11.4, 8.8 and 23.1%, respectively. SDAI scores for low disease activity (3.3 to 11) for groups 1, 2 and 3, response was 34.3, 28.8 and 25.6%, respectively. At week 160, 59, 65 and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively.
Weinblatt et al[103] (GO-FURTHER) golimumab 2 mg/kg, at weeks 0 and 4 and every	DB, MC, PC, RCT Adult patients with RA for ≥3 months and were receiving	N=592 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab group compared to the placebo group (58.5 and 24.9%: P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
8 weeks plus MTX vs placebo and MTX	15 to 25 mg/week oral MTX for RA for ≥4 weeks before study and active RA (≥6/66 swollen joints and ≥6/68 tender joints at screening/ baseline) and CRP >1.0 mg/dL, anti- cyclic citrullinated peptide antibody-positive and/or rheumatoid factor-positive		Secondary: DAS28 and HAQ-DI week 14, ACR 50 at week 24, and safety	Secondary: Significantly more patients in the golimumab treatment groups achieved DAS28 scores for moderate-good response to treatment compared to placebo at 14 weeks (81.3 vs 40.1%; P<0.001). Patients randomized to golimumab treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.5 vs 0.19; P<0.001). Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; P≤0.001) at 24 weeks. Adverse events reported at rates ≥1.0% higher in the golimumab group vs placebo were observed for infections and infestations (24.3 vs 20.8%); nervous system disorders (6.8% vs 4.1%); gastrointestinal disorders (6.6 vs 5.6%); skin and subcutaneous tissue disorders (6.6% vs 3.6%); respiratory, thoracic and mediastinal disorders (4.8 vs 2.5%); vascular disorders (3.8 vs 2.5%); and metabolism and nutrition disorders (2.3 vs 0.0%).
Jones et al[104] (AMBITION) Tocilizumab 8 mg/kg every 4 weeks vs MTX 7.5 to 20 mg every week or	DB, DD, PG, RCT Patients ≥18 years of age, with moderate to severe RA for ≥3 months, oral glucocorticoids (up to 10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dose	N=673 24 weeks	Primary: Proportion of patients achieving ACR 20 response at week 24 Secondary: Proportion of patients with ACR 50/70 responses at	Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (P<0.001). Compared to the placebo arm, a larger proportion of patients treated with tocilizumab also achieved an ACR 20 response at week eight (55.6 vs 13.1%; 95% CI, 0.34 to 0.52). Secondary: The proportion of patients achieving ACR 50 (44.0%) and ACR 70 (28.0%) at week 24 was also statistically significant for tocilizumab as compared to MTX (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on	was stable for ≥6 weeks		week 24 and the time to onset of ACR 20/50/70 responses, changes from baseline at week 24 in 28-joint count DAS 28, the proportion of patients in clinical remission (DAS 28 <2.6), with low disease activity (DAS 28 ≤3.2) and with good/ moderate responses at week 24, improvement in physical function was assessed by change from baseline at week 24 in HAQ-DI, and adverse events	Improvements in DAS 28 at week 24 were greater in the tocilizumab group than in the MTX group. Additionally, the proportion of patients in remission at week 24 was higher with tocilizumab (P<0.001). By week 24, tocilizumab patients were five times more likely to achieve DAS 28 remission and four times more likely to achieve at least a moderate response (OR vs MTX, 4.24; 95% CI, 2.92 to 6.14). A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX. There was no statistically significant difference with regard to the number of adverse events experienced in the tocilizumab group compared to the MTX group (79.9 vs 77.5%; P=0.484). Infection rates/patient year were also found to be similar (1.06 vs 1.09). However, skin and subcutaneous infections were reported more frequently in the tocilizumab group (4.1 vs 1.4%; P value not reported).
Smolen et al[105] (OPTION) Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs tocilizumab 4 mg/kg every	DB, PC, PG, RCT Patients ≥18 years of age, with moderate to severe RA >6 months duration, who had an inadequate response to MTX; all other DMARDs were	N=622 24 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50/70, DAS 28, and EULAR responses at week 24,	Primary: At week 24, significantly greater proportion of patients receiving tocilizumab 4 and 8 mg/kg had an ACR 20 response than patients who received placebo (59 and 48 vs 26%, respectively; P<0.0001 for both). Secondary: Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups achieved ACR 50 (31 and 44 vs 11%, respectively; P<0.0001) and ACR 70 at week 24 (12 and 22 vs 2%, respectively; P<0.0001) compared to patients in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
4 weeks plus MTX (stable, 10 to 25 mg weekly) vs placebo every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	discontinued before the start of the study, oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if doses were stable for six weeks or more		difference in HAQ-DI, SF-36, and FACIT-F, scores from baseline, and adverse events	Significantly greater proportion of patients in tocilizumab 4 and 8 mg/kg groups had reduced disease activity as measured by a DAS 28 score <2.6 (13.0 and 27.0 vs 0.8%, respectively; P<0.0002 for 4 mg/kg and P<0.0001 for 8 mg/kg groups) compared to the placebo group. EULAR response was also found to be significantly decreased in both tocilizumab 4 and 8 mg/kg groups (21 and 38 vs 3%, respectively; P<0.0001 for both) compared to the placebo group. Greater improvements in physical function were seen in both tocilizumab 4 and 8 mg/kg groups as assessed by the HAQ-DI score (-0.52 and -0.55 vs -0.34, respectively; P<0.0296 for 4 mg/kg and P<0.0082 for 8 mg/kg). Significant differences were seen with regard to changes in the SF-36 physical score in both tocilizumab 4 and 8 mg/kg groups (9.7 and 9.5 vs 5.0, respectively; P<0.0001 for both) and in the SF-36 mental score (5.7 and 7.3 vs 2.7, respectively; P<0.0394 for 4 mg/kg and P<0.0012 for 8 mg/kg). The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab 4 and 8 mg/kg groups (7.3 and 8.6 vs 4.0, respectively; P<0.0063 for 4 mg/kg and P<0.0001 for 8 mg/kg). Greater proportions of patients in the tocilizumab 4 and 8 mg/kg groups reported experiencing at least one adverse event compared to the placebo group (71 and 69 vs 63%, respectively). The rate of all infections/100 patient years was 98.7 in the tocilizumab 4 mg/kg group, 101.9 in the 8 mg/kg group, and 96.1 in the placebo group.
Genovese et al[106] (TOWARD) Tocilizumab 8 mg/kg plus DMARD every 4 weeks vs	DB, MC, PC, RCT Patients ≥18 years of age, with moderate to severe RA, who received stable doses of	N=1,220 24 weeks	Primary: ACR 20 responses at week 24 Secondary: ACR 50/70	Primary: At week 24, the proportion of patients in the tocilizumab group that were ACR 20 responders was significantly higher than in the control group (61 vs 25%; P<0.0001). No obvious differences were seen in ACR 20 response with regard to patients who received two or more DMARDs. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo plus DMARD every 4 weeks	permitted DMARDs (MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and leflunomide) for ≥8 weeks prior to study entry and oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs or COX2 inhibitors if the doses were stable for ≥6 weeks		responses at week 24, number of swollen and tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events	At week 24, significantly more patients in the tocilizumab group achieved ACR 50 and ACR 70 responses when compared to the placebo group (ACR 50, 30 vs 9%; ACR 70, 21 vs 3%; P<0.0001 for both). Compared to baseline, a significant decrease was seen in the number of swollen and tender joints in patients receiving tocilizumab when compared to the placebo group (swollen joint count, -10.3 vs -4.9; tender joint count, -15.7 vs -8.5; P<0.0001). Mean DAS 28 improved incrementally over time with greater changes in the tocilizumab group seen by week 24 (-3.17 and -1.16, respectively; P<0.0001). Remission rates at week 24 were also higher in the tocilizumab group when compared to the placebo group (30 vs 3%; P<0.0001). By week 24, 80% of patients in the tocilizumab group and 38% of patients in the placebo group achieved a good or moderate EULAR response (P<0.0001). At week 24, 60% of patients in the tocilizumab group had a clinically meaningful improvement in physical function as compared to 34% with placebo (change from baseline in HAQ ≥0.3). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to the placebo group for the disability index of the HAQ (-0.5 vs -0.2; P<0.0001) and FACIT-F scores (8.0 vs 3.6; P<0.0001). Mean improvements from baseline in SF-36 scores were higher for both physical and mental components at week 24 in the tocilizumab group (8.9 vs 4.1 and 5.3 vs 2.3, respectively; P<0.0001 for both). The occurrence of adverse events was found to be higher with tocilizumab (73 vs 61%). The most frequently occurring adverse events in both groups were infections and infestations (37.4 vs 31.6%), gastrointestinal disorders (20.8 vs 14.7%), and musculoskeletal and connective tissue disorders (13.0 vs 17.9%). Infections with a higher incidence in the tocilizumab group were upper respiratory infections (9 vs 7%), other respiratory infections (12 vs 10%), and skin and subcutaneous tissue infections (5 vs 3%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kremer et al[107] (LITHE) Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for four weeks Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry.	DB, MC, PC, PG, RCT Patients with RA, as determined by ACR criteria that was moderate to severe and lasted for ≥6 months; inadequate response to MTX therapy, defined as a swollen joint count of ≥6, a tender joint count of ≥8, and either CRP level ≥1 mg/dl or an ESR ≥28 mm/hour; and had ≥1 radiographically confirmed joint erosion despite having received MTX for ≥12 weeks before baseline	N=1,196 12 months	Primary: Change from baseline in the total Genant-modified Sharp score and change in HAQ-DI Secondary: Change from baseline in erosion and JSN scores (at week 24 and 52), total Genant-modified Sharp score at week 24, proportions of patients with no progression of total, erosion, or JSN scores, ACR 20, ACR 50, and ACR 70, change in DAS 28, and proportions of patients with low levels of disease activity (DAS28 ≤3.2) and DAS remission (DAS28 <2.6).	Primary: The proportion of patients without radiographic progression (change in total Genant-modified Sharp score ≤0 from baseline to week 52) was significantly higher in patients treated with tocilizumab 8 or 4 mg/kg (84 and 81 vs 67%; P<0.0001). The AUC of the change in the HAQ-DI score from baseline to week 52 demonstrated a significantly greater decrease in the 8 and 4 mg/kg tocilizumab groups compared to the placebo group (-144.1 and -128.4 vs -58.1 units; P<0.0001 for both comparisons). Secondary: At week 52, the ACR 20, ACR 50, and ACR 70 response rates were higher in patients treated with tocilizumab compared to placebo; however the difference was only statistically significant for the 8 mg/kg group compared to the placebo group (P<0.0001 for all response rate comparisons). The DAS28 scores were reduced over 52 weeks in all treatment groups, with mean improvements of -3.8, -3.0, and -2.0 in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively; however, the difference was only significant with the 8 mg/kg dose compared to placebo (P<0.0001). At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the DAS28 score (<2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; P<0.0001). DAS28 remission rates continued to improve between weeks 24 and 52, with the highest proportion of patients in remission in the tocilizumab 8 mg/kg treatment group. The progression of structural damage from baseline to week 52 was reduced by 74 and 70% with tocilizumab 8 and 4 mg/kg, respectively, compared to patients treated with placebo (P<0.0001). The total Genant-modified Sharp score at week 52 showed a decreased frequency and severity of disease progression with tocilizumab therapy.
Yazici et al[108]	DB, MC, PC, RCT	N=619	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(ROSE) Tocilizumab 8 mg/kg plus DMARD every four weeks vs placebo plus DMARD every four weeks Permitted DMARD (at stable doses ≥7 weeks before study) included MTX, chloroquine, hydroxychloroquine, parenteral gold, SSZ, azathioprine and leflunomide. Doses were required to remain stable throughout the study; however, dose reductions were allowed as clinically warranted for safety reasons.	Patients ≥18 years of age with active RA for ≥6 months and an inadequate clinical response to DMARD in addition to ≥6 swollen joints and ≥6 tender joints at screening and baseline, with either a CRP ≥95.24 nmol/l or an ESR ≥28 mm/h or greater at screening	24 weeks	ACR 50 response at week 24 Secondary: ACR 20, ACR 50, ACR 70, EULAR response, DAS28, clinically meaningful improvement (change from baseline in DAS28 of ≥1.2), patients achieving low disease activity (DAS28 ≤3.2), clinical remission (DAS28 <2.6), ESR and CRP levels, FACIT-F, and RAPID3 scores	A significantly higher proportion of patients randomized to receive tocilizumab achieved an ACR 50 response at week 24 compared to placebo (30.1 vs 11.2%; P<0.0001). Secondary: A higher proportion of patients randomized to receive tocilizumab achieved an ACR 20 response at all time points evaluated compared to placebo (P<0.0001). Similarly, an ACR 50 response was achieved in significantly more patients in the tocilizumab group compared to placebo at all treatment weeks except week 16 (P<0.05 at all time points). A significantly greater proportion of patients in the tocilizumab group compared to the placebo group achieved an ACR 70 response at all time points from week eight onward (P<0.05 for all time points). A higher proportions of patients achieved a EULAR good response in the tocilizumab group compared to placebo at all time points starting at week four (13.2 vs 2.0%; P<0.0001). The mean DAS28 score decreased from baseline to week 24 in both treatment groups starting at week four; however, the improvement was significantly greater in tocilizumab group compared to placebo (P<0.0001). Significantly more patients achieved a clinically meaningful decrease in DAS28 (≥1.2 points from baseline) in the tocilizumab group compared to the placebo group at all time points from week four onward (87.9 vs 53.4%; P<0.0001). Moreover, a greater proportion of patients randomized to receive tocilizumab achieved a low disease activity (P<0.0001) and clinical remission at week 24 (P<0.0001) compared to those in the placebo group. There were significantly greater improvements from baseline in the RAPID3 scores at 24 weeks in the tocilizumab treatment group compared to placebo (-2.33 vs -1.29; P<0.0001). There was a statistically significant improvement in mean FACIT-F scores over 24 weeks of treatment with tocilizumab compared to placebo (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients treated with tocilizumab achieved significantly lower mean CRP levels at all time points evaluated compared to the placebo group (P<0.0001). Similarly, the mean ESR was significantly reduced from baseline to a greater degree with tocilizumab compared to the placebo group at week 24 (-34.72 vs -5.70 mm/h; P<0.0001).
Emery et al[109] (RADIATE) Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks	DB, PC, PG Patients ≥18 years of age with moderate to severe active RA with failure to respond to one or more TNF antagonists within the past year; patients must have discontinued TNF agents (Enbrel®, Humira®, Remicade®) or DMARDs (other than MTX) before enrolling	N=499 24 weeks	Primary: ACR 20 responses Secondary: DAS 28, number of patients requiring rescue therapy, and adverse events	Primary: ACR 20 was achieved at week 24 by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control group respectively (P<0.001). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (P<0.001). Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments. Secondary: DAS 28 remission rates at week 24 were dose related, being achieved in 30.1, 7.6, and 1.6% of 8 mg/kg, 4 mg/kg and control groups (P<0.001 for 8 mg/kg; P=0.053 for 4 mg/kg vs control). Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both tender and swollen joints). More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after week 16 compared to 11% of patients in the 8 mg/kg group. Adverse events noted were mild or moderate with overall incidences of 84.0% in the tocilizumab 8 mg/kg group, 87.1% in the tocilizumab 4 mg/kg group, and 80.6% in the placebo plus MTX group. The most common adverse events were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in the control group (11.3%) than in the tocilizumab 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Dougados et al[110] (ACT-RAY) Tocilizumab 8 mg/kg plus	DB, PC, PG Patients ≥18 years of age with active	N=556 24 weeks	Primary: DAS 28 remission	Primary: DAS 28 remission rates at week 24 were 40.4% with the tocilizumab/MTX group vs 34.8% with tocilizumab monotherapy (P=0.19).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MTX (stable >15 mg weekly) every 4 weeks vs tocilizumab 8 mg/kg plus placebo every 4 weeks	RA with failure to respond to > 12 weeks of MTX treatment (stable dose >15 mg week for 6 weeks prior to study)		Secondary: DAS 28 low disease activity, ACR 20, ACR 50, ACR 70, ACR 90, and adverse events	Secondary: DAS 28 scored for low disease activity was significantly lower with combination therapy (tocilizumab/MTX) at week 24 that with the with tocilizumab monotherapy (61.7 vs 51.4%; P=0.029). ACR 20/50/70/90 was 71.5%/45.5%/24.5%/5.8% with tocilizumab/MTX. ACR 20/50/70/90 was 70.3%/40.2%/25.4%/5.1% with tocilizumab monotherapy. The differences between treatment groups were not considered significant. Adverse events noted were comparable in each treatment group with 6.1% of patients on tocilizumab/MTX reporting a serious adverse event while 5.8% reported a serious adverse event with tocilizumab monotherapy. Discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab/MTX patients and 2.5% and 18.5% of tocilizumab monotherapy patients, respectively. Increases in alanine aminotransferase elevations from normal at baseline to greater than upper limit of normal and to more than three times upper limit of normal at one or more time points during 24 weeks occurred in 48.8% and 7.8% on tocilizumab/MTX and in 27.6% and 1.2% of tocilizumab monotherapy patients, respectively.
Maxwell et al[111] Abatacept 2 to 10 mg/kg alone or in combination with DMARDs or biologics vs placebo or DMARDs or biologics	SR RCTs of patients ≥16 years of age with RA meeting the ACR 1987 revised criteria	N=2,908 (7 trials) ≥3 months	Primary: ACR 50 response and safety Secondary: ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, and changes in HAQ and SF-36	Primary: At three months, the ACR 50 response in the abatacept group was not significantly higher than the control group (RR, 2.50; 95% CI, 0.52 to 11.96). At six and 12 months, the ACR 50 response was significantly higher in the abatacept group compared to the control group (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82, respectively). At one year the NNT in order to achieve ACR 50 was 5 (95% CI, 4 to 7). The RR for adverse events with abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections with abatacept compared to controls (OR, 1.91; 95% CI, 1.07 to 3.42). However, after removing a study in which patients were treated with combination of etanercept and abatacept, the OR decreased to 1.82 (95% CI, 1.00 to 3.32). Abatacept treated patients had increased number of headaches and infusion reactions (RR, 1.45; 95% CI, 1.20 to 1.74 and RR,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				1.30; 95% CI, 1.13 to 1.50). Secondary: ACR 20 response was achieved in significantly more patients treated with abatacept compared to controls at six and 12 months (RR, 1.79; 95% CI, 1.59 to 2.02 and RR, 1.79; 95% CI, 1.55 to 2.07, respectively) but not at three months (RR, 1.70; 95% CI, 0.93 to 3.12). More patients treated with abatacept achieved an ACR 70 at six and 12 months (RR, 3.53; 95% CI, 2.41 to 5.16 and RR, 4.02; 95% CI, 2.62 to 6.18) but not at three months (RR, 5.00; 95% CI, 0.25 to 100.20). There was a statistically significant reduction in the progression of joint damage at 12 months with abatacept (mean difference, -0.27; 95% CI, -0.42 to -0.12). The abatacept treated patients were significantly more likely to reach low DAS (DAS 28 <3.2) compared to controls at six and 12 months (RR, 3.36; 95% CI, 2.28 to 4.96 and RR, 4.33; 95% CI, 2.84 to 6.59), and a NNT of 4 (95% CI, 3 to 5). At 12 months, patients in the abatacept group were significantly more likely to achieve DAS remission (DAS 28 <2.6) with RR of 12.74 (95% CI, 4.76 to 34.15). For clinically meaningful improvement on the HAQ; RR, 1.69 (95% CI, 1.51 to 1.90) in favor of abatacept. There was an absolute difference of 24% (95% CI, 16 to 32) and a NNT to achieve HAQ >0.3 of 5 (95% CI, 4 to 7). Improvement in the physical component of the SF-36 was significantly more likely in the abatacept group (RR, 1.90, 95% CI, 1.52 to 2.39). There was no significant difference between the groups in likelihood of scoring worse. The RR of scoring the same was 0.66 in favor of placebo (95% CI, 0.56 to 0.78). There were significantly fewer patients that scored worse on the mental component of the SF-36 (RR, 0.64; 95% CI, 0.44 to 0.94). Scoring the same was not significantly different between the groups. A score of better was significantly higher in the abatacept group (RR, 1.42; 95% CI, 1.14 to 1.76).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Navarro-Sarabia et al[112] Adalimumab 20, 40, 80 mg every week to every other week, alone or in combination with DMARDs vs placebo or placebo plus DMARDs	SR RCTs of patients with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either failed MTX or other DMARDs therapy, or DMARD naive	N=2,381 (6 trials) 12 to 52 weeks	Primary: ACR, EULAR responses, DAS 28, components of ACR responses, and radiographic data Secondary: Safety	Primary: Adalimumab 40 mg every other week was associated with a RR of 1.52 to 4.63 to attain an ACR 20 response at 24 weeks with a NNT of 1.9 to 5.4. The RR to achieve an ACR 50 response was 4.63 (95% CI, 3.04 to 7.05) and NNT was 3.0 (95% CI, 2.0 to 6.0). The RR to achieve an ACR 70 response was reported as 5.14 (95% CI, 3.14 to 8.41) and a NNT of 7 (95% CI, 5 to 13). At 52 weeks, the RRs were reported for ACR 20, ACR 50 and ACR 70 as 2.46 (95% CI, 1.87 to 3.22), 4.37 (95% CI, 2.77 to 6.91) and 5.15 (95% CI, 2.60 to 10.22) and NNTs were 2.9, 3.1 and 5.3, respectively. A significantly slower rate of radiological progression was detected with either adalimumab 40 mg every other week or 20 mg every week in combination with MTX compared to placebo plus MTX, at 52 weeks. Adalimumab monotherapy (40 mg every other week) was associated with a RR of 1.91 (95% CI, 1.17 to 3.10), 2.84 (95% CI, 1.58 to 5.12) and 7.33 (95% CI, 2.25 to 33.90) to achieve an ACR 20, ACR 50 and ACR 70 response, respectively, with NNTs of 5 (95% CI, 3 to 9), 7 (95% CI, 4 to 20) and 9 (95% CI, 3 to 38), respectively at 24 weeks. Secondary: Only one study demonstrated that adalimumab was associated with a significantly higher risk of developing serious infection (RR, 7.64; 95% CI, 1.02 to 57.18; NNH, 30.2).
Mertens et al[113] Anakinra 50 to 150 mg daily vs placebo	SR RCTs of patients >18 years of age with RA	N=2,876 (5 trials) 24 weeks	Primary: Patients achieving ACR 20 Secondary: Patients achieving ACR	Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to patients taking placebo (23%; RR, 1.61; 95% CI, 1.32 to 1.98). It was concluded that this 15% difference represented a modest yet clinically meaningful difference. Secondary: Both ACR 50 and ACR 70 were obtained at a significantly greater rate with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			50 and ACR 70, and safety	anakinra as opposed to placebo (18 vs 7%; RR, 2.52; 95% CI, 1.56 to 4.03 and 7 vs 2%; RR, 3.71; 95% CI, 1.44 to 9.57, respectively). Anakinra was also associated with significant improvements in HAQ, visual analog score, Larsen radiographic scores and change in ESR compared to placebo. The number of withdrawals, deaths, adverse events and infections were not significantly different between active treatment and placebo. However, injection site reaction was significantly more prevalent in the anakinra group vs the placebo group (71 vs 28%).
Blumenauer et al[114] Etanercept 10 mg or 25 mg twice weekly alone or in combination with MTX vs MTX or placebo	SR RCTs of patients ≥16 years of age meeting the ACR 1987 revised criteria for RA with evidence of active disease as demonstrated by ≥2 of the following: tender joint count, swollen joint count, duration of early morning stiffness >30 minutes, acute phase reactants such as Westergren ESR or CRP	N=949 (3 trials) ≥6 months	Primary: ACR 20, ACR 50, ACR 70 responses, and erosion scores Secondary: Safety	Primary: At six months, 64% of individuals on etanercept 25 mg attained an ACR 20 response vs 15% of patients on control with either MTX alone or placebo (RR, 3.8; 95% CI, 2.5 to 6.0; NNT, 2). ACR 50 was achieved by 39% in the etanercept group compared to 4% in the control group (RR, 8.89; 95% CI, 3.61 to 21.89; NNT, 3). An ACR 70 response was reported in 15 and 1% of etanercept and control patients, respectively (RR, 11.31; 95% CI, 2.19 to 58.30; NNT, 7). Etanercept 10 mg was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and JSN were not significantly reduced by either etanercept dose, however etanercept 25 mg was associated with a significantly reduced total Sharp score (WMD, -10.50; 95% CI, -13.33 to -7.67). Secondary: Injection site reactions were reported in 34% of patients on etanercept 10 mg compared to 9% of controls (RR, 3.86; 95% CI, 2.59 to 5.77; NNH, 4) and 41% of patients receiving etanercept 25 mg vs 9% of controls (RR, 4.77; 95% CI, 3.26 to 6.97; NNH, 3.1). The number of withdrawals was reported less frequently in the etanercept

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				25 mg group (4%) compared to the control group (8%; RR, 0.50; 95% CI, 0.27 to 0.94) and no difference was found between the etanercept 10 mg group and control in the rate of discontinuation.
van Vollenhoven et al[115] (SWEFOT) Infliximab 3 mg/kg at weeks zero, two and six then every eight weeks plus MTX 20 mg weekly (Group B) vs MTX 20 mg weekly plus SSZ 1,000 mg twice-daily plus hydroxychloroquine 400 mg daily (Group A)	MC, OL, PG, RCT Patients ≥18 years of age with RA (ACR) criteria, no previous DMARD treatment, no oral glucocorticoid treatment or stable glucocorticoid treatment for ≥4 weeks of at most 10 mg daily prednisolone (or equivalent), a DAS28 >3.2	N=487 24 months	Primary: Proportion of patients achieving a EULAR-define good response (a decrease of DAS28 by ≥1.2 and a resulting DAS28 ≤3.2 or less Secondary: EULAR and ACR responses at months 18 and 24, radiological outcomes at months 24	Primary: At month 18, there was no statistically significant difference in the proportion of patients achieving an EULAR-defined good response for patients treated with infliximab compared to conventional therapy (38 vs 29%, respectively; 95% CI, 0.93 to 1.85). Furthermore there was no statistically significant difference between the treatment groups at 24 months (38 vs 31%, respectively; P=0.204). Secondary: At 18 months, no statistically significant differences were reported between infliximab and conventional therapy with regard to ACR 20 (45 vs 34%, respectively; 95% CI, 0.99 to 1.82) ACR 70 (17 vs 11%, respectively; 95% CI, 0.86 to 2.98) or EULAR good or moderate response (58 vs 47%, respectively; 95% CI, 0.97 to 1.56). There was, however, a statistically significant difference favoring infliximab with regard to ACR 50 (30 vs 19%, respectively; 95% CI, 1.02 to 2.46). At 24 months there was no statistically significant difference between infliximab and conventional therapy with regard to ACR 20 response (40 vs 33%, respectively; P=0.259), ACR 50 (30 vs 22%; P=0.134), ACR 70 (16 vs 14%; P=0.566) or EULAR good to moderate response (59 vs 50%; P=0.166). Radiological outcomes were not statistically significant between infliximab and conventional therapy at 24 months with regard to total score (P=0.118), erosion score (P=0.0730) or joint-space narrowing score (P=0.054).
Wiens et al[116] Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX vs	MA RCTs of adult patients with RA	N=2,129 (7 trials) ≥14 weeks	Primary: ACR 20, ACR 50, and ACR 70 response Secondary: Safety and	Primary: Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to the control group (RR, 1.87; 95% CI, 1.43 to 2.45). An ACR 50 was achieved in 33% of infliximab treated patients and 12% of controls (RR, 2.68; 95% CI, 1.79 to 3.99). The RR of achieving an ACR 70 was 2.68 (95% CI, 1.78 to 4.03) with 17 and 5% of infliximab and control groups achieving an ACR 70, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo plus MTX			discontinuation of therapy	After ≥1 year of treatment, 62% of patients in the infliximab group and 26% of controls achieved an ACR 20 (RR, 2.33; 95% CI, 1.90 to 2.87). An ACR 50 was achieved in 43% of the infliximab treated patients and 27% of controls (RR, 1.61; 95% CI, 1.14 to 2.27). The RR for reaching ACR 70 was 1.69 (95% CI, 0.87 to 3.28), and 29% of patients in the infliximab group compared to 17% of patients in the control group achieved an ACR 70. Secondary: There were no statistically significant differences in serious adverse events. There was a higher number of patients that withdrew due to adverse events in the infliximab group compared to the placebo group (7 vs 3%; RR, 2.05, 95% CI, 1.33 to 3.16); however, fewer patients in the infliximab group withdrew due to lack of efficacy compared to the control group (4 vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).
Nixon et al[117] Adalimumab, anakinra, etanercept, or infliximab with or without MTX vs MTX or placebo	MA RCTs of patients with a clinical diagnosis of RA	N=6,694 (13 trials) ≥6 months	Primary: ACR 20 response and ACR 50 response Secondary: Not reported	Primary: The OR for an ACR 20 response was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab, all compared to placebo. The OR to achieve an ACR 50 response with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) with infliximab, all compared to placebo. The addition of MTX to any of the agents was found to enhance the efficacy of each treatment. The TNF blockers in combination with MTX were associated with higher ACR 20 and ACR 50 responses than anakinra and MTX (OR, 6.35 vs 3.20 and OR, 8.53 vs 4.56, respectively). Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50 response (adalimumab vs anakinra; OR, 1.88; 95% CI, 0.83 to 4.49 and OR, 1.84; 95% CI, 0.84 to 3.70; adalimumab vs etanercept; OR, 0.89; 95% CI, 0.42 to 1.79 and OR, 0.94;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95% CI, 0.50 to 1.62; adalimumab vs infliximab; OR, 0.92; 95% CI, 0.39 to 2.37 and OR, 0.96; 95% CI, 0.48 to 1.90; etanercept vs anakinra; OR, 2.11; 95% CI, 0.90 to 5.68 and OR, 1.94; 95% CI, 0.87 to 4.36; infliximab vs anakinra; OR, 2.05; 95% CI, 0.74 to 5.50 and OR, 1.93; 95% CI, 0.79 to 4.29; and infliximab vs etanercept; OR, 0.97; 95% CI, 0.34 to 2.33 and OR, 0.98; 95% CI, 0.45 to 1.93. However, the TNF blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI, 1.05 to 3.50; P<0.05). Secondary: Not reported
Gabay et al[118] (ADACTA) Tocilizumab 8 mg/kg vs adalimumab 40 mg every 2 weeks	DB, PG, RCT Patients ≥18 years of age with RA > 6 months, intolerant to MTX or were inappropriate for continued MTX treatment	N=326 24 weeks	Primary: DAS 28 improvement Secondary: Percentage of patients with: a remission response (DAS28 <2.6); low disease activity (DAS28 ≤ 3.2); improvements of at least 20%, 50%, or 70% in ACR Score (ACR 20, ACR 50, and ACR 70); and with a EULAR good Response, and a EULAR good or moderate response	Primary: The change from baseline in DAS28 was significantly greater in the tocilizumab group (-3.3) than in the adalimumab group (-1.8) patients (difference -1.5; 95% CI, -1.8 to -1.1; P<0·0001). Secondary: DAS 28 remission rates at week 24 were achieved in 39.9% with tocilizumab and 10.5% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0·0001). The proportion of patients with low disease activity (DAS 28 ≤3.2) at 24 weeks was 51.5% in tocilizumab group and 19.8% in the adalimumab group (difference -1.5, 95% CI, -1.8 to -1.1; P<0.0001). The proportion of patients on tocilizumab vs adalimumab with improvements of at least 20% in ACR score was 65.0 vs 49.4%, respectively, a 50% improvement was seen in 47.2 vs 27.8% respectively and a 70% improvement was observed in 32.5 vs 17.9%, respectively. The proportion of patients on tocilizumab vs adalimumab with a EULAR good response was 51.5 vs 19.8%, respectively, and percentage with a EULAR good or moderate was response 77.9 vs 54.9%, respectively.

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Weinblatt et al[119] Abatacept 125 mg subcutaneously once weekly and MTX vs adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.	MC, RCT Patients 18 years of age with a confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy	N=646 12 months	Primary: Noninferiority, assessed based on ACR20 at one year Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤ 3.2), and HAQ-DI	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (46.2 and 46%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (29.2 and 26%, respectively; 95% CI not reported). Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.30 and -2.27, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (43.3 and 41.9%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (59.3 and 61.4%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (60.4 and 57.0%, respectively; difference, 3.4%; 95% CI, -4.5 to 11.3%).
Schiff et al[120] Abatacept 125 mg subcutaneously once	MC, RCT Patients 18 years of age with a	N=646 2 years	Primary: ACR20 at two years	Primary: The proportions of patients achieving ACR 20 response were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; 95% CI not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weekly and MTX vs adalimumab 40 mg subcutaneously every other week and MTX Patients were concomitantly treated with a stable dosage of MTX (15 to 25 mg weekly, or ≥7.5 mg weekly in patients with intolerance to higher doses). Concomitant treatment with SSZ, HCQ, NSAIDs and stable low-dose oral corticosteroids (≤10 mg/day prednisone equivalent) were allowed.	confirmed diagnosis of RA for ≤5 years, inadequate response to MTX, and who had not received previous biologic therapy		Secondary: ACR 50, ACR 70, DAS 28, remission response (DAS28 <2.6), low disease activity (DAS28 ≤3.2), HAQ-DI, and mTSS	Secondary: The proportions of patients achieving ACR 50 response were comparable between abatacept and adalimumab treatment groups (44.7 and 46.6%, respectively; 95% CI not reported). The proportions of patients achieving ACR 70 response were comparable between abatacept and adalimumab treatment groups (31.1 and 29.3%, respectively; 95% CI not reported). Mean improvements in DAS 28 were comparable between abatacept and adalimumab treatment groups (-2.35 and -2.33, respectively; 95% CI not reported). The proportions of patients achieving remission (DAS28 <2.6) were also comparable between abatacept and adalimumab treatment groups (50.6 and 53.3%, respectively; 95% CI not reported). In addition, the proportions of patients achieving low disease activity (DAS28 ≤3.2) were comparable between abatacept and adalimumab treatment groups (65.3 and 68.0%, respectively; 95% CI not reported). Improvements in the HAQ-DI score were comparable between abatacept and adalimumab treatment groups (54.1 and 48.8%, respectively; 95% CI not reported). The non-progression rate (change from baseline mTSS ≤smallest detectable change of 2.2) was 84.8% (95% CI, 80.4 to 89.2) vs 83.8% (95% CI, 79.4 to 88.3) in the abatacept and adalimumab groups, respectively.
Fleischmann et al[121] (ORAL Solo) Tofacitinib 5 mg twice daily vs	DB, PC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6	N=611 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI at month three, and proportion of	Primary: Greater proportions of patients receiving tofacitinib 5 mg and tofacitinib 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (59.8 and 65.7 vs 26.7%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than

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tofacitinib 10 mg twice daily vs placebo	swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L), and inadequate response or adverse reaction to at least one DMARD; all DMARDs except stable doses of antimalarial agents had to be discontinued; the use of NSAIDs and glucocorticoids (≤10 mg of a prednisone equivalent daily) was permitted		patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, DAS28-4(ESR) and DAS28-4(CRP), proportion of patients with DAS28-4(ESR) and DAS28-4(CRP) <2.6 and ≤3.2 at all visits up to month six, and FACIT-F scores at month three	those receiving placebo (least-squares mean changes from baseline, -0.50 and -0.57 vs -0.19; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (5.6 and 8.7 vs 4.4%; P=0.62 and P=0.10, respectively); however, improvement was not statistically significant. Secondary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving placebo (31.1 and 36.8 vs 12.5%; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR70 response at month three than those receiving placebo (15.4 and 20.3 vs 5.8%; P=0.003 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) <2.6 at month six were 9.8 and 14.2%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three than those receiving placebo (12.5 and 17.0 vs 5.3%; P=0.02 and P<0.001, respectively). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(ESR) ≤3.2 at month six were 22.0% and 28.0%, respectively. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) <2.6 at month three than those receiving placebo (18.7 and 24.4 vs 5.0%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) <2.6 at month six were 26.6 and 34.3%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(CRP) ≤3.2 at month three than those receiving placebo (28.2 and 36.8 vs 6.7%; P<0.001 for both comparisons). Proportions of patients receiving tofacitinib 5 and 10 mg twice daily who achieved DAS28-4(CRP) ≤3.2 at month six were 43.6 and 50.8%, respectively. The least-squares mean changes from baseline at month three in FACIT-F scores were 6.7 points with the tofacitinib 5 mg and 8.0 points with the tofacitinib 10 mg doses, as compared to 2.8 points with placebo (P<0.001).
van Vollenhoven et al[122] (ORAL Standard) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs adalimumab 40 mg once every 2 weeks vs placebo Patients were also receiving MTX 7.5 to 25 mg weekly with an incomplete response.	DB, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L)	N=717 12 month	Primary: ACR20 response rate at month six, change in HAQ-DI at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI, and DAS28-4(ESR) over time	Primary: Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab met the criteria for an ACR20 response at month six than those receiving placebo (51.5, 52.6, and 47.2 vs 28.3%; P<0.001 for all comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab at month three than those receiving placebo (least-squares mean changes from baseline: -0.55, -0.61 and -0.49 vs -0.24; P≤0.001 for all comparisons). Greater proportions of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily and adalimumab achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (6.2, 12.5, and 6.7 vs 1.1%; P≤0.05, P≤0.001, and P≤0.05, respectively). Secondary: Compared to placebo, significantly greater proportions of patient receiving active treatments achieved ACR50 and ACR70 responses and the changes from baseline in DAS28-4(ESR) and HAQ-DI scores over time (P≤0.05 for all comparisons). A significant difference in ACR20 and ACR50 responses with each

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				tofacitinib treatment as compared to placebo was noted after one month (P≤0.001 for all comparisons). Data on comparison between adalimumab and placebo was not reported.
Burmester et al[123] (ORAL Step) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo for 3 months, followed by tofacitinib 5 mg or 10 mg twice daily Patients were also receiving oral or parenteral MTX continuously for ≥4 months at a stable dose of 7.5 to 25 mg weekly for ≥6 weeks. Stable background doses of antimalarial agents (≥8 weeks) were permitted.	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of moderate to severe active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response or intolerance to ≥1 TNF-blocking agents	N=399 6 month	Primary: ACR20 response rate at month three, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month three Secondary: ACR20, ACR50, and ACR70 response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR) and DAS28-3(CRP), rates of DAS28-4(ESR) and DAS28-3(CRP) <2.6 and ≤3.2, patient's assessment of arthritis pain, and FACIT-F at all visits	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (41.7 and 48.1 vs 24.4%; P=0.0024 and P<0.0001, respectively). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 mg and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.43 and -0.46 vs -0.18; P<0.0001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three than those receiving placebo (6.7 and 8.8 vs 1.7%; P=0.0496 and P=0.0105, respectively). Secondary: Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily met the criteria for an ACR20 response at all visits through month three (P≤0.05 for all visits, except P<0.0001 for 10 mg group vs placebo at month three). Compared to placebo, significantly greater proportion of patients in the tofacitinib 5 mg twice daily group achieved ACR50 at all visits through month three (P≤0.05 at two week and one month visits and P<0.0001 at three month visit). Compared to placebo, significantly greater proportion of patients in the tofacitinib 10 mg twice daily group achieved the ACR50 at three month study visit (P<0.0001); however, responses at two week and at one month visits were not significantly different (P values not reported). Compared to placebo, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR70 at one month and three months visits (P≤0.05 for all visits, except P<0.001 for 5 mg group vs placebo at month three). The responses between both active treatment groups and placebo at two week visit were not significantly

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				different (P values not reported). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 10 mg twice daily at all visits through month three (P≤0.05 for all comparisons, except P<0.0001 at month three). Compared to placebo, significantly greater reductions from baseline in the HAQ-DI score were also observed at three month visit in patients receiving tofacitinib 5 mg twice daily (P<0.0001); however, the changes at two week and one month visits were not significantly different (P values not reported). Compared to placebo, changes from baseline in DAS28-4(ESR) were greater in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P=0.01 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater changes from baseline in DAS28-3(CRP) were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits through month three (P<0.0001 for all comparisons). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month three (P=0.0496 and P=0.0105, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) <2.6 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) ≤3.2 at month three (P≤0.05 and P<0.0001, respectively; P values not reported for all other visits). Compared to placebo, significantly greater proportions of patients receiving

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				tofacitinib 5 and 10 mg twice daily achieved DAS28-3(CRP) ≤3.2 at month three (P<0.0001 for both comparisons; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month three were greater in tofacitinib 5 and 10 mg twice daily treatment groups than in those receiving placebo (−27.2 and −25.0 vs −8.3; P<0.0001 for both comparisons; P values not reported for all other visits). Improvements in FACIT-F at month three were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (6.3 and 4.6 vs 1.1; P<0·0001 and P=0.0043, respectively; P values not reported for all other visits).
Van der Heijde et al[124] (ORAL Scan) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 mg or 10 mg	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥6 tender or painful joints [68 joint count] and ≥6 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and evidence of ≥3 joint erosions on posteroanterior hand and wrist radiographs or anteroposterior foot radiographs (if radiographic evidence of joint erosions was unavailable,	N=797 12 month	Primary: ACR20 response rate at month six, mean change from baseline in mTSS at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70 response rates, DAS28-4(ESR) at all visits, changes from baseline in the	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (51.5 and 61.8% vs 25.3%; P=0.0001 for both comparisons). The least squares mean changes in mTSS at month six were 0.12 and 0.06 for patients receiving tofacitinib 5 and 10 mg twice daily, respectively, vs 0.47 for placebo (P=0.0792 and P≤0.05, respectively). The least squares mean changes in the HAQ-DI score at month three for tofacitinib at 5 and 10 mg twice daily were -0.40 and -0.54, respectively, vs -0.15 for placebo (P value not reported and P<0.0001, respectively). Proportions of patients achieving DAS28-ESR <2.6 at month six were 7.2% and 16.0% for tofacitinib at 5 and 10 mg twice daily, respectively, vs 1.6% for placebo (P value not reported and P<0.0001, respectively). Secondary: Compared to placebo at month six, significantly greater proportions of patients in the tofacitinib 5 mg and 10 mg twice daily groups achieved ACR50 (32.4 and 43.7 vs 8.4%; P<0.0001 for both comparisons) and ACR70 (14.6 and 22.3 vs 1.3%; P<0.0001 for both comparisons). At month 12, ACR20, ACR50, and ACR70 response rates were 48.5, 32.7, and

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twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving stable doses of MTX (15 to 25 mg weekly or <15 mg if there were safety issues at higher doses) for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) and NSAIDs were permitted. Prior use of biologic or nonbiologic DMARDs was permitted.	presence of IgM rheumatoid factor positivity or antibodies to cyclic citrullinated peptide).		ACR code disease activity measures at month six, rates of nonprogressors (≤0.5 unit change from baseline in mTSS or erosion score) at months six, 12, and 24, changes from baseline in mTSS (at months 12 and 24), changes from baseline in erosion score and JSN score (at months six, 12, and 24), change from baseline in HAQ-DI score, the FACIT-F, and the patient's assessment of arthritis pain	18.8%, respectively, for tofacitinib 5 mg and 57.0, 41.1, and 27.5%, respectively, for tofacitinib 10 mg. At month 12, the proportions of patients with DAS28-ESR <2.6 were 10.6 and 15.2% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively. At month six, the proportions of patients with DAS28-ESR ≤3.2 were 14.3 and 28.4% in the groups receiving tofacitinib 5 and 10 mg twice daily, respectively, compared to 3.1% of patients receiving placebo (P<0.0001 for both comparisons). At month 12, the rates of DAS28-ESR <3.2 for patients receiving tofacitinib at 5 and 10 mg twice daily increased to 23.4 and 30.7%, respectively. At month six, least squares mean changes from baseline in DAS28-ESR were greater for tofacitinib 5 and 10 mg twice daily compared to placebo (-2.1 and -2.5 vs -1.3; P<0.0001 for both comparisons); at month 12, least squares mean changes from baseline in DAS28-ESR were -2.3 and -2.5 for tofacitinib 5 and 10 mg twice daily, respectively. Compared to placebo a month six, statistically significant improvements from baseline were observed in all ACR core components in both tofacitinib 5 and 10 mg twice daily groups, including improvements in tender or painful joint count (P≤0.05 and P<0.01, respectively), swollen joint count (P<0.01 and P<0.0001, respectively), CRP (P<0.0001 for both comparisons), patient's global assessment of disease activity (P<0.0001 for both comparisons), physician's global assessment of disease activity (P<0.0001 for both comparisons), patient's assessment of pain (P<0.01 and P<0.0001, respectively), and HAQ-DI (P<0.0001 for both comparisons). The proportion of patients with no radiographic progression (≤0.5 unit increase from baseline in mTSS) at months six and 12 was similar in both tofacitinib treatment groups and significantly greater than in the placebo treatment group (P≤0.05 for both). At month six, the proportion of patients with no progression in erosion score (≤0.5 unit increase from baseline) was numerically greater, but not statistically significantly different, in the tofacitinib treatment groups compared to the placebo-treated group (P>0.05). The proportion of patients with no progression in erosion score at month 12 was significantly greater in both tofacitinib treatment groups

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				compared to the placebo-treated group (P≤0.05). The plots of changes from baseline in mTSS, JSN score, and erosion score at months six and 12 for both tofacitinib-treated groups were very similar and were different from the plot for the placebo-treated group (P values not reported). Compared to placebo, greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at all visits (P<0.001 for all comparisons, except P<0.01 for tofacitinib 5 mg vs placebo at one month visit). Improvements in FACIT-F from baseline to month six were greater in patients receiving tofacitinib 5 and 10 mg twice daily than in those receiving placebo (5.6 and 6.9 vs 2.1; P<0.001 and P<0.0001, respectively; P values not reported for all other visits). Changes from baseline in patient's assessment of arthritis pain at month six were greater in 5 and 10 mg twice daily treatment groups than in those receiving placebo (-26.4 and -29.7 vs -15.70; P<0.01 and P<0.0001, respectively; P values not reported for all other visits).
Kremer et al[125] (ORAL Sync) Tofacitinib 5 mg twice daily vs tofacitinib 10 mg twice daily vs placebo	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of active RA (≥4 tender or painful joints [68 joint count] and ≥4 swollen joints [66 joint count] and either ESR>28 mm/hour or CRP>7 mg/L) and inadequate response to ≥1	N=792 12 month	Primary: ACR20 response rate at month six, change from baseline in HAQ-DI score at month three, and proportion of patients with DAS28-4(ESR) <2.6 at month six Secondary: ACR20, ACR50, and ACR70	Primary: Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month six than those receiving placebo (52.1 and 56.6 vs 30.8%; P<0.001 for both comparisons). Greater reductions from baseline in the HAQ-DI score were observed in patients receiving tofacitinib 5 and 10 mg twice daily at month three than those receiving placebo (least-squares mean changes from baseline: -0.44 and -0.53 vs -0.16; P<0.001 for both comparisons). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily achieved DAS28-4(ESR) <2.6 at month six than those receiving placebo (8.5 and 12.5 vs 2.6%; P=0.005 and P<0.001, respectively). Secondary:

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Patients receiving placebo and not achieving ≥20% improvement in swollen and tender joint counts after 3 months were switched to a predetermined dose of tofacitinib 5 or 10 mg twice daily. All patients continuing to receive placebo were switched in a blinded manner to tofacitinib after 6 months. Patients were also receiving ≥1 nonbiologic DMARDs. Patients receiving MTX ≤25 mg weekly required ≥4 months of therapy at a stable dose for ≥6 weeks. Stable doses of low-dose corticosteroids (≤10 mg daily prednisone or equivalent) were permitted.	stably dosed nonbiologic or biologic DMARDs		response rates, change from baseline in HAQ-DI score, changes in DAS28-4(ESR), and FACIT-F score over time	Over time, statistically significant response rates were observed for ACR20 and ACR50 by week two in both tofacitinib groups compared to placebo (P≤0.001 for all comparisons) and for ACR70 by week two in the tofacitinib 10 mg group (P≤0.05 at week two and P≤0.001 at all visits thereafter) and one month in the tofacitinib 5 mg group (P≤0.001 for all comparisons). Mean treatment differences in changes from baseline in HAQ-DI, DAS28-4(ESR), and FACIT-F response rates for both tofacitinib groups compared to placebo were statistically significant over time (P≤0.001 for all).
He et al[126] Tofacitinib 1, 3, 5, 10, or 15 mg twice daily vs	MA, SR RCTs including patients ≥18 years of age with a diagnosis of RA	N=3,791 (8 trials) 12 to 24 weeks	Primary: ACR20 and ACR50 response rate at month three and six Secondary:	Primary: At month three, the differences in ACR20 response rates between tofacitinib 1 mg twice daily and placebo groups did not reach statistical significance (RR, 1.83; 95% CI, 1.00 to 3.32). Greater proportions of patients receiving tofacitinib 3 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo

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adalimumab 40 mg once every 2 weeks vs placebo			Incidence of infections, immunological or hematological adverse events, incidence of withdrawal from the trials, changes in neutrophil count, hemoglobin and serum creatinine levels, incidence of ALT and AST more than one times upper limit of the normal range, and mean percentage changes of LDL and HDL	(RR, 2.20; 95% CI, 1.20 to 4.04). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.20; 95% CI, 1.58 to 3.07) and (RR, 2.38; 95% CI, 1.81 to 3.14), respectively. The effect was maintained at month six for both 5 mg twice daily (RR, 1.94; 95% CI, 1.55 to 2.44) and 10 mg twice daily (RR, 2.20; 95% CI, 1.76 to 2.75) treatment groups. Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving placebo (RR, 2.91; 95% CI, 2.03 to 4.16) and (RR, 3.32; 95% CI, 2.33 to 4.72), respectively. Greater proportions of patients receiving tofacitinib 15 mg twice daily met the criteria for an ACR20 response at month three than those receiving placebo (RR, 2.29; 95% CI, 1.19 to 4.41). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR20 response at month three than those receiving adalimumab (RR, 1.65; 95% CI, 1.08 to 2.53) and (RR, 1.97; 95% CI, 1.32 to 2.92), respectively. At month six, there were no significant differences in ACR20 response rates in patients receiving tofacitinib vs adalimumab (P values not reported). Greater proportions of patients receiving tofacitinib 5 and 10 mg twice daily met the criteria for an ACR50 response at month three than those receiving adalimumab (RR, 1.95; 95% CI, 1.00 to 3.80) and (RR, 2.35; 95% CI, 1.26 to 4.38), respectively. Secondary: Compared to placebo, there were no statistically significant differences in the incidences of infections, neutropenia and withdrawal due to adverse events in patients receiving tofacitinib (P values not reported). However, significantly fewer patients withdrew from tofacitinib than placebo (RR, 0.60; 95% CI, 0.45 to 0.78). The withdrawal rate due to lack of efficacy was

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				significantly lower in the patients receiving tofacitinib than placebo (RR, 0.18; 95% CI, 0.09 to 0.35). Compared to placebo, the mean neutrophil count significantly declined in patients receiving tofacitinib (P value not reported). The mean hemoglobin level was not significantly different in tofacitinib group compared to placebo group (P value not reported). Compared to placebo, the mean serum creatinine was found to be significantly higher for tofacitinib 10 mg twice daily (P value not reported). The risk ratios of the mean changes of ALT or AST exceeding one times upper limit of the normal range were statistically significant (P values not reported). Compared to placebo, the mean percentage change of HDL and LDL was significant higher in patients receiving tofacitinib (P values not reported).
Berhan et al[127] Tofacitinib 3, 5, 10, or 15 mg twice daily (with or without MTX) vs placebo	MA DB, RCT including patients with a diagnosis of active RA for ≥6 months who were on at least one of nonbiologic or biologic DMARD	N=3,260 (8 trials) 12 to 24 weeks	Primary: ACR20 response rate, change from baseline in HAQ-DI score Secondary: Safety	Primary: Compared to placebo, tofacitinib treated patients had higher odds of meeting the criteria for an ACR20 response (OR, 4.15; 95% CI, 3.23 to 5.32). With the exception of one study, ACR20 response rates for patients receiving tofacitinib dosages ≥3 mg twice daily was significantly greater than those who received placebo (P value not reported). The subgroup odds ratios in the subgroups of tofacitinib 10 mg twice daily (OR, 4.3; 95% CI, 3.023 to 6.376) and 15 mg twice daily (OR, 6.06; 95% CI, 2.383 to 15.428) was higher than 3 mg twice daily (OR, 4.06; 95% CI, 1.340 to 12.305) and 5 mg twice daily (OR, 3.55; 95% CI, 2.435 to 5.169) treated groups. A statistically significant improvement in HAQ-DI scores were seen in patients receiving tofacitinib than placebo treated patients (SMD, −0.62; 95% CI, -0.735 to -0.506). Patients treated with tofacitinib dosages ≥5 mg twice daily have shown a statistically significant reduction in HAQ-DI scores (P value not reported). Secondary: The proportion of infections was higher in the tofacitinib treated groups than

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				in the placebo groups (SMD, 1.96, 95% CI, 1.428 to 2.676). In contrast to the subgroups of tofacitinib 10 mg (SMD, 3.08; 95% CI, 1.694 to 5.570) and 15 mg (SMD, 1.97; 95% CI, 1.088 to 3.558), the proportion of infections in the subgroups of tofacitinib 3 mg (SMD, 1.64; 95% CI, 0.858 to 3.142) and 5 mg (SMD, 1.52; 95% CI, 0.644 to 3.594) were not significantly different from placebo. There were significant increases from baseline in tofacitinib treated groups in the mean hemoglobin level (SMD, 0.11; 95% CI, 0.130 to 0.210), mean serum creatinine (SMD, 0.24; 95% CI, 0.112 to 0.372), HDL (SMD, 1.01; 95% CI, 0.332 to 1.682), and LDL (SMD, 0.95; 95% CI, 0.337 to 1.555). A significant number of patients with ALT (OR, 1.7; 95% CI, 1.29 to 2.46) and AST (OR, 2.19; 95% CI, 1.50 to 3.19) exceeding one times upper limit of the normal range were reported among tofacitinib treated groups. The rate of tofacitinib discontinuation due to adverse events was not significantly different from placebo (SMD, 1.27; 95% CI, 0.949 to 1.700).
Ulcerative Colitis				
Rutgeerts et al[128] (ACT 1 and ACT 2) Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks vs placebo	DB, MC, PC, RCT Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12) and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine	N=364 (ACT 1) N=364 (ACT 2) 30 weeks (ACT 2) 54 weeks (ACT1)	Primary: Clinical response at week eight Secondary: Clinical response or clinical remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal healing at weeks eight and 30	Primary: At week eight in ACT 1, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (69.4 and 61.5%) compared to the placebo group (37.2%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (64.5 and 69.2%) compared to the placebo group (29.3%; P<0.001 for both). Secondary: In ACT 1, the proportion of patients with clinical response at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (52.1 and 50.8%) compared to the placebo group (29.8%; P<0.001 and P=0.002, respectively). In ACT 2 at week 30, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (47.1 and 60.0%) compared to the placebo group (26.0%; P<0.001 for both). In ACT 1 at week 54, the clinical response rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	(ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-aminosalicylates (ACT 2)		(ACT 1 and ACT 2) and week 54 (ACT 1), and clinical response at week eight in patients with a history of corticosteroid refractory disease	group (45.5 and 44.3 vs 19.8%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (38.8 and 32.0%) compared to the placebo group (14.9%; P<0.001 and P=0.002, respectively). In ACT 2 at week eight, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 27.5%) compared to the placebo group (5.7%; P<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 36.9%) compared to the placebo group (15.7%; P=0.001 and P<0.001, respectively). In ACT 2 at week 30, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (25.6 and 35.8%) compared to the placebo group (10.6%; P=0.003 and P<0.001, respectively). In ACT 1 at week 54, the clinical remission rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (34.7 and 34.4 vs 16.5%; P=0.001 for both). In ACT 1 at week eight, the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (77.4 and 67.7 vs 35.3%; P<0.001 and P=0.010, respectively). In ACT 2 at week eight when compared to the placebo group (37.5%), the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 10 mg/kg (65.5%; P=0.011), but not 5 mg/kg group (63.3%; P=0.053). In ACT 1, the proportion of patients with mucosal healing at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (62.0 and 59.0%) compared to the placebo group (33.9%; P<0.001 for both). In ACT 2 at week eight, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (60.3 and 61.7%) compared to the placebo group (30.9%; P<0.001 for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (50.4 and 49.2%) compared to the placebo group (24.8; P<0.001 for both). In ACT 2

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				at week 30, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (46.3 and 56.7%) compared to the placebo group (30.1%; P=0.009 and P<0.001, respectively). In ACT 1 at week 54, the mucosal healing rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 46.7 vs 18.2%; P=0.001 for both).
Hyams et al[129] (abstract) Infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 8 weeks through week 46 vs infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 12 weeks through week 42	MC, OL, R Patients 6 to 17 years of age with active ulcerative colitis (Mayo score 6 to 12, including endoscopic subscore ≥2) who failed to respond to or tolerate treatment with mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylates	N=60 54 weeks	Primary: Clinical response at week eight (decrease from baseline in Mayo score ≥30% and ≥3 points, with a decrease in rectal bleeding subscore of 0/1) compared to baseline Secondary: Not reported	Primary: At week eight, 73.3% of patients had a clinical response with infliximab (95% CI, 62.1 to 84.5). Clinical remission by Mayo score was achieved in 33.3% of patients. At week 54, there was a greater proportion of patients achieving clinical remission with infliximab 5 mg/kg every eight weeks compared to infliximab 5 mg/kg every 12 weeks; though, this difference was not significant (P=0.146). Secondary: Not reported
Reinisch et al[130] Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA 160/80 group) vs Adalimumab 80 mg at week 0, 40 mg at weeks 2, 4 and 6 (ADA 80/40 group)	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis, (Mayo score of 6 to 12 with an endoscopy subscore of 2–3) who failed concurrent and stable treatment with oral corticosteroids	N=390 8 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) compared to baseline Secondary: Proportion of patients with a clinical response	Primary: At week eight, 18.5% of patients in the ADA 160/80 group (P=0.031 vs placebo) and 10.0% in the ADA 80/40 group (P=0.833 vs placebo) were in remission compared to placebo (9.2%). Secondary: At week eight, 54.6% of patients in the ADA 160/80 group (P vs placebo not reported), 51.5% in the ADA 80/40 group (P vs placebo not reported) and 44.6% in the placebo group had a clinical response. At week eight, 46.9% of patients in the ADA 160/80 group (P vs placebo not reported), 37.7% in the ADA 80/40 group (P vs placebo not reported) and 41.5% in the placebo group had mucosal healing.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	and/or immunomodulators		(decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	At week eight, 77.7% of patients in the ADA 160/80 group (P=0.038 vs placebo), 70.0% in the ADA 80/40 group (P vs placebo not reported) and 66.2% in the placebo group had a rectal bleeding subscore of ≤ 1. At week eight, 60.0% of patients in the ADA 160/80 group (P=0.035 vs placebo), 53.8% in the ADA 80/40 group (P vs placebo not reported) and 46.9% in the placebo group had a PGA subscore of ≤ 1 At week eight, 48.5% of patients in the ADA 160/80 group (P vs placebo not reported), 36.2% in the ADA 80/40 group (P vs placebo not reported) and 37.7% in the placebo group had a stool frequency subscore of ≤ 1
Sandborn et al[131] Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every other week vs placebo	DB, MC, PC, RCT Adult patients with moderate to severe active ulcerative colitis >3 months, (Mayo score of 6 to 12 with an endoscopy subscore >2) despite concurrent treatment with oral corticosteroids	N=494 52 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) at week 8 and 52 Secondary: Proportion of patients in remission at week 8 and 52;	Primary: At week 8, 16.5% of patients in the adalimumab group were in remission compared to placebo (9.3%; P=0.019; 95% CI, 1.2 to 12.9). At week 52, 17.3% of patients in the adalimumab group were in remission compared to placebo (8.5%; P=0.004; 95% CI, 2.8 to 14.5). Secondary: At week 8 and 52, 8.5% of patients in the adalimumab group (P=0.47 vs placebo) and 4.1% in the placebo group were in sustained remission. At week 8, 50.4% of patients in the adalimumab group (P<0.001 vs placebo) and 34.6% in the placebo group had a clinical response. At week

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	and/or azathioprine or 6-mercaptopurine.		proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients who discontinued corticosteroid; proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	52, 30.2% of patients in the adalimumab group and 18.3% in the placebo group had a clinical response. (P=0.002). At week 8 and 52, 23.8% of patients in the adalimumab group (P<0.001 vs placebo) and 12.2% in the placebo group were in sustained remission. Mucosal healing was achieved at week 8 in 41.1% of patients in the adalimumab group and 31.7% of patients receiving placebo (P=0.032). At week 52, 25% of patients in the adalimumab group and 15.4% of patients receiving placebo (P=0.009) had mucosal healing. Mucosal healing at week 8 and 52, 18.5% of patients in the adalimumab group (P<0.013 vs placebo) and 10.6% in the placebo group. At week 8, 46.0% of patients in the adalimumab group (P=0.028 vs placebo) and 37.4% in the placebo group had a PGA subscore of ≤ 1. At week 8, 37.9% of patients in the adalimumab group (P=0.058 vs placebo) and 28.5% in the placebo group had a stool frequency subscore of ≤ 1. At week 8, 70.2% of patients in the adalimumab group (P=0.006 vs placebo) and 58.1% in the placebo group had a rectal bleeding subscore of ≤ 1. Proportion of patients that discontinued corticosteroid use before week 52 and achieved remission at week 52 was13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group. Proportion of patients that for ≥90 days before week 52 and achieved remission at week 52 was 13.3% of patients in the adalimumab group (P=0.35 vs placebo) and 5.7% in the placebo group.
Sandborn et al[132] (PURSUIT-SC) Phase 2 (dose-finding): Golimumab 400 mg subcutaneously at week 0	2 DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative	Phase 2 N=169 Phase 3 N=774	Primary: Phase 2: Change in Mayo score from baseline to week six	Primary: In phase 2, median changes from baseline in the Mayo score were -3.0, -2.0, and -3.0 in the 100 mg/50 mg, 200 mg/100 mg, and 400 mg/200 mg golimumab treatment groups, respectively, compared to -0.1 in the placebo group (P=0.038, P=0.332 and P=0.038, respectively).

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and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs golimumab 100 mg subcutaneously at week 0 and 50 mg subcutaneously at week 2 (100 mg/50 mg) vs placebo Phase 3 (dose-confirming): Golimumab 400 mg subcutaneously at week 0 and 200 mg subcutaneously at week 2 (400 mg/200 mg) vs golimumab 200 mg	colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent	6 weeks	Phase 3: Clinical response at week six defined as a decrease from baseline in the Mayo score ≥30% and ≥3 points with either a rectal bleeding subscore of 0 to 1 or a decrease from baseline in the rectal bleeding subscore ≥1 Secondary: Phase 2: Not reported Phase 3: Clinical remission defined as Mayo score ≤2 points, with no individual subscore >1, mucosal healing defined as a Mayo endoscopy subscore of 0 or 1, and IBDQ change from baseline, all at week 6	In phase 3, the proportion of patients with clinical response at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (51.0 and 54.9 vs 30.3%; P≤0.0001 for both comparisons). Secondary: In phase 3, the proportion of patients in clinical remission at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (17.8 and 17.9 vs 6.4%; P≤0.0001 for both comparisons). In phase 3, the proportion of patients achieving mucosal healing at week six was greater for patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (42.3 and 45.1 vs 28.7%; P=0.0014 and P≤0.0001, respectively). In phase 3, the improvements from baseline in IBDQ score at week six were greater in patients treated with golimumab 200 mg/100 mg and 400 mg/200 mg compared to placebo (mean 27.0±33.72 and 26.9±34.28 vs 14.8±31.25%; P<0.0001 for both comparisons).

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subcutaneously at week 0 and 100 mg subcutaneously at week 2 (200 mg/100 mg) vs placebo Patients were required to maintain stable doses of concurrent oral aminosalicylates, oral corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX.				
Sandborn et al[133] (PURSUIT-M) Golimumab 50 mg SC every four weeks vs golimumab 100 mg SC every four weeks vs placebo Patients were required to maintain stable doses of concurrent oral aminosalicylates, oral	DB, MC, PC, RCT Patients ≥18 years of age with moderate to severe active ulcerative colitis (Mayo score of 6 to 12 with an endoscopy subscore ≥2) despite treatment with ≥1 conventional therapy (oral mesalamine, oral corticosteroids, azathioprine or 6-mercaptopurine) or corticosteroid dependent who	N=464 54 weeks	Primary: Clinical response through week 54 among golimumab-induction responders Secondary: Clinical remission at weeks 30 and 54, mucosal healing at weeks 30 and 54, clinical remission at both weeks 30 and 54 among patients who had clinical remission	Primary: The proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47.0 vs 31.2%; P<0.001 and P=0.010, respectively). Secondary: The proportion of patients in clinical remission at both weeks 30 and 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (27.8 and 23.2 vs 15.6%; P=0.004 and P=0.091, respectively); however, the difference was only statistically significant for golimumab 100 mg treatment group. The proportion of patients with mucosal healing at both weeks 30 and 54 was significantly greater for patients receiving golimumab 100 mg compared to placebo (42.4 vs 26.6%; P=0.002). The mucosal healing rate for patients receiving golimumab 50 mg was 41.7% (P value not reported). Greater proportions of patients who received golimumab 100 mg or 50 mg

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corticosteroids (<40 mg/day), azathioprine, 6-mercaptopurine, and/or MTX. After induction, patients in clinical response and receiving concomitant corticosteroids at baseline were required to taper corticosteroids (for dose of >20 mg/day prednisone or equivalent: taper daily dose by 5 mg/week; for dose of ≤20 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week) beginning at baseline.	completed PURSUIT-IV or PURSUIT-SC studies		at baseline, and corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at baseline	maintained clinical remission compared to placebo (40.4 and 36.5 vs 24.1%; P=0.073 and P=0.365, respectively); however, the differences were not statistically significant. Greater proportions of patients who received golimumab 100 mg or 50 mg were in corticosteroid-free clinical remission at week 54 compared to placebo (22.9 and 27.8 vs 18.4%; P=0.464 and P=0.299, respectively) ; however, the differences were not statistically significant.
Feagan et al[134] (GEMINI-1) Vedolizumab 300 mg intravenous at weeks 0 and 2 (induction) followed by vedolizumab 300 mg intravenous every four or eight weeks (maintenance) vs placebo Patients could continue to take mesalamine, ≤30 mg	DB, MC, PC, RCT Patients 18 to 80 years of age with ulcerative colitis (Mayo Clinic score of 6 to 12) with a sigmoidoscopy subscore of ≥2 and disease that extended ≥15 cm from the anal verge. All patients had a lack of response or unacceptable adverse events with ≥1 glucocorticoid,	N=895 52 weeks	Primary: Induction Clinical response at week six Maintenance Clinical remission at week 52 Secondary: Induction Clinical remission at week six Maintenance Durable clinical response	Primary: Induction In the double-blind cohort, clinical response at week six was achieved in 47.1 and 25.5% of patients treated with vedolizumab and placebo, respectively (95% CI, 11.6 to 31.7; P<0.001). In the open-label vedolizumab cohort, 44.3% achieved a clinical response and 19.2% achieved clinical remission. Maintenance A significantly greater proportion of patients treated with vedolizumab every four or eight weeks achieved clinical remission at week 52 compared to placebo (44.8 and 41.8% vs 15.9% respectively; 95% CI, 14.9 to 37.2; P<0.001). Secondary: Induction

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of prednisone (or equivalent) per day or immunosuppressive agents at stable doses.	immuno-suppresive agent or TNF antagonist.		(response at weeks 6 and 52), durable clinical remission (remission at weeks 6 and 52), glucocorticoid-free remission at week 52 in patients receiving glucocorticoids at baseline	Clinical remission was achieved in 16.9 and 5.4% of patients treated with vedolizumab and placebo, respectively (P=0.001). Maintenance Rates of durable clinical response, durable clinical remission, mucosal healing and glucocorticoid-free remission were higher among patients in the vedolizumab group compared to placebo. There was no difference observed between vedolizumab regimens. In addition, concurrent treatment with glucocorticoids or immunosuppressants or previous treatment with TNF antagonists did not substantively affect the efficacy of vedolizumab.
Neonatal-Onset Multisystem Inflammatory Disease				
Sibley et al[135] Anakinra 1 to 5 mg/kg/day	OL Patients with NOMID with at least 2 of the following clinical manifestations: urticaria-like rash, CNS involvement (papilledema, cerebrospinal fluid CSF pleocytosis, or sensorineural hearing loss), or epiphyseal and/or patellar overgrowth on radiographs	N=43 60 months	Primary: Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, CHAQ scores, parent's/patient's pain scores, and inflammatory markers (CRP level, ESR, and SAA) Secondary: Reduction or elimination CNS organ inflammation and damage and the absence of	Primary: Scores for daily diaries, parent's and physician's global assessment of disease activity, parent's assessment of pain, and C-HAQ decreased significantly from baseline to 36 months (P=0.0016 for C-HAQ and P<0.001 for all other assessments). These parameters did not show significant change from month 36 to month 60. Significant decreases in inflammatory markers (CRP level, ESR, and SAA) were observed from baseline to 12 months and from baseline to 36 months (all P<0.001). These parameters did not show significant change from month 36 to month 60. Secondary: CNS inflammation, including CSF leukocyte count and elevated opening pressure, decreased significantly at the study end points 36 and 60 months compared to baseline (P=0.0026 and P=0.0076, respectively, for CSF WBC count and P=0.0012 and P<0.001, respectively, for opening pressure). These parameters did not show significant change from month 36 to month 60. The number of patients with leptomeningeal enhancement decreased to three of 26 patients at 36 months (P=0.039) and one of 20 patients at 60 months (P=0.016).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			leptomeningeal enhancement on MRI, and in the eyes as the absence of eye inflammation on examination. Other endpoints include improvements in hearing, vision, bone lesions and growth, and safety.	Improvement in hearing occurred in 30% of ears, and progression of hearing loss was halted in the majority of the patients. Visual acuity and peripheral vision improved or stabilized in most patients over five years. One patient had worsening of visual acuity, and two other patients had worsening of peripheral vision in the absence of clinically detectable intraocular inflammation. (Note-All three of these patients had severely atrophic nerves at baseline). Bony overgrowth was present in 10 of 26 patients, and during the study period the volume of the bony lesions increased significantly; however, no new bone lesions developed in patients while they were receiving anakinra therapy. No dose-limiting toxicity was observed during the study. Upper respiratory infections (58 to 62%), rash (27 to 32%), malaise (17 to 19%) gastroenteritis (11 to 12%), and urinary tract infections (4 to 12%), nausea/vomiting (10 to 11%) injection site reactions (1 to 10%) were frequently observed.
Lachmann et al[136] Part-1 Canakinumab 150 mg once Part-2 Canakinumab 150 mg every eight weeks vs placebo Part-3 Canakinumab 150 mg	DB, MC, PC, RCT 3-part study Patients with a CAPS diagnosis 4 to 75 years of age with a weight of ≥ 15 kg and < 100 kg Part-1 All patients received canakinumab Part-2 Patients with a	N=35 48 weeks Part-1: 8 weeks Part-2: 24 weeks Part-3: 16 weeks	Primary: Proportion of patients with CAPS relapse during treatment compared to placebo in Part 2 Secondary: Proportion of patients with a complete response in Part 1, values of inflammatory markers, global	Primary: All patients in the canakinumab treatment group 15 (100%) remained in remission. In contrast, 13 of the 16 patients in the placebo group (81%) had a disease flare (P<0.001). Secondary: Of the 35 patients enrolled in the study 34 (97%) had a complete response to a single dose of canakinumabtreatment. CAPS symptoms diminished within 24 hours in patients who experienced a response. A complete response was experience by day-8 in 25 patients, by day-15 by eight patients and by day-29 in one patient. By the end of Part 2, CRP levels and SAA levels were normal in the canakinumab group having increased by 1.1 mg/liter and 2.3 mg/liter respectively. This is in contrast to the placebo group where CRP levels increased by 19.9 mg/liter and SAA levels by 71.1 mg/liter. Differences in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every eight weeks for a minimum of two doses	complete response from treatment in Part-1 Part-3 Patients who completed Part 2 or at the time of relapse		assessments scores by physicians and patients, safety	levels were statistically significant (P<0.001and P=0.002, respectively). By the end of Part 2, all patients in the canakinumab group were rated by physicians as having no or minimal disease activity compared to 25% of patients in the placebo group (P<0.001). By the end of Part 2, 40% of patients in the canakinumab group reported having no or minimal disease activity compared to no patients in the placebo group (P=0.28). At the final assessment of third part of the study, 30 of the 31 patients (97%) who had entered the final phase had no or minimal disease activity, with the remaining having only mild disease activity. No P values were reported. No deaths or life-threatening adverse events occurred. Two patients, one case of urosepsis, and one case of vertigo, had serious adverse events while receiving canakinumab during Part 3 causing both to discontinue the study. The use of canakinumab was not associated with a clear pattern of adverse events other than an increase in the rate of suspected infections (P=0.03). In Part 2, 87% receiving canakinumab and 94% receiving placebo reported no injection site reactions. No immunogenicity against canakinumab was detected.
Study Part A (PI)[3] Rilonacept 320 mg load followed by 160 mg weekly vs placebo	DB, PC, PG, RCT Patients with FCAS and MWS, 22 to 78 years of age Note: Six patients 12 to 17 years of age were enrolled directly into the open-label	N=47 6 weeks	Primary: Mean symptom score using the change from baseline to the end of treatment Secondary: Patients experiencing 30%, 50%, and	Primary: Rilonacept-treated patients showed a statistically significant reduction in mean symptom score compared to placebo. The mean symptom scores were 3.1 vs 2.4 at baseline and 0.5 vs 2.1 at endpoint resulting in a –2.4 vs –0.5 adjusted difference for rilonacept vs placebo, respectively (CI, –2.4 to –1.3; P value not reported). Secondary: A higher percentage of rilonacept-treated patients experienced ≥30%, ≥50, and ≥75% improvements in composite score compared to placebo (96% vs 29%, 87% vs 8%, and 70% vs 0%, respectively; P values not reported). In rilonacept-treated patients, mean levels of SAA and CRP were reduced at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	extension phase		75% improvements in composite score, SAA, CRP	baseline compared with week 6 (60 mg/ L vs 4 mg/L and 22 mg/L vs 2 mg/L, respectively). Mean levels of SAA and CRP in the placebo group at baseline and week six were 110 mg/ L vs 110 mg/L and 30 mg/L vs 28 mg/L, respectively (P values not reported).
Study Part B (PI)[3] Rilonacept 160 mg weekly for first nine weeks followed by rilonacept 160 mg weekly vs placebo	SB for first nine weeks followed by DB, PC, PG, RCT for second nine weeks Patients with FCAS and MWS, 22 to 78 years of age	N=47 18 weeks	Primary: Mean symptom score using the change from baseline to the end of treatment Secondary: Not reported	Primary: The mean symptom scores increased more in patients withdrawn to placebo compared to patients who continued rilonacept. The mean symptom scores were 0.3 vs 0.2 at baseline and 0.4 vs 1.2 at endpoint resulting in a 0.1 vs 0.9 adjusted difference for rilonacept vs placebo, respectively (CI, –1.3 to –0.4, P value not reported). Secondary: Not reported

*Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=alanine transaminase, AS=ankylosing spondylitis, ASAS=Assessment of Spondyloarthritis International Society criteria, AST=aspartate aminotransferase, AUC=area under the curve, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CDAI-100=Crohn's disease activity index decrease of ≥100 points from baseline, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=clinical remission, CR-100=clinical remission 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, CT=computed tomography, DAS 28=Disease Activity Score in 28 joints, DLQI=Dermatology Life Quality Index, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL=electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI=Harvey-Bradshaw index, HCQ=hydroxychloroquine, HDL=high density lipoprotein, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JIA=juvenile idiopathic arthritis, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, LDL=low density lipoprotein, MCR=major clinical response, MRE=magnetic resonance enterography, MRI=magnetic resonance imaging, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, SIAQ=Self-Injection Assessment Questionnaire, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA=serum amyloid A, SMD=standardized mean differences, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1-15]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Abatacept	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children six years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Adalimumab	No evidence of overall differences in efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children four years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Anakinra	No evidence of overall differences in efficacy observed between	Renal dose adjustment is required; for	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	elderly and younger adult patients. Approved for use in children for the treatment of neonatal onset multisystem inflammatory disease. Safety and efficacy in the pediatric population have not been established for other indications.	creatinine clearances <30 mL/ minute, a dose of 100 mg for rheumatoid arthritis or 1 to 2 mg/kg for neonatal onset multisystem inflammatory disease every other day is recommend-ed.			
Canakinumab	Not studied in elderly. Approved for use in children ages 4 to 18 years of age. Efficacy and safety in the pediatric population was found to be similar to the adult population.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Certolizumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Etanercept	No evidence of overall differences in efficacy observed between elderly and younger adult patients. Approved for use in children two years of age and older for the treatment of juvenile idiopathic arthritis. Safety and efficacy in the pediatric population have not	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	been established for other indications.				
Golimumab	Simponi®: No evidence of overall differences in efficacy observed between elderly and younger adult patients. Safety and efficacy in the pediatric population have not been established. Simponi Aria®: Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Infliximab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients for the treatment of rheumatoid arthritis and psoriasis. Safety and efficacy in elderly patients have not been established for the treatment of ankylosing spondylitis, Crohn's disease, psoriatic arthritis or ulcerative colitis. Approved for use in children six years of age and older for the treatment of Crohn's disease and ulcerative colitis. Safety and efficacy in the pediatric population have not been established for	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	other indications.				
Rilonacept	Age differences do not appear to have any significant effects on steady-state trough concentrations. However, limited data is available for this population. Safety and efficacy in patients <12 years has not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Secukinumab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Tocilizumab	Frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children two years of age and older for the treatment of systemic and polyarticular juvenile idiopathic arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	No dosage adjustment required in mild renal impairment. Not studied in patients with moderate to severe renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Tofacitinib	Frequency of serious infection and malignancy was higher in patients ≥65 years of age. Safety and efficacy in the pediatric population have not been established.	Renal dose adjustment is required; dose reduction to 5 mg once daily is recommended in moderate to severe renal	Hepatic dose adjustment is required; dose reduction to 5 mg once daily is recommended in moderate hepatic impairment;	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		impairment; not studied in patients with creatinine clearance <40 mL/minute.	not studied in patients with severe hepatic impairment.		
Ustekinumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Vedolizumab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Adverse Drug Events

The anti-tumor necrosis factor-α agents (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) share similar adverse event profiles including risk of reactivation of latent tuberculosis, severe infection, heart failure, lupus-like syndrome, and lymphoma. Table 6 highlights the adverse drug events with a focus on those noted in ≥5% of study populations.

Table 6. Adverse Drug Events (%)[1-15,39,40]

Adverse Event	Abatacept	Adalimumab	Anakinra*	Canakinumab	Certolizumab	Etanercept	Golimumab†	Infliximab	Rilonacept	Secukinumab	Tocilizumab	Tofacitinib	Ustekinumab	Vedolizumab
Gastrointestinal														
Abdominal pain	-	7	5	2.4 to 16	-	5 to 10	-	12	4	-	-	-	-	-
Diarrhea	-	-	7	7	-	8 to 16	-	12	4	2.6 to 4.1	-	-	-	-
Dyspepsia	6	-	-	-	-	4 to 11	-	10	-	-	-	-	-	-
Gastroenteritis	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Nausea	≥10	9	8	5	-	9 to 15	-	21	4	-	-	-	-	9
Vomiting	-	-	14‡	-	-	3 to 5	-	-	-	-	-	-	-	-
Laboratory Tests														
Abnormal test	-	8	-	-	-	-	-	-	-	-	3 to 6	-	-	-
Alkaline phosphatase increased	-	5	-	-	-	-	-	-	-	-	-	-	-	-
Hematuria	-	5	-	-	-	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	6	-	-	-	-	-	-	-	-	-	-	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory														
Bronchitis	5 to 13	-	-	4	3	-	-	10	-	-	-	-	-	-
Coughing	8	-	-	-	-	5 to 6	-	12	9	-	-	-	-	5
Flu syndrome	-	7	-	-	-	-	-	14	-	11.4 to 12.3	-	-	-	-
Nasopharyngitis	12	-	-	12	5	-	-	-	-	-	4 to 7	-	7 to 8	13
Non-upper respiratory infection	-	-	-	-	-	21 to 54	-	-	-	-	-	-	-	-
Pharyngitis	-	-	11.6‡	4	3	6 to 7	-	-	-	-	-	-	-	-
Respiratory disorder	-	-	-	-	-	5	-	-	-	-	-	-	-	-
Rhinitis	-	-	-	6	-	12 to 16	-	-	-	1.4	-	-	-	-
Sinusitis	5 to 13	11	7	-	-	3 to 5	-	14	9	-	-	-	-	-
Upper respiratory infection	≥10	17	14	6	6	38 to 65	13§ to 16	32	26	2.5 to 3.2	6 to 8	-	4 to 5	7
Skin														
Pruritus	-	-	-	-	-	-	-	7	-	-	-	-	-	-
Rash	-	12	-	-	3	3 to 13	-	10	-	-	-	-	-	-
Other														
Accidental injury	-	10	-	-	-	-	-	-	-	-	-	-	-	-
Alopecia	-	-	-	-	-	1 to 6	-	-	-	-	-	-	-	-
Arthralgia	-	-	6, 11.6‡	-	-	-	-	-	-	-	-	-	-	12

Adverse Event	Abatacept	Adalimumab	Anakinra*	Canakinumab	Certolizumab	Etanercept	Golimumab†	Infliximab	Rilonacept	Secukinumab	Tocilizumab	Tofacitinib	Ustekinumab	Vedolizumab
Asthenia	-	-	-	-	-	5 to 11	-	-	-	-	-	-	-	-
Back pain	7	6	-	-	4	-	-	8	-	-	-	-	-	-
Body pain	-	-	-	-	-	-	-	8	-	-	-	-	-	-
Dizziness	9	-	-	-	-	7 to 8	-	-	-	-	-	-	-	-
Fatigue	-	-	-	-	3	-	-	9	-	-	-	-	-	6
Fever	-	-	11.6‡	-	3	2 to 3	-	7	-	-	-	-	-	-
Flu like symptoms	-	-	6	-	-	-	-	-	-	-	-	-	-	-
Headache	18	12	12, 14‡	5	5	17 to 24	-	18	-	-	5 to 7	-	5	12
Hypertension	7	5	-	-	5	-	-	7	-	-	4 to 6	-	-	-
Infections (overall)	-	-	-	12 to 55	-	-	-	-	48	18.9 to 47.5	20	-	-	-
Injection site pain	-	12	-	-	-	-	-	-	-	-	-	-	-	-
Injection site reaction	-	8	16‡, 71	9	-	37 to 43	6	-	48	-	7.1‖ to 10.1‖	-	-	-
Moniliasis	-	-	-	-	-	-	-	5	-	-	-	-	-	-
Mouth ulcer	-	-	-	-	-	2 to 6	-	-	-	-	-	-	-	-
Muscle Pain	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Oral Herpes	-	-	-	-	-	-	-	-	-	0.1 to 1.3	-	-	-	-
Peripheral edema	-	-	-	-	-	2 to 8	-	-	-	-	-	-	-	-
Pyrexia	-	-	-	-	-	-	-	-	-	-	-	-	-	9
Urinary tract infection	6	8	-	-	-	-	-	8	4	-	-	-	-	-
Vertigo	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Viral infection	-	-	-	-	-	-	5	-	-	-	-	-	-	-
Weight Gain	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Worsening of rheumatoid arthritis	-	-	19	-	-	-	-	-	-	-	-	-	-	-

-Event not reported or incidence <5%.
*Unless otherwise specified, adverse reaction observed in patients treated for rheumatoid arthritis.
†With or without disease modifying antirheumatic agents. Unless otherwise specified, adverse reaction observed in patients treated with subcutaneous formulation.
‡Neonatal-onset multisystem inflammatory disease during the first six months of therapy.
§Intravenous formulation (Simponi Aria®) only.
‖Subcutaneous formulation only.

Contraindications/Precautions

The immunomodulators are contraindicated in patients with a known hypersensitivity to any of the agents or to any component of the individual products.[3-17] Patients treated concomitantly with abatacept or anakinra and anti-tumor necrosis factor (TNF) agents experienced more infections than patients treated with TNF agents alone. There was no significant increase in efficacy with combination therapy; therefore, concomitant administration of abatacept or anakinra and TNF agents is not recommended.[3-17]

Serious and sometimes fatal infections have been reported with abatacept. Live vaccines should not be given concurrently or within three months of discontinuation with abatacept. Patients with chronic pulmonary obstructive disease treated with abatacept developed adverse reactions associated with worsening of their respiratory symptoms. Due to the inhibition of T-cell activation by abatacept, host defenses against infections and malignancies may be affected.[13]

Anakinra is contraindicated in patients with a known hypersensitivity to *Escherichia coli*-derived proteins. Serious infections have been associated with anakinra and should not be initiated in patients with active infections. In rheumatoid arthritis, discontinue use if serious infection develops. In neonatal-onset multisystem inflammatory disease (NOMID) patients, the risk of a NOMID flare when discontinuing anakinra treatment should be weighed against the potential risk of continued treatment. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have occurred with anakinra. Live vaccines are not recommended to be given concurrently with anakinra. Combination therapy with a TNF blocking agent is not recommended. Decreases in neutrophil count have been reported with anakinra.[1]

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. Additionally, viral reactivation, gastrointestinal perforations, and increased lipid levels were reported with tocilizumab. The impact of tocilizumab on demyelinating disorders is not known, although multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were rarely reported in clinical trials. Caution should be used when considering tocilizumab in patients with preexisting or recent onset demyelinating disorders. Treatment is not recommended in patients with an increased incidence of neutropenia, reduced platelets, increased transaminase levels, or in patients with active hepatic disease or hepatic impairment. Hypersensitivity reactions, including anaphylaxis reactions and death, have been reported with tocilizumab. Live vaccines are not recommended to be given concurrently with tocilizumab.[4]

Ustekinumab is associated with an increased risk of infections and reactivation of latent infections. In addition, serious infection requiring hospitalization have been reported in clinical trials, including diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with ustekinumab. Ustekinumab may increase the risk of malignancies. Live vaccines are not recommended to be given concurrently with ustekinumab.[6]

Serious and sometimes fatal infections have been reported in patients receiving tofacitinib, including pneumonia, cellulitis, herpes zoster, and urinary tract infection. Opportunistic infections included tuberculosis and other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, and cytomegalovirus. Some patients have presented with disseminated rather than localized disease and were often taking concomitant immunomodulating agents (e.g., methotrexate, corticosteroids). Treatment should not be initiated in patients with an active infection and should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. The risks and benefits of treatment should be considered prior to initiation in patients with chronic or recurrent infection, who have been exposed to tuberculosis, with a history of a serious opportunistic infection, who have resided or traveled in areas of endemic tuberculosis or mycoses or with underlying conditions that may predispose them to infection.[14]

In clinical trials, treatment with tofacitinib has resulted in viral reactivation, including cases of herpes virus reactivation. Screening for viral hepatitis should be performed before initiating tofacitinib.[14]

Malignancies were observed in clinical studies of tofacitinib. Risks and benefits of treatment should be considered prior to initiating therapy in patients with malignancy other than successfully treated non-melanoma skin cancer. Non-melanoma skin cancers have been reported in patients treated with tofacitinib. As such, periodic skin examination is recommended for patients at increased risk for skin cancer. Gastrointestinal perforation has been reported in clinical studies with tofacitinib; caution should be used in patients who may be at increased risk (e.g., history of diverticulitis). Treatment with tofacitinib is also associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Lymphocyte and neutrophil counts and hemoglobin level should be monitored at baseline and during treatment. Treatment with tofacitinib was associated with an increased incidence of neutropenia compared to placebo. As such, initiation of tofacitinib should be avoided in patients with a low neutrophil count. Treatment with tofacitinib should be avoided in patients with a low hemoglobin level and treatment should be interrupted in patients who develop hemoglobin levels <8g/dL or whose hemoglobin level drops >2 g/dL on treatment.[14]

Treatment with tofacitinib is associated with an increased incidence of liver enzyme elevation compared to placebo, particularly with background disease modifying antirheumatic drug therapy. Monitoring of liver enzymes is recommended and treatment should be interrupted if drug-induced liver injury is suspected. [14]

Treatment with tofacitinib is associated with increases in lipid parameters including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined. Lipid parameters should be monitored approximately four to eight weeks following initiation of therapy.[14]

Patients should be brought up-to-date on vaccines in accordance with current vaccine guidelines prior to initiating tofacitinib.[14]

In clinical trials, hypersensitivity reactions occurred with vedolizumab, including a case of anaphylaxis in one patient. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing rash and increased blood pressure and heart rate have been observed. If serious allergic reactions or anaphylaxis occur, vedolizumab should be discontinued immediately and appropriate treatment should be initiated (e.g., epinephrine, antihistamines).[15]

Patients treated with vedolizumab are at increased risk for infection, with the most commonly reported infections in clinical trials involving the upper respiratory and nasal mucosa. Serious infections have also been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.[15]

Given that another integrin receptor antagonist had been associated with progressive multifocal leukoencephalopathy (PML), patients treated with vedolizumab in clinical trials were actively monitored for the development of PML. Although no cases of PML were identified over 24 months of exposure, the risk of PML cannot be ruled out.[15]

Treatment with vedolizumab has been associated with elevations of transaminase and/or bilirubin. vedolizumab should be discontinued in patients with jaundice or other signs of liver injury.[15]

Prior to initiating vedolizumab, patients should be brought up-to-date with all immunizations according to current guidelines. Although patients treated with vedolizumab may receive non-live vaccines, live vaccines should be administered only if the benefits outweigh the risks.[15]

Treatment with immunosuppressants, including canakinumab and rilonacept, may result in an increase in the risk of malignancies. Hypersensitivity reactions have been reported with both agents. Live vaccines should not be given concurrently with canakinumab or rilonacept. Macrophage activation syndrome (MAS) is a known, life-threatening disorder that may develop in patients with rheumatic conditions and treated with canakinumab, and should be aggressively treated.[2,3]

Evaluate patients for tuberculosis infection prior to initiating treatment with secukinumab. Exercise caution when prescribing secukinumab to patients with active Crohn's disease, as exacerbations of Crohn's disease, in some cases serious, were observed in secukinumab-treated patients during clinical trials. Anaphylaxis and cases of urticaria occurred in secukinumab-treated patients. The removable cap of the secukinumab Sensoready pen and the secukinumab prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals. Patients treated with secukinumab should not receive live vaccines.[5]

Numerous precautions are associated with the TNF-blockers (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), many of which are shared throughout the class and include:

- Infection, active or chronic (including localized), or history of recurrent infection; increased risk of developing a serious infection.
- Infections, serious (sepsis, tuberculosis, fungal, and other opportunistic infections); fatalities have been reported; discontinue if serious infection develops.
- Tuberculosis, history of latent or active; increased risk of developing infection; initiate treatment for latent tuberculosis before starting anti-TNF therapy.
- Tuberculosis, risk factors or potential exposure; infection should be ruled out prior to initiation of therapy.
- Central nervous system demyelinating disorder, preexisting or recent onset; risk for exacerbation.
- Close personal contact with person with active tuberculosis.
- Congestive heart failure; new-onset or worsening reported in patients with and without history.
- Hematologic abnormalities (e.g., pancytopenia, aplastic anemia) have been reported; discontinue if significant abnormalities develop.
- Hepatitis B virus carriers; risk of reactivation including after discontinuation of therapy, fatal outcomes have occurred; monitor for signs and symptoms of Hepatitis B virus infections during and for several months after adalimumab therapy and discontinue if Hepatitis B virus is reactivated.
- Live vaccine use or infectious agents such as live attenuated bacteria; not recommended.
- Malignancy; increased risk of lymphoma and possibly other malignancies such as breast, colon, prostate, lung, and melanoma.
- Lupus-like syndrome may occur secondary to autoantibodies[7-11]

Some of the immunomodulators are associated with boxed warnings, which are outlined below.

Black Box Warning for Adalimumab and Infliximab[7,10]

WARNING
Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with tumor necrosis factor blockers including Humira® and Remicade®. These cases have had a very aggressive disease course and have been fatal. All reported Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority was in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Humira® or Remicade® at or prior to diagnosis.

Black Box Warning for Tocilizumab[4]

WARNING
Serious Infections Patients treated with Actemra® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra® until the infection is controlled. Reported infections include: · Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra® use and during therapy. Treatment for

WARNING
latent infection should be initiated prior to Actemra® use. · Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. · Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with Actemra® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra®, including the possible development of tuberculosis in patients who tested negative for infection prior to initiating therapy.

Black Box Warning for adalimumab, certolizumab pegol, etanercept, golimumab, infliximab[7-11]

WARNING
Serious Infections Patients treated with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Cimzia®, Enbrel®, Humira®, Remicade® and Simponi® should be discontinued if a patient develops a serious infection or sepsis. Reported infections include: · Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Cimzia®, Enbrel®, Remicade®, or Simponi® use and during therapy. Treatment for latent infection should be initiated prior to Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® use. · Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. · Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria. The risks and benefits of treatment with Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Malignancy Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are members.

Black Box Warning for Tofacitinib[14]

WARNING
Serious Infections Patients treated with Xeljanz® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant

WARNING

immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Xeljanz® until the infection is controlled. Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease.
- Patients should be tested for latent tuberculosis before Xeljanz® use and during therapy.
- Treatment for latent infection should be initiated prior to Xeljanz® use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Xeljanz® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Xeljanz®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies
Lymphoma and other malignancies have been observed in patients treated with Xeljanz®. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Xeljanz® and concomitant immunosuppressive medications.

Drug Interactions

Cytokines such as interleukin (IL)-6 have been shown to decrease the expression of CYP450 isoenzymes in patients with infections and inflammatory conditions such as rheumatoid arthritis. Inhibition of IL-6 signaling in rheumatoid arthritis patients treated with tocilizumab may restore CYP450 activities to normal levels which would have the potential to increase the metabolism of CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes (1A2, 2B6, 2C9, 2C19, 2D6, and 3A4). Upon initiation or discontinuation of tocilizumab it is recommended that therapeutic monitoring for any medication with a narrow therapeutic index be initiated and the dose of the medication be adjusted as needed.[4]

Table 7. Drug Interactions[40]

Generic Name	Interacting Medication or Disease	Potential Result
Abatacept, adalimumab, anakinra, canakinumab certolizumab, etanercept, golimumab, infliximab, rilonacept, secukinumab, tocilizumab, ustekinumab	Live vaccines	Concomitant use may result in an increased risk of secondary transmission of infection by the live vaccine.
Interleukin-receptor blockers	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Interleukin-receptor blockers	CYP450 substrates with a narrow therapeutic index	Increased cytokine levels (interleukins) suppress the effect of CYP450 and should be normalized with interleukin-receptor blocking agents. Monitor effect of agents that may have metabolism increased.
Tumor Necrosis Factor Blocking Agents	Other biologic immunomodulators	Concurrent use may increase the risk of infections.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing

Generic Name	Interacting Medication or Disease	Potential Result
		noncutaneous solid malignancies.
Infliximab	Tocilizumab	Concurrent use may increase immunosuppression and the risk of infections.
Tofacitinib	Biological DMARDs	Concurrent use may increase the risk of serious infections. Coadministration should be avoided.
Tofacitinib	CYP2C19 potent and CYP3A moderate inhibitors (e.g., fluconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inhibitors (e.g., ketoconazole)	Concurrent use may elevate tofacitinib concentrations, increasing the pharmacologic effects and risk of adverse reactions; the dose of tofacitinib should be reduced to 5 mg once daily.
Tofacitinib	CYP3A strong inducers (e.g., rifampin)	Concurrent use may reduce tofacitinib concentrations, decreasing the clinical response. Coadminister with caution. Close clinical monitoring is warranted.
Tofacitinib	Immunosuppressants (e.g., azathioprine, cyclosporine, tacrolimus)	Concurrent use may increase the risk of added immunosuppression and serious infections. Coadministration of tofacitinib with potent immunosuppressants should be avoided.

DMARD=disease-modifying antirheumatic drug

Dosage and Administration

Table 8. Dosing and Administration[3-15]

Generic Name	Adult Dose	Pediatric Dose	Availability
Abatacept	Rheumatoid arthritis: Prefilled syringe and single use vial: initial (<60 kg), 500 mg IV over 30 minutes at weeks zero, two and four; (60 to 100 kg), 750 mg IV over 30 minutes at weeks zero, two and four; (>100 kg), 1,000 mg IV over 30 minutes at weeks zero, two and four; maintenance (<60 kg), 500 mg IV over 30 minutes every four weeks; (60 to 100 kg), 750 mg IV over 30 minutes every four weeks; (>100 kg), 1,000 mg IV over 30 minutes every four weeks or initial (<60 kg), 500 mg IV over 30 minutes followed by 125 mg SC within 24 hours; 750 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (>100 kg), 1,000 mg IV over 30 minutes followed by	Juvenile idiopathic arthritis (six to 17 years of age): Prefilled syringe and single use vial: initial, (<75 kg),10 mg/kg IV over 30 minutes at weeks zero, two and four; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV	Prefilled syringe: 125 mg/mL Single use vial: 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	125 mg SC within 24 hours; maintenance, 125 mg SC every four weeks	over 30 minutes every four weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose	
Adalimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week Crohn's disease, ulcerative colitis: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29) Plaque psoriasis: Prefilled pen and syringe, single use vial: initial, 80 mg SC; maintenance, 40 mg SC every other week starting one week after the initial dose Rheumatoid arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate	Juvenile idiopathic arthritis (four to 17 years of age): 15 to <30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other week There is limited data in pediatric patients with a weight <15 kg.	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL
Anakinra	CAPS: NOMID: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily Rheumatoid arthritis: Prefilled syringe: initial, 100 mg SC daily; maintenance, 100 mg SC daily	Neonatal-onset multisystem inflammatory disease: Prefilled syringe: initial: 1 to 2 mg/kg daily; maintenance, maximum of 8 mg/kg daily	Prefilled syringe: 100 mg/0.67 mL
Canakinumab	CAPS: FCAS or MWS: Vial: initial (≥15 to <40 kg), inject 2 mg/kg SC every eight weeks; initial (≥40 kg), 150 mg SC every eight weeks; maximum (≥15 to <40 kg), 3 mg/kg; maximum (≥40 kg), 150 mg SC every eight weeks	Systemic juvenile idiopathic arthritis (≥2 years of age): Vial: initial (≥7.5 kg), 4 mg/kg SC every four weeks, maximum: 300 mg SC every four weeks	Vial: 180 mg (150 mg/mL)
Certolizumab	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis:	Safety and efficacy in the pediatric	Prefilled syringe:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks two and four; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every four weeks Crohn's disease: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 400 mg SC (as two SC injections of 200 mg) once every four weeks	population have not been established.	200 mg/mL Vial (powder for injection): 200 mg
Etanercept	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled autoinjector and syringe and vial: initial/maintenance, 50 mg SC weekly Plaque psoriasis: Prefilled autoinjector and syringe and vial: initial, 50 mg SC twice weekly for three months; maintenance, 50 mg SC weekly	Juvenile idiopathic arthritis (two to 17 years of age): Prefilled autoinjector and syringe and vial: initial and maintenance (<63 kg), 0.8 mg/kg SC weekly; (≥63 kg), 50 mg SC weekly	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg
Golimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly; maintenance, 50 mg SC once monthly Rheumatoid arthritis: Prefilled autoinjector and syringe: initial, 50 mg SC once monthly in combination with methotrexate; maintenance, 50 mg SC once monthly in combination with methotrexate Vial (Simponi Aria®): initial, 2 mg/kg IV over 30 minutes at weeks zero and four; maintenance, 2 mg/kg IV over 30 minutes every eight weeks; all in combination with methotrexate Ulcerative colitis: Prefilled autoinjector and syringe: initial, 200 mg SC once, followed by 100 mg SC at week two; maintenance, 100 mg SC once every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL 100 mg/mL Prefilled syringe: 50 mg/0.5 mL 100 mg/mL Single use vial (Simponi Aria®): 50 mg/4 mL
Infliximab	Ankylosing spondylitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every six weeks	Crohn's disease, ulcerative colitis (six years of age and older): Vial: initial, 5 mg/kg	Single use vial: 100 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Crohn's disease: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg in patients who respond and then lose response Plaque psoriasis, psoriatic arthritis, ulcerative colitis : Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks Rheumatoid arthritis: Vial: initial, 3 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 3 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg IV over two hours every eight weeks or 3 mg/kg IV over two hours every four weeks if incomplete response; all in combination with methotrexate	IV over two hours at weeks zero, two and six; maintenance, 5 mg/kg IV over two hours every eight weeks	
Rilonacept	CAPS: FCAS/MWS: Vial: loading dose, 320 mg SC (160 mg at two different sites); then 160 mg SC once weekly	CAPS: FCAS/MWS (≥2 years of age): Vial: loading dose, 4.4 mg/kg SC (maximum: 320 mg) as one or two injections with a maximum volume of 2 mL; then 2.2 mg/kg (maximum 160 mg) SC once weekly.	Vial: 220 mg (80 mg/mL)
Secukinumab	Plaque psoriasis: Pen, syringe, vial: Initial, 300 mg (two injections of 150 mg) SC at weeks 0, 1, 2, 3, and 4; some patients may only need 150 mg; maintenance, 300 mg (two injections of 150 mg) SC every four weeks; some patients may only need 150 mg.	Safety and efficacy in the pediatric population have not been established.	Prefilled pen, syringe: 150 mg/mL Vial: 150 mg/mL
Tocilizumab	Rheumatoid arthritis: Prefilled syringe: initial and maintenance (<100 kg), 162 mg SC every other week, followed by 162 mg SC every week; (≥100 kg), 162 mg SC every week Vial: initial, 4 mg/kg IV every four weeks as a 60 minute infusion; maintenance, dose may be increased to 8 mg/kg IV every four weeks; maximum, 800 mg/infusion	Polyarticular juvenile idiopathic arthritis (two years of age and older): Vial: initial and maintenance (<30 kg), 10 mg/kg IV every four weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every four weeks as a 60	Prefilled syringe: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
		minute infusion Systemic juvenile idiopathic arthritis (two years of age and older): Vial: initial and maintenance (<30 kg), 12 mg/kg IV every two weeks as a 60 minute infusion; (≥30 kg), 8 mg/kg IV every two weeks as a 60 minute infusion	
Tofacitinib	Rheumatoid arthritis: Tablet: 5 mg by mouth twice daily	Safety and efficacy in the pediatric population have not been established.	Tablet: 5 mg
Ustekinumab	Plaque psoriasis (with or without psoriatic arthritis): Prefilled syringe and single use vial: initial (≤100 kg), 45 mg SC followed by 45 mg four weeks later; (>100 kg), 90 mg SC followed by 90 mg SC four weeks later; maintenance (≤100 kg), 45 mg SC every 12 weeks; (>100 kg), 90 mg SC every 12 weeks Psoriatic arthritis: Prefilled syringe and single use vial: initial, 45 mg SC followed by 45 mg four weeks later; maintenance, 45 mg SC every 12 weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vial: 45 mg/0.5 mL 90 mg/mL
Vedolizumab	Crohn's disease: Injection: initial, 300 mg IV at zero, two and six weeks; maintenance, 300 mg IV every eight weeks. Ulcerative colitis: Injection: initial, 300 mg IV at zero, two and six weeks; maintenance, 300 mg IV every eight weeks.	Safety and efficacy in the pediatric population have not been established.	Single use vial: 300 mg/20 mL

IV=intravenously, SC=subcutaneously
CAPS=Cryopyrin-Associated Periodic Syndromes, FCAS= Familial Cold Autoinflammatory Syndrome, JIA=juvenile Idiopathic Arthritis, MWS=Muckle-Wells Syndrome, NOMID=Neonatal-Onset Multisystem Inflammatory Disease

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Assessment of Spondyloarthritis International Society/European	· Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic

Clinical Guideline	Recommendations
League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[18]	indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. · Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. · Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. · Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. · Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. · Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. · Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence. · There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. · Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in AS. · Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.
Assessment of	· All patients should have had adequate therapeutic trials of at least two

Clinical Guideline	Recommendations
Spondyloarthritis International Society: **2010 Update of the International Assessment of Spondyloarthritis International Society Recommendations for the Use of Anti-Tumor Necrosis Factor Agents in Patients with Axial Spondyloarthritis (2010)**[19]	NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a four-week period in total at a maximum recommended dose unless contraindicated. · Patients with pure axial manifestations do not have to take DMARDs before TNF-α inhibitor treatment can be started. · Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate, and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine. · Patients with symptomatic enthesitis must have failed appropriate local treatment.
National Institute for Health and Clinical Excellence: **Adalimumab, Etanercept and Infliximab for Ankylosing Spondylitis (2008)**[20]	· Adalimumab or etanercept are recommended as treatment options for adults with severe active AS only if all of the following criteria are fulfilled: o The patient's disease satisfies the modified New York criteria for diagnosis of AS. o There is confirmation of sustained active spinal disease, demonstrated by: a score of at least four units on the Bath AS Disease Activity Index and at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (these should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment). o Conventional treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended dosage for four weeks has failed to control symptoms. · It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should only be continued in the presence of an adequate response. · Infliximab is not recommended for the treatment of AS; patients currently receiving infliximab for the treatment of AS should have the option to continue therapy until they and their clinicians consider it appropriate to stop. · Golimumab was not incorporated into the guidelines at last publication due to the recent Food and Drug Administration (FDA) approval (April 24, 2009).
National Institute for Health and Clinical Excellence: **Golimumab for the treatment of Ankylosing Spondylitis (2011)**[21]	· Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if it is used as described for adalimumab and etanercept in NICE Guideline (2008) 'Adalimumab, etanercept and infliximab for ankylosing spondylitis'.
American College of Gastroenterology: **Management of Crohn's Disease in Adults (2009)**[22]	Mild to moderate active disease · Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2 to 4.0 g daily or sulfasalazine for ileocolonic or colonic disease as 3 to 6 g daily in divided doses. · Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared to placebo and less effective than budesonide or conventional corticosteroids.

Clinical Guideline	Recommendations
	· Alternatively, metronidazole at a dose of 10 to 20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine. · Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon. · Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with Crohn's disease. <u>Moderate to severe disease</u> · Patients with moderate to severe disease are treated with prednisone 40 to 60 mg daily until resolution of symptoms and resumption of weight gain (generally seven to 28 days). · Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). · Elemental diets are less effective than corticosteroids, but can avoid corticosteroid-induced toxicities. · Azathioprine and 6-mercaptopurine are effective for maintaining a steroid induced remission, and parenteral methotrexate at a dose of 25 mg/week is effective for steroid-dependent and steroid-refractory Crohn's disease. · The TNF-α inhibitors, adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active Crohn's disease in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. · Infliximab monotherapy and infliximab in combination with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. · Adalimumab, certolizumab, and infliximab may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. · The anti-alpha 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active Crohn's disease who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies and TNF-α inhibitor therapy. <u>Severe/fulminant disease</u> · Because of the acuteness and diversity of presentation of patients with severe Crohn's disease and the potential for development of complications, the management decisions for these patients are based more on practicality than controlled trial evidence. · Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an TNF-α inhibitor (adalimumab or infliximab), or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. · Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass. · An abdominal mass should be evaluated through transabdominal ultrasound, magnetic resonance imaging scan. · Once the presence of an abscess has been excluded or if the patient has been receiving oral corticosteroids, parenteral corticosteroids equivalent to 40 to 60 mg of prednisone daily or its equivalent are administered in divided doses or as a continuous infusion.

Clinical Guideline	Recommendations
	· There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after five to seven days, for patients who are unable to maintain adequate nutritional requirements. Perianal and fistulizing disease · Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons. · Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives or infliximab. Maintenance therapy · Mesalamine and sulfasalazine have not had consistent maintenance benefits after medical inductive therapy. · Conventional corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. · Budesonide at a dose of 6 mg/day reduces the time to relapse in ileal and/or right colonic disease, but does not provide significant maintenance benefits after six months. · Azathioprine/6-mercaptopurine and methotrexate have demonstrable maintenance benefits after inductive therapy with corticosteroids. · Azathioprine can maintain remissions induced by infliximab in steroid-naive patients. · Maintenance therapy with adalimumab, certolizumab, and infliximab is effective. · Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. · Maintenance therapy with natalizumab is effective. · Infliximab, mesalamine, metronidazole or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence, whereas conventional corticosteroids and budesonide at a dose of 6 mg/day are not effective.
National Institute for Health and Clinical Excellence: **Crohn's Disease Management in Adults, Children and Young People (2012)**[23]	Monotherapy · Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. · Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for: o Children in whom there is concern about growth or side effects. o Young people in whom there is concern about growth. · In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. · In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. · Do not offer budesonide or 5-ASA treatment for severe presentations or

Clinical Guideline	Recommendations
	exacerbations. · Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. <u>Combination therapy</u> · Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. · Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). · Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. <u>Infliximab and adalimumab</u> · Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. · Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. · People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again. <u>Remission maintenance</u> · For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications. · Consider methotrexate to maintain remission only in patients who: o Needed methotrexate to induce remission. o Did not tolerate azathioprine or mercaptopurine for maintenance. o Contraindicated to azathioprine or mercaptopurine. · Do not offer conventional glucocorticosteroids or budesonide to maintain remission. <u>Remission maintenance following surgery</u> · After surgery ,consider azathioprine or mercaptopurine to maintain remission in people with factors such as:

Clinical Guideline	Recommendations
	o More than one resection. o Previously complicated or debilitating disease (e.g. abscess, involvement of adjacent structures, fistulising or penetrating disease). · Consider 5-ASA treatment to maintain remission after surgery. · Do not offer budesonide or enteral nutrition to maintain remission after surgery.
American College of Rheumatology: **Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features (2011)**[24]	General considerations · Recommendations for the treatment of juvenile idiopathic arthritis (JIA) are divided into five treatment groups that were developed by the core expert panel responsible for the literature review in the recommendation development. The treatment groups are as follows: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features (and without active arthritis) and systemic arthritis with active arthritis (and without active systemic features). · Glucocorticoid joint injections for active arthritis are recommended regardless of concurrent therapy (no DMARD, nonbiologic DMARD, biologic DMARD) or JIA treatment group. Due to its "superior" efficacy, triamcinolone hexacetonide should be used. · When initiating a TNF-α inhibitor (etanercept or adalimumab), continuation of methotrexate is recommended for patients that had a partial previous response. History of arthritis in four or fewer joints · For patients with low disease activity, no joint contractures and without features of poor prognosis, initiation of therapy with NSAID monotherapy is recommended as a treatment option. Therapy with an NSAID without additional therapy is not recommended longer than two months. · For all patients regardless of disease activity level, prognostic features or joint contractures, initiation of intra-articular joint injections (with or without additional therapy is recommended. · For patients with high disease activity and poor prognostic features, methotrexate is recommended as initial treatment (without prior therapy). For patients with high disease activity without poor prognostic features or with moderate disease activity and poor prognostic features, methotrexate is recommended after initial joint injection. For patients with low disease activity and poor prognostic features or moderate disease activity without poor prognostic features, methotrexate is recommended after repeated joint injections. · For patients with enthesitis-related arthritis category of JIA with moderate or high disease activity with and without poor prognostic features, sulfasalazine is recommended after glucocorticoid injections or an adequate trial of NSAIDs. · Initiation of a TNF-α inhibitor is recommended for patients with moderate or high disease activity with poor prognostic features after receiving glucocorticoid joint injections and three months of methotrexate at maximum tolerated dose. Initiation of a TNF-α inhibitor is also recommended in patients with high disease activity without poor prognostic features after receiving glucocorticoid joint injections and six months of methotrexate. For patients with enthesitis-related arthritis category of JIA and moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving

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	glucocorticoid joint injections and an adequate trial of sulfasalazine (without prior methotrexate). History of arthritis of five or more joints · Initial treatment with methotrexate is recommended in patients with high disease activity with or without poor prognostic features and in patients with moderate disease activity and poor prognostic features. For patients with low disease activity and poor prognostic features, methotrexate therapy is recommended after one month of therapy with NSAIDs. In patients with moderate disease activity without poor prognostic features, methotrexate is recommended after one to two months of therapy with NSAIDs. · Leflunomide is a treatment alternative to methotrexate as initial therapy in patients with high disease activity and poor prognostic features. In patients with high disease activity without poor prognostic features or moderate disease activity with poor prognostic features, leflunomide is a treatment alternative after a brief trial with NSAIDs. · For patients with moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for three months at the maximum tolerated typical doses. For patients with low disease activity with or without poor prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for six months. · For patients with moderate or high disease activity regardless of prognostic features, switching from one TNF-α inhibitor to another is recommended as a treatment option after receiving four months of therapy with current TNF-α inhibitor. · Abatacept is recommended as a treatment option after receiving four months of therapy with a TNF-α inhibitor in patients with high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features. For patients with moderate or high disease activity regardless of prognostic features or patients with low disease activity with features of poor prognosis, abatacept is recommended as a treatment option after receiving more than one TNF-α inhibitor sequentially. · Switching to a TNF-α inhibitor is recommended as a treatment option in patients that received abatacept for three months and have high disease activity with poor prognostic features and in patients that received abatacept for six months and have moderate to high disease activity with or without features of poor prognosis. Active sacroiliac arthritis · For patients with high disease activity and features of poor prognosis, TNF-α inhibitors are recommended after receiving an adequate trial of NSAIDs. · A TNF-α inhibitor is recommended in patients with high disease activity regardless of prognostic features or moderate disease activity with features of poor prognosis that have received three months of methotrexate, or in patients with moderate disease without poor prognosis that received six months of methotrexate. · A TNF-α inhibitor is recommended in patients with moderate or high disease activity regardless of prognostic features that have received three months of sulfasalazine, or in patients with low disease with poor

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	prognosis that received six months of sulfasalazine. Systemic arthritis with active systemic features · NSAID monotherapy is appropriate during clinical evaluation for possible systemic arthritis. NSAID monotherapy is not recommended for patients with active fever and physician global assessment of overall disease activity ≥7 of 10. In patients with active fever, continuation of NSAID monotherapy longer than one month is not appropriate. · Initial therapy with systemic glucocorticoids (with or without additional concurrent therapy) is recommended for patients with active fever and physician global assessment of seven or greater. For all patients with active fever, systemic glucocorticoids are recommended following up to two weeks of NSAIDs. · Anakinra is recommended for all patients with active fever and poor prognostic features, regardless of current therapy. For patients that sustain or develop fever while receiving systemic glucocorticoid, anakinra is recommended. Systemic arthritis with active arthritis · NSAID monotherapy (with or without glucocorticoid joint injections) for up to one month is recommended for patients with low disease activity without features of poor prognosis. · For all patients with active arthritis, regardless of prognostic features, methotrexate is recommended after one month or less of NSAID monotherapy (with or without glucocorticoid injections). · After three months of methotrexate, anakinra is recommended for patients with moderate or high disease activity with or without poor prognostic features. Anakinra is recommended for patients with high or moderate disease activity, regardless of prognostic features, and have received methotrexate and a TNF-α inhibitor or methotrexate and abatacept. Initiation of anakinra later in the disease course may be less appropriate compared to nearer to the onset of disease. · For patients with moderate or high disease activity with or without poor prognosis features, TNF-α inhibitors are recommended after receiving three months of methotrexate. Switching from anakinra to TNF-α inhibitors may be appropriate for patients with moderate to high disease activity regardless of prognostic features. · Abatacept is recommended for patients that received methotrexate and a TNF-α inhibitor and have high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features.
American College of Rheumatology: **2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children**	Initial treatment of systemic JIA with active systemic features and varying degrees of synovitis · Anakinra is recommended as one initial treatment option for patients with a physician global assessment (MD global) ≥5 irrespective of the active joint count (AJC), or an MD global <5 and an AJC >0. · Systemic glucocorticoid monotherapy (oral or intravenous) is recommended for a maximum period of two weeks for patients with an MD global <5 and an AJC >4 and for all patients with an MD global ≥5 irrespective of the AJC. · Initiating NSAID monotherapy in a patient without prior treatment is recommended as one approach for patients with an MD global <5 irrespective of the AJC.

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With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications (2013)[25]	Treatment of systemic JIA with active systemic features and varying degrees of synovitis in patients with continued disease activity · Use of abatacept is recommended only in patients with an MD global ≥5 and an AJC >4 after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). · Use of abatacept for patients with an AJC of zero irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is uncertain. · Use of abatacept for patients with an MD global <5 and an AJC >0 or an MD global ≥5 and an AJC <4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Use of abatacept for patients with an MD global ≥5 and an AJC >4 is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Anakinra is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy or NSAID monotherapy. · Use of a calcineurin inhibitor is recommended only for patients with an MD global ≥5 and an AJC of zero after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). · Use of a calcineurin inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who received either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Use of a calcineurin inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially), in which case it is appropriate, or patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Use of a calcineurin inhibitor for patients with an AJC >0 irrespective of the MD global is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or an alternate DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Canakinumab is recommended for patients with continued disease activity after treatment with glucocorticoid monotherapy, methotrexate or leflunomide, anakinra, or tocilizumab irrespective of the MD global and AJC. · Canakinumab is also recommended for patients with an MD global ≥5 irrespective of the AJC, despite prior NSAID monotherapy. · Glucocorticoid monotherapy is recommended as a treatment option after failure of NSAID monotherapy for patients with an MD global <5 and an AJC >0 and for patients with an MD global ≥5 irrespective of the AJC. Adjunct glucocorticoid therapy at any point is appropriate to consider. · Intraarticular glucocorticoid injection is recommended as adjunct therapy at any time. · Methotrexate or leflunomide is recommended for patients with an MD global <5 and an AJC >0 after treatment with glucocorticoid monotherapy, an IL-1 inhibitor, or tocilizumab. Methotrexate or leflunomide is recommended for patients with an MD global ≥5 and an AJC >0, only

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	after a trial of an IL-1 inhibitor or tocilizumab. · Initiation of a TNF-α inhibitor is recommended for patients with an AJC >4 irrespective of the MD global after a trial of an IL-1 inhibitor or tocilizumab. Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 irrespective of the MD global after a trial of both an IL-1 inhibitor and tocilizumab (sequentially). · Use of a TNF-α inhibitor for patients with an MD global <5 and an AJC of zero is inappropriate, with the exception of patients who had tried both an IL-1 inhibitor and tocilizumab (sequentially) or a DMARD plus either an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Use of a TNF-α inhibitor for patients with an MD global ≥5 and an AJC of zero is inappropriate, with the exception of patients who had tried an IL-1 inhibitor or tocilizumab, in which case it is uncertain. · Tocilizumab is recommended as a treatment option for patients with continued disease activity following glucocorticoid monotherapy, methotrexate or leflunomide, or anakinra irrespective of the MD global and AJC. · Tocilizumab is also recommended for patients with an MD global ≥5 irrespective of the AJC despite prior NSAID monotherapy. <u>Initial treatment of systemic JIA without active systemic features and varying degrees of synovitis</u> · Intraarticular glucocorticoid injection is recommended as an initial treatment for patients with an AJC ≤4. The utility of repeating injections in the same joint(s) as the only intervention is uncertain. · Initiation of methotrexate or leflunomide is recommended for patients with an AJC >4. · Initiation of NSAID monotherapy in a patient without prior treatment for a maximum period of one month is recommended as one treatment approach for patients with an AJC >0. Continuing NSAID monotherapy for longer than two months for patients with continued disease activity is inappropriate. <u>Treatment of systemic JIA without active systemic features and varying degrees of synovitis in patients with continued disease activity</u> · Use of abatacept is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. · Anakinra is recommended as a treatment option for patients with an AJC >4 following failed intraarticular injection or NSAID monotherapy. Use of anakinra is also recommended for patients with an AJC >0 following treatment with methotrexate or leflunomide. · Initiation of canakinumab is recommended for patients with an AJC >4 only after a trial of a DMARD plus anakinra or tocilizumab, a DMARD plus a TNF-α inhibitor, or abatacept. · Use of methotrexate or leflunomide is recommended as a treatment option for an AJC >0 following treatment with intraarticular injection, NSAID monotherapy, an IL-1 inhibitor, or tocilizumab. · Initiation of a TNF-α inhibitor is recommended for patients with an AJC >0 after treatment with methotrexate or leflunomide, anakinra, or tocilizumab. · Initiation of tocilizumab is recommended for an AJC >0 following treatment with anakinra or methotrexate or leflunomide. <u>Initial treatment of systemic JIA with features concerning for macrophage</u>

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	activation syndrome (MAS) · Use of anakinra is recommended as one treatment option for patients with features concerning for MAS. · Use of a calcineurin inhibitor is recommended as one therapeutic option for patients with features concerning for MAS. · Use of systemic glucocorticoid monotherapy (administered by oral or intravenous route) is also recommended as a therapeutic option for patients with features concerning for MAS. · Continuing glucocorticoid monotherapy for longer than two weeks is inappropriate.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[26]	Recommendations for treatment · In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. · In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage. · In patients with active psoriatic arthritis and clinically relevant psoriasis, a DMARD that also improves psoriasis, such as methotrexate, should be preferred. · Local corticosteroid injections should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution. · In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as methotrexate, therapy with a TNF-α inhibitor should be commenced. · In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or steroid injections, a TNF-α inhibitor may be considered. · In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF-α inhibitor should be considered. · A TNF-α inhibitor might be considered for a very active patient treatment naïve to DMARDs (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement). · In patients who fail to respond adequately to one TNF-α inhibitor, switching to another TNF-α inhibitor should be considered. · When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.
National Psoriasis Foundation: **Consensus Guidelines for the Management of Plaque Psoriasis (2012)**[27]	Oral therapies · Acitretin is the only antipsoriatic retinoid available for systemic use in the United States. The use of acitretin is limited due to its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene or biological therapy or phototherapy may increase rates of clearance. Acitretin is especially useful in patients with severely sun-damaged skin, in which it may suppress actinic keratoses and even invasive malignant neoplasms. · Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects, hypertension and hyperglycemia. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term

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	treatment agent to control a flare of psoriasis, after which therapy is switched for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity. · Methotrexate is directly anti-inflammatory because of its effects on T-cell gene expression patterns. Compared to cyclosporine, methotrexate has a more modest effect on psoriasis severity, but can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver. Biologic agents · Adalimumab may be used as first-line systemic treatment of plaque psoriasis and has a higher efficacy and lower rate of adverse effects compared to methotrexate. · Etanercept is commonly used as a first-line systemic drug for chronic plaque psoriasis. · Infliximab is administered via intravenous infusion, is a fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis · Ustekinumab is associated with favorable results when compared to etanercept in terms of efficacy and safety. It may be used as first-line systemic treatment for chronic plaque psoriasis. · Alefacept is generally used for intermittent use. There is little evidence to support use to achieve full clearance, and it is often used in combination regimens. It may be used as first-line systemic drug for chronic plaque psoriasis.
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3 and 4 (2008-2009)**[28-30]	Topical therapies · Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. · Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. · Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. · Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. · Other topical agents include anthralin, coal tar, nonmedicated topical moisturizers, pimecrolimus, salicylic acid, tacrolimus, tazarotene, vitamin D analogues, and combination products. · Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA indication. · There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid however the agent is typically used in combination with other topical therapies. Systemic therapies · Although biologics are often less toxic and not teratogenic, traditional systemic therapies (acitretin, cyclosporine, methotrexate) are still used more often due to oral route of administration and low cost. · Used more than 50 years ago, methotrexate is most commonly

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	prescribed for severe, recalcitrant, disabling psoriasis when used in a weekly, single low-dose regimen for its effect on the immune system; concurrent folate supplementation may be warranted. · Though highly effective and known for its rapid effects, cyclosporine is associated with nephrotoxicity and hypertension; its use is restricted to one and two years in the United States and United Kingdom, respectively. · When used in conjunction with ultraviolet radiation B or psoralen and ultraviolet radiation A phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression; effects are dose-dependent and response is observed after three to six months. · Agents not FDA-indicated but used in psoriasis with limited supporting evidence include: azathioprine, fumarates (not approved in the United States), leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine. <u>Biologics</u> · Three TNF-α inhibitors are FDA-approved for the treatment of psoriatic arthritis; adalimumab, etanercept, and infliximab (please note that the publication of these guidelines was before FDA-approval of golimumab). · Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy associated with psoriasis that if left untreated can lead to persistent inflammation with progressive joint damage that can result in severe physical limitations and disability. · NSAIDs and/or intra-articular injections of corticosteroids may be appropriate treatment options in patients with milder, localized disease. · Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with methotrexate, TNF-α inhibitors, or both. These treatment options are considered the standard of care. · Other DMARDs which may be used in the treatment of psoriatic arthritis include leflunomide and sulfasalazine. Antimalarials, cyclosporine, and gold are used less frequently due to the evidence for their efficacy being less convincing than for leflunomide, methotrexate, and sulfasalazine. · Although expensive, there are potential long-term cost savings and benefits associated with the use of biologics in the treatment of psoriatic arthritis, including reduced need for joint replacement surgery; reduced demands on medical, nursing, and therapy services; reduced needs for concomitant medicines; reduced demands on social services and careers; improved quality of life; improved prospect of remaining in the work force; and increased life expectancy. · Because the clinical trial efficacy data (primary endpoint of American College of Rheumatology 20% improvement) with all three FDA-approved TNF-α inhibitors are roughly equivalent, the choice of which agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration. · Adalimumab and infliximab both demonstrated significant benefit for the treatment of psoriatic arthritis in clinical trials, while etanercept demonstrated significant improvements in signs and symptoms of psoriatic arthritis.
American College of Rheumatology:	<u>Initiating and switching among DMARDs</u> · If a patient deteriorates from low to moderate/high disease activity after

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2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)[31]	three months of DMARD monotherapy (in patients without poor prognostic features), then methotrexate, hydroxychloroquine, or leflunomide should be added. · Add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD if the patient still experiences moderate or high disease activity following three months of methotrexate or methotrexate/DMARD combination therapy. Switching from DMARDs to biologic agents · For patients with continued moderate or high disease activity following three months of methotrexate monotherapy or DMARD combination therapy, an alternative to DMARD therapy is adding or changing therapy to a TNF-α inhibitor, abatacept or rituximab. · Add or switch to a TNF-α inhibitor if a patient continues to have moderate or high disease activity, following three months of intensified DMARD combination therapy or after a second DMARD has been tried. Switching among biologic agents due to lack of benefit or loss of benefit · In patients with moderate or high disease activity despite three months of TNF-α inhibitor therapy due to a lack or loss of benefit, switching to another TNF-α inhibitor or a non-TNF-α inhibitor biologic is recommended. · In patients with moderate or high disease activity despite six months of a non-TNF-α inhibitor biologic and the failure is due to a lack or loss of benefit, the patient should switch to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Switching among biologic agents due to harms/adverse events · Patients with high disease activity following treatment failure of a TNF-α inhibitor due to a serious adverse event, an attempt should be made to switch to a non-TNF-α inhibitor biologic. · In patients with moderate or high disease activity after failing an TNF-α inhibitor because of a nonserious adverse event, switch to another anti-TNF-α inhibitor or a non-TNF-α inhibitor biologic. · Patients with moderate or high disease activity after failing a non-TNF-α inhibitor biologic because of an adverse event (serious or nonserious) should be switched to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. Biologic use in Hepatitis B or C · Etanercept could potentially be used in rheumatoid arthritis patients with hepatitis C requiring rheumatoid arthritis treatment; however, biologic agents should not be used in rheumatoid arthritis patients with untreated chronic hepatitis B and in rheumatoid arthritis patients with treated chronic hepatitis B with Child-Pugh class B and higher. Malignancies · Patients treated for solid malignancies more than five years ago or who have been treated for nonmelanoma skin cancer more than five years ago, treatment with a biologic agent may be initiated or continued if the patient would otherwise qualify for biologic therapy. · Rituximab should only be started or initiated in rheumatoid arthritis patients with a previously treated solid malignancy within the last five

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	years, a previously treated nonmelanoma skin cancer within the last five years, a previously treated melanoma skin cancer, or a previously treated lymphoproliferative malignancy. · Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past five years. Congestive heart failure · Anti-TNF biologic in rheumatoid arthritis patients with congestive heart failure is not recommended in those with a New York Heart Association class III or IV and who have an ejection fraction of 50% or less.
European League Against Rheumatism: **Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying Antirheumatic Drugs: 2013 Update (2013)**[32]	· Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. · Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. · Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. · Treatment should be aimed at reaching a target of remission or low disease activity in every patient. · Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis. · If methotrexate is contraindicated or is not tolerated, treatment with sulfasalazine or leflunomide should be considered. · In DMARD-naïve patients, treatment with conventional synthetic DMARD monotherapy or combination therapy of conventional synthetic DMARDs is recommended. · Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible. · If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another conventional synthetic DMARD strategy should be considered; when poor prognostic factors are present, addition of a biologic DMARD should be considered. · In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF-α inhibitors, abatacept or tocilizumab) should be commenced with methotrexate; treatment with rituximab may be considered in the patients with recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a tuberculosis-endemic region, or a previous history of demyelinating disease. · If a first biologic DMARD has failed, patients should be treated with another biologic DMARD; if a first TNF-α inhibitor therapy has failed, patients may receive another TNF-α inhibitor or a biological agent with a different mechanism of action. · Given the paucity of clinical experience and long-term safety data, tofacitinib should primarily be used when biological treatment has failed; additional clinical experience and safety data from registries, with a particular focus on serious infections, herpes zoster and malignancies, will be needed before the place of tofacitinib in the treatment sequence can be clarified. · If a patient is in persistent remission after having tapered glucocorticoids, tapering of biologic DMARDs can be considered, especially if this treatment is combined with a conventional synthetic DMARD.

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	· In cases of sustained long-term remission, cautious reduction of the conventional synthetic DMARD dose could be considered, as a shared decision between patient and physician.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis National Clinical Guideline for Management and Treatment in Adults (2009)**[33]	· In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. · In people with recent-onset rheumatoid arthritis receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. · In people with newly diagnosed rheumatoid arthritis for which combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. · In people with established rheumatoid arthritis whose disease is stable, cautiously reduce dosages of disease modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. · When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. · In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. · Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy. · Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. · In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. · On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. · Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. · Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. · Oral NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. · When offering treatment with an oral NSAID or COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either

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	case, these should be co-prescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost. · All oral NSAIDs or COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. · If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient. · If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen. · The TNF-α inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. · TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy. · Treatment with TNF-α inhibitors should be continued only if there is an adequate response at six months following initiation of therapy. An adequate response is defined as an improvement in DAS 28 of 1.2 points or more. · After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. · An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy provided the risks and benefits have been fully discussed with the patient and documented. · Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended. · Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. · Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. · Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.
National Institute for	· Rituximab in combination with methotrexate is recommended as an

Clinical Guideline	Recommendations
Health and Clinical Excellence: **Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After the Failure of a Tumor Necrosis Factor Inhibitor (2010)**[33]	option in adult patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor. · Treatment with rituximab should be given no more frequently that every six months and should be continued only if an adequate response is maintained at this dosing interval. · Abatacept, adalimumab, etanercept and infliximab each in combination with methotrexate, are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with rituximab. · Adalimumab and etanercept monotherapy are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with methotrexate. · Treatment with abatacept, adalimumab, etanercept and infliximab should be continued only if there is an adequate response six months after therapy. · Abatacept, adalimumab, etanercept, infliximab and rituximab should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.
National Institute for Health and Clinical Excellence: **Golimumab for the Treatment of Rheumatoid Arthritis After the Failure of Previous Disease-Modifying Antirheumatic Drugs (2011)**[34]	· Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only, including methotrexate, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. · Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
American College of Gastroenterology, Practice Parameters Committee: **Ulcerative Colitis Practice Guidelines in Adults**	Management of mild-moderate distal colitis · Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates. · The combination of oral and topical agents is “superior” to each agent used alone. · Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-

Clinical Guideline	Recommendations
(2010)[35]	analysis demonstrated topical mesalamine to be "superior" to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. · Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. · Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. <u>Maintenance of remission in distal disease</u> · Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. · Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. · Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. · When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. <u>Management of mild-moderate extensive colitis: active disease</u> · Oral sulfasalazine is considered first line. · Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. · 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. · Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. <u>Maintenance of remission for mild-moderate extensive colitis</u> · Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses. · 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. · Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. <u>Management of severe colitis</u> · If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent hospitalization is not required. · Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. · Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence). · Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.

Conclusions

Immunomodulators inhibit the pro-inflammatory response involved in the pathophysiology of several chronic inflammatory diseases. The immunomodulators interfere with this inflammatory pathway through slightly different mechanisms.[1-15] Few head-to-head trials have been performed amongst these agents, making it difficult to compare the efficacy, although all have been shown to be efficacious compared to placebo for their respective Food and Drug Administration (FDA)-approved indication(s).[41-136] Current clinical guidelines do not generally distinguish among the different agents for any indication for which the specific agent is approved.[15-35] Given the paucity of clinical experience and long-term safety data, guidelines recommend that tofacitinib be reserved for patients in whom biological treatment has failed.[18] The adverse event profiles are similar across the class. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class; however, several other agents have recently gained additional indications.[1-15]

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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators
Last Reviewed by the DUR Board: January 22, 2015

Actemra® (tocilizumab)
Amevive® (alefacept)
Arcalyst® (rilonacept)
Cimzia® (certolizumab pegol)
Cosentyx® (secukinumab)
Enbrel® (etanercept)
Entyvio® (vedolizumab)
Humira® (adalimumab)
Ilaris® (Canakinumab)
Kineret® (ankinra)
Orencia® (abatacept)
Remicade® (infliximab)
Simponi® (golimumab)
Simponi® ARIA™ (golimumab)
Stelara® (ustekinumab)
Xeljanz® (tofacitinib)

Immunomodulator Drugs are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the Social Security Act (SSA) and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and limitations:

Approval will be given if the following criteria are met and documented:

a. For all requests:
   1. The recipient has had a negative tuberculin test
      AND
   2. The recipient does not have an active infection or a history of recurring infections
      AND
   3. Approval will not be given for the use of more than one biologic at a time (combination therapy).
      AND
   4. Each request meets appropriate diagnosis-specific criteria

b. Rheumatoid Arthritis (RA):
   1. The recipient has a diagnosis of moderately to severely active RA; and
   2. The recipient is 18 years of age or older
   3. The recipient has had a rheumatology consultation, including the date of the visit; and
   4. One of the following:
      i. The recipient has had RA for ≤ six months (early RA) and has high disease activity; and an inadequate or adverse reaction of a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or
      ii. The recipient has had RA for ≥ six months (intermediate or long –term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline or sulfasalazine); or
      iii. The recipient has had RA for ≥ six months (intermediate or long-term disease duration) and has high disease activity.

c. Psoriatic Arthritis
   1. The recipient has a diagnosis of moderate or severe psoriatic arthritis; and
   2. The recipient is 18 years of age or older

3. The recipient has had a rheumatology consultation including the date of the visit or a dermatology consultation including the date of the visit; and
4. The recipient had an inadequate response to any one nonsteroidal antiinflammatory drug (NSAID) or a contraindication to treatment with an NSAID or to any one of the following DMARDs (methotrexate, leflunomide, cyclosporine or sulfasalazine); and.

d. Ankylosing Spondylitis
1. The recipient has a diagnosis of ankylosing spondylitis; and
2. The recipient is 18 years of age or older
3. The recipient has had an inadequate response to NSAIDs; and
4. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalzine, leflunomide, minocycline); and

e. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis
1. The recipient has a diagnosis of moderately or severely active juvenile RA; and
2. The recipient is an appropriate age, based on the requested agent:
    i. Abatacept: 6 years of age or older
    ii. Adalimumab, canakinumab, etanercept, tocilizumab: 2 years of age or older
3. The recipient has at least five swollen joints; and
4. The recipient has three or more joints with limitation of motion and pain, tenderness or both; and
5. The recipient has had an inadequate response to one DMARD; and

f. Plaque Psoriasis
1. The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis; and
2. The recipient is 18 years of age or older
3. The agent is prescribed by a dermatologist; and
4. The recipient has failed to adequately respond to a topical agent; and
5. The recipient has failed to adequately respond to at least one oral treatment; and

g. Crohn's Disease
1. The recipient has a diagnosis of moderate to severe Crohn's Disease; and
2. The recipient is an appropriate age, based on the requested agent:
    i. adalimumab, infliximab: 6 years of age or older
    ii. All others: 18 years of age or older
3. The recipient has failed to adequately respond to conventional therapy (e.g. sulfasalzine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide); or
4. The recipient has fistulizing Crohn's disease, and;

h. Ulcerative Colitis
1. The recipient has a diagnosis of moderate to severe ulcerative colitis; and
2. The recipient is an appropriate age, based on the requested agent:
    i. Infliximab: six years of age or older
    ii. All others: 18 years of age or older
3. The recipient has failed to adequately respond to one or more of the following standard therapies:
    i. Corticosteroids;
    ii. 5-aminosalicylic acid agents
    iii. Immunosuppressants; and/or
    iv. Thiopurines; and

i. Cryopyrin-Associated Periodic Syndromes (CAPS): Familial Cold Autoinflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS)
1. The recipient has a diagnosis of FCAS or MWS; and
2. The recipient is an appropriate age, based on the requested agent:
    i. Canakinumab: four years of age or older
    ii. Rilonacept: 12 years of age or older

j. Cryopyrin-Associated Periodic Syndromes (CAPS): Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
    1. The recipient has a diagnosis of NOMID

2. Prior Authorization Guidelines:
    a. Prior authorization approval will be for one year