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, hidradenitis suppurativa, uveitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. Overall, 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®), ixekizumab (Taltz®), 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.[1-16]

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®, Orencia ClickJet®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥six years)	Auto-injector: 125 mg/mL Prefilled syringe: 125 mg/mL Vial: 250 mg	-
Adalimumab (Humira®, Humira Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (age ≥six years); ulcerative colitis (adults only); plaque psoriasis (adults only); uveitis (adults only); hidradenitis suppurativa (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 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 syndrome (age ≥ four years); juvenile idiopathic arthritis (age ≥ two years)	Vial: 180 mg (150 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: 200 mg	-

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Etanercept (Enbrel®, Enbrel SureClick®)	rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥2 years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 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])	Auto-injector (Simponi®): 50 mg/0.5 mL, 100 mg/mL Prefilled syringe (Simponi®): 50 mg/0.5 mL 100 mg/mL Vial* (Simponi Aria®): 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)	Vial: 100 mg	-
Ixekizumab (Taltz®)	Plaque Psoriasis (adults)	Auto-injector: 80 mg/mL Prefilled Syringe: 80 mg/mL	-
Rilonacept (Arcalyst®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years)	Vial: 220 mg (80 mg/mL)	-
Secukinumab (Cosentyx®, Cosentyx SensoReady Pen®)	Ankylosing Spondylitis (adults only), Juvenile idiopathic arthritis/juvenile rheumatoid arthritis, Plaque Psoriasis (adults only)	Auto-injector: 150 mg/mL Prefilled syringe: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ 2 years) ; systemic juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥ 2 years); rheumatoid arthritis (adults only);	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®,	Rheumatoid arthritis (adults only)	Extended-release tablet	-

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Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Xeljanz XR®)		(Xeljanz XR®): 11 mg Tablet (Xeljanz®): 5 mg	
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	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.[48-151]
- The safety and efficacy of adalimumab for the treatment of non-infectious intermediate, posterior and panuveitis was established in two unpublished randomized, double-blind, placebo-controlled clinical trials.[8] The total length of each study was not reported; however, data is reported up to 18 weeks. The primary efficacy endpoint in both studies was time to treatment failure, defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA), on or after week six (study one) or week two (study two). At week 18 in study one, 60 patients (54.5%) failed adalimumab on or after week six compared with 84 patients (78.5%) who received placebo (hazard ratio [HR], 0.5; 95% CI, 0.36 to 0.70). Median time to failure was 5.6 months (95% CI, 3.9 to 9.2) for patients who received adalimumab and 3.0 months (95% CI, 2.7 to 3.7) for patients who received placebo. At week 18 in study two, 45 patients (39.1%) failed adalimumab on or after week two compared with 61 patients (55.0%) who received placebo (HR, 0.57; 95% CI, 0.39 to 0.84). Median time to failure for the adalimumab group was not estimable as fewer than half of the at-risk subjects had an event. Median time to failure for the placebo group was 8.3 months (95% CI, 4.8 to 12.0).[8]
- The safety and efficacy of Humira in the treatment of hidradenitis suppurativa was established in two clinical trials PIONEER I and PIONEER II. Both were 36-week, multicenter, randomized, double-blind clinical trials with a total of 633 adult patients with moderate to severe (Hurley Stage II and III) hidradenitis suppurativa who had an inadequate response to a trial of oral antibiotics, total abscess and inflammatory nodule count of ≥3 and lesions present in ≥2 body areas. At 12 weeks, therapy was evaluated and effectiveness was defined as improvement in abscesses and inflammatory nodules at 12 weeks using the Hidradenitis Suppurativa Clinical Response (HiSCR). In PIONEER I and PIONEER II, adalimumab achieved a statically significant improvement using the HiSCR measure when compared to placebo (P=0.003 and P<0.001, respectively).[48,49]
- 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).[79]

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- Secukinumab for the treatment of ankylosing spondylitis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, MEASURE 1 and 2. The primary endpoint in both studies was the proportion of patients who had an Assessment of Spondyloarthritis International Society (ASAS) criteria improvement ≥20% (ASAS20) at week 16. In MEASURE 1, ASAS20 was significantly greater at week 16 in the secukinumab 150 mg group (61%) and 75 mg group (60%) than the placebo group (29%, P<0.001 for both vs placebo). In MEASURE 2, ASAS20 at week 16 was significantly greater in the secukinumab 150 mg group (61%) when compared to the placebo group (28%, P<0.001). There was no significant difference between the placebo group and the secukinumab 75 mg group (41%, P=0.10).[60]
- The safety and efficacy of secukinumab for the treatment of plaque psoriasis 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.[5,89-91]
- Secukinumab for the treatment of psoriatic arthritis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, FUTURE 1 and 2. The primary endpoint for both studies was the proportion of patients who had an American College of Rheumatology (ACR) improvement ≥20% (ACR20 response) at week 24.[100,101] In FUTURE 1, ACR20 response at week 24 was significantly greater in the secukinumab 150 mg group (50%) and 75 mg group (50.5%) than the placebo group (17.3%, P<0.001 for both vs placebo).[100] In FUTURE 2, ACR20 response at week 24 was significantly greater in the secukinumab 300 mg group (54%), the secukinumab 150 mg group (51%) and the secukinumab 75 mg group (29%), when compared to placebo (15%, P<0.001 for 300 mg and 150 mg groups vs placebo and P=0.0399 for the 75 mg group vs placebo).[101]
- The safety and efficacy of ixekizumab, for the treatment of moderate-to-severe psoriasis, was established in three multicenter, randomized, double-blind, placebo-controlled trials in patients 18 years of age or older (UNCOVER-1, UNCOVER-2 and UNCOVER-3). Patients had to have body surface area (BSA) involvement ≥10%, static Physician's Global Assessment (sPGA) ≥3 and Psoriasis Area Severity Index (PASI) ≥12. The three trials evaluated two different induction phase doses of ixekizumab: 80 mg every two weeks and 80 mg every four weeks over 12 weeks. In addition, two of the trials (UNCOVER-1 and UNCOVER-2) evaluated two different maintenance phase doses of 80 mg every four weeks and 80 mg every 12 weeks over 48 weeks. Two of the trials (UNCOVER-2 and UNCOVER-3) had etanercept as an active comparator arm during the induction phase.[82-84] In UNCOVER-1, treatment with ixekizumab, with an initial dose of 160 mg and subsequent induction period dosages of 80 mg every two weeks or 80 mg every four weeks resulted in significant improvement during the induction period. Across all efficacy end points, response rates associated with the dosage of 80 mg every two weeks were higher than those associated with the 80 mg every four weeks dose. In UNCOVER-1 and UNCOVER-2, for ixekizumab week 12 responders, efficacy was also maintained through the 60-week maintenance period.[82,83] In UNCOVER-2 and UNCOVER-3, treatment with both induction doses of ixekizumab (80 mg every two weeks and 80 mg every four weeks) demonstrated significantly greater efficacy than etanercept. Across all efficacy endpoints, response rates associated with 80 mg every two weeks was higher than those associated with 80 mg every four weeks.[82,84]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[19-36]
    - 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.[27,28,31] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary.

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- In general, no one agent is preferred over another.

- Other Key Facts:
  - The recently upheld Patient Protection and Affordable Care Act provides a legal framework for regulatory approval of biosimilar drugs.[43]
  - While none of the agents in this class are available generically, a biosimilar for infliximab was recently approved (Inflectra®). Due to ongoing patent litigation, it is unknown when the product will become available.
  - Another biosimilar, adalimumab, is being considered by the FDA and was recently recommended for approval unanimously by an FDA panel 26-0. However, the manufacturer does not expect the biosimilar adalimumab to be available until sometime between 2018 and 2022 due to patent litigation issues.[152]
  - Dosing and administration varies both by drug and by dosage form.[1-16]
    - Oral: tofacitinib (tablet, extended-release tablet)
    - Intravenous Injection: abatacept, golimumab (Simponi ARIA®), infliximab, tocilizumab, 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 is the only injectable immunomodulator that requires daily dosing.
    - Tofacitinib immediate release is taken twice daily while the extended-release formulation can be taken once daily.
    - 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.
    - 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 in pediatric patients varies based on drug and indication.[1-16]
    - 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 (age two to 17 years), canakinumab, etanercept, and tocilizumab (all two or older).
    - Both adalimumab and infliximab have been FDA-approved for the treatment of pediatric Crohn's disease in pediatric patients aged six or older. Additionally, infliximab is also indicated to treat pediatric ulcerative colitis in pediatric patients six years of age or older.
  - 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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