Therapeutic Class Overview
Psoriatic Arthritis Agents: Phosphodiesterase 4 Inhibitors

Therapeutic Class

- **Overview/Summary:** Psoriasis is an autoimmune inflammatory disease that has significant medical, psychological, and quality of life implications.[1-3]

  Psoriasis affects approximately 1 to 3% of the population, with approximately 15 to 30% of those afflicted with the condition developing psoriatic arthritis, a chronic, inflammatory spondyloarthropathy. Although the exact underlying cause of psoriasis is not clearly understood, it is believed to involve a genetic component.[1-3]

  The course of psoriatic arthritis is variable and unpredictable, ranging from a mild non-destructive disease to debilitating arthropathy. The condition is characterized by stiffness, pain, swelling, and tenderness of the joints as well as the surrounding ligaments and tendons (i.e., enthesitis). In addition, peripheral arthritis, axial involvement, dactylitis, uveitis may also develop.[4,5]

  Once psoriatic arthritis is diagnosed, treatment should be initiated to alleviate symptoms, inhibit structural damage, and maximize quality of life. Current treatment options for psoriatic arthritis include nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, ustekinumab, tumor necrosis factor-alpha inhibitors, and apremilast. In certain patients, oral or locally injected corticosteroids may also be used.[1-5]

  Apremilast (Otezla®) is a phosphodiesterase 4 inhibitor approved by the Food and Drug Administration for the treatment of adults with active psoriatic arthritis.[6] Apremilast is a small-molecule inhibitor of phosphodiesterase 4, specific for cyclic adenosine monophosphate (cAMP). The inhibition of phosphodiesterase 4 results in increased intracellular cAMP levels, helping to regulate the inflammatory mediators involved in the pathophysiology of psoriatic arthritis.[6,7]

Medications:

Table 1. Medications Included Within Therapeutic Class Review

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Apremilast (Otezla®)	Treatment of adult patients with active psoriatic arthritis	Tablet, oral: 30 mg*† Starter pack‡	-

* Supplied in 60-count bottles.
† Supplied as a 28-count carton, consisting of two-30 mg blister cards containing fourteen 30 mg tablets.
‡ Supplied in a two-week starter pack consisting of 13 tablets of 10, 20, and 30 mg tablets with an additional 14 tablets of 30 mg.

Evidence-based Medicine:

- The Food and Drug Administration-approval of apremilast was based upon the safety and efficacy results from three multi-center, randomized, double-blind, placebo-controlled trials (PALACE 1 through 3); however, only the PALACE 1 trial is currently available in the published literature.
- The PALACE 1 trial was double-blind, multi-center, placebo-controlled trial that evaluated the safety and efficacy of apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo among adults with active psoriatic arthritis affecting at least three swollen and tender joints despite prior treatment with traditional Disease-modifying antirheumatic drugs and/or biologics or concomitant treatment with traditional disease-modifying antirheumatic drugs.

- The efficacy of apremilast was demonstrated across patients with varying treatment experience.
- At week 16, significantly more patients receiving apremilast 20 mg twice daily (31.3%) and apremilast 30 mg twice daily (39.8%) achieved an American College of Rheumatology 20 Response (ACR20) response vs placebo (19.4%).
- At week 16, apremilast was associated with significantly greater reductions in Health Assessment Questionnaire Disability Index compared to placebo, and a greater proportion of patients receiving either dose of apremilast also achieved ACR50 and ACR70 vs placebo.
- During the 24-week placebo-controlled phase, the majority of reported adverse events were mild to moderate in severity. Study discontinuation due to adverse events was comparable across groups, including 6.0% among the apremilast 20 mg twice daily group, 7.1% among the apremilast 30 mg twice daily group, and 4.8% among the placebo group.[11]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current clinical guidelines for the management of psoriasis and psoriatic arthritis, the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life.[1-3,8]
  - Nonsteroidal anti-inflammatory drugs and/or intra-articular injections of corticosteroids are appropriate treatment options in patients with mild, localized disease.
  - Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that has significantly impacted quality of life should be treated with methotrexate, a tumor necrosis factor-alpha inhibitor, or both. Other effective disease-modifying antirheumatic drugs include leflunomide and sulfasalazine.
  - The currently available clinical guidelines note a relatively comparable efficacy profile for the biologics approved by the Food and Drug Administration and do not recommend any one particular biologic agent over another. In addition, they also do not currently include recommendations for the use of apremilast in the management of psoriatic arthritis.[1-3,8,9]
- Other Key Facts:
  - Apremilast is the first in-class oral therapy for the management of psoriatic arthritis and does not require routine laboratory monitoring.[6,7]
  - Apremilast is administered over a five-day titration period, to minimize gastrointestinal symptoms, to a target dose of 30 mg twice daily.[7]

References:

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Therapeutic Class Review
Psoriatic Arthritis Agents: Phosphodiesterase 4 Inhibitors

Overview/Summary

Psoriasis is an autoimmune inflammatory disease that has significant medical, psychological, and quality of life implications. Psoriasis affects approximately 1 to 3% of the population, with approximately 15 to 30% of those afflicted with the condition developing psoriatic arthritis, a chronic, inflammatory spondyloarthropathy.[1-3] Although the exact underlying cause of psoriasis is not clearly understood, it is believed to involve a genetic component. The development of psoriatic arthritis primarily appears between the fourth and sixth decades of life; however it may appear during early childhood as well. The condition is characterized by stiffness, pain, swelling, and tenderness of the joints as well as the surrounding ligaments and tendons (i.e., enthesitis). In addition, peripheral arthritis, axial involvement, dactylitis, uveitis may also develop.[4,5]

The course of psoriatic arthritis is variable and unpredictable, ranging from a mild non-destructive disease to debilitating arthropathy. Psoriatic arthritis may be classified as mild, moderate, or severe. Mild forms typically have minimal impact on quality of life and generally respond to non-steroidal anti-inflammatory drugs. Moderate disease severity impacts activities of daily living as well as physical and/or mental function. These forms tend to be unresponsive to non-steroidal anti-inflammatory drugs and require treatment with disease-modifying antirheumatic drugs or tumor necrosis factor-alpha inhibitors. Severe disease typically requires both disease-modifying antirheumatic drugs and tumor necrosis factor-alpha inhibitors or other biologic therapies and have a significant impact on quality of life. Patients with severe disease may not be able to perform the majority of routine activities of daily living without significant pain or dysfunction, which often further impacts their physical and emotional well-being.[1-5] Overall, the disease course is characterized by flares and remissions, leading to chronic joint damage, especially if not properly treated.[4,5]

Once psoriatic arthritis is diagnosed, treatment should be initiated to alleviate symptoms, inhibit structural damage, and maximize quality of life. Current treatment options for psoriatic arthritis include non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, ustekinumab, tumor necrosis factor-alpha inhibitors, and apremilast. In certain patients, oral or locally injected corticosteroids may also be used.[1-5]

Apremilast (Otezla®) is a phosphodiesterase 4 inhibitor approved by the Food and Drug Administration (FDA) for the treatment of adults with active psoriatic arthritis.[6] Apremilast is a small-molecule inhibitor of phosphodiesterase 4, specific for cyclic adenosine monophosphate (cAMP). The inhibition of phosphodiesterase 4 results in increased intracellular cAMP levels, helping to regulate the inflammatory mediators involved in the pathophysiology of psoriatic arthritis.[6,7] According to a press release from the manufacturer, apremilast is the first oral therapy for the management of psoriatic arthritis and does not require routine laboratory monitoring. It is administered over a five-day titration period to a target dose of 30 mg twice daily.[7] The titration course over five days is intended to minimize the gastrointestinal symptoms associated with the initiation of therapy.[6] The safety and efficacy of apremilast has been evaluated in the PALACE 1 through 3 trials among adults with psoriatic arthritis who were inadequately controlled by disease-modifying antirheumatic drugs and/or biologics.[7]

According to current clinical guidelines for the management of psoriasis and psoriatic arthritis, the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life.[1-3,8] non-steroidal anti-inflammatory drugs and/or intra-articular injections of corticosteroids are appropriate treatment options in patients with mild, localized disease. Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that has significantly impacted quality of life should be treated with methotrexate, a tumor necrosis factor-alpha inhibitor, or both. Other effective disease-modifying antirheumatic drugs include leflunomide and sulfasalazine. The currently

available clinical guidelines note a relatively comparable efficacy profile for the biologics approved by the Food and Drug Administration and do not recommend any one particular biologic agent over another. In addition, they also do not currently include recommendations for the use of apremilast in the management of psoriatic arthritis.[1-3,8,9]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Apremilast (Otezla®)	Phosphodiesterase 4 inhibitor	-

Indications

Table 2. Food and Drug Administration-Approved Indications[6]

Generic Name	Treatment of Adult Patients with Active Psoriatic Arthritis
Apremilast	✔

Pharmacokinetics

Table 3. Pharmacokinetics[6,10]

Generic Name	Bioavailability (%)	Plasma Protein Binding	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Apremilast	~73%	68%	3% (unchanged)	None reported	6 to 9

Clinical Trials

The Food and Drug Administration-approval of apremilast was based upon the safety and efficacy results from three multi-center, randomized, double-blind, placebo-controlled trials (PALACE 1 through 3); however, only the PALACE 1 trial is currently available in the published literature. The available published trial demonstrating the safety and efficacy of apremilast in the management of psoriatic arthritis is outlined in Table 4.[11]

The PALACE 1 trial was double-blind, multi-center, placebo-controlled trial that evaluated the safety and efficacy of apremilast 20 mg twice daily, apremilast 30 mg twice daily, or placebo among adults with active psoriatic arthritis affecting at least three swollen and tender joints despite prior treatment with traditional disease-modifying antirheumatic drugs and/or biologics or concomitant treatment with traditional disease-modifying antirheumatic drugs. The efficacy of apremilast was demonstrated across patients with varying treatment experience. At week 16, significantly more patients receiving apremilast 20 mg twice daily (31.3%) and apremilast 30 mg twice daily (39.8%) achieved an American College of Rheumatology 20 Response (ACR20) response vs placebo (19.4%). At week 16, apremilast was associated with significantly greater reductions in Health Assessment Questionnaire Disability Index compared to placebo, and a greater proportion of patients receiving either dose of apremilast also achieved ACR50 and ACR70 vs placebo. During the 24-week placebo-controlled phase, the majority of reported adverse events were mild to moderate in severity. Study discontinuation due to adverse events was comparable across groups, including 6.0% among the apremilast 20 mg twice daily group, 7.1% among the apremilast 30 mg twice daily group, and 4.8% among the placebo group.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kavanaugh et al[11] (2014) (PALACE 1) Apremilast 20 mg twice daily vs apremilast 30 mg twice daily vs placebo Apremilast dosing was stratified by baseline DMARD use. Apremilast dosing was titrated over the first week (10 mg on the first day, with increases of 10 mg daily until target dose reached).	DB, IN, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active psoriatic arthritis with ≥3 swollen and ≥3 tender joints, despite prior treatment with traditional DMARDs and/or biologics or concurrent treatment with traditional DMARDs	N=504 24 weeks	Primary: The proportion of patients meeting 20% improvement in the modified ACR response criteria (ACR20) at week 16 Secondary: The change from baseline in HAQ-DI at week 16, and improvements in the signs and symptoms of psoriatic arthritis, physical function, enthesitis, dactylitis and psoriasis at week 24, and safety	Primary: Efficacy was demonstrated across patients with varying treatment experience. At week 16, significantly more patients receiving apremilast 20 mg twice daily (31.3%; P=0.0140) and 30 mg twice daily (39.8%; P=0.0001) achieved an ACR20 response vs placebo (19.4%). The intent to treat analysis demonstrated consistent results among the apremilast 20 mg twice daily (30.4%; P=0.0166); apremilast 30 mg twice daily (38.1%; P=0.0001) and the placebo (19.0%) groups. Patients naïve to biological therapy generally experienced higher absolute ACR20 response rates compared to biologic-experienced patients and those with a history of previous biologic failure. A dose-related effect was observed with higher ACR20 response rates achieved in those receiving apremilast 30 mg twice daily vs 20 mg twice daily (statistical analysis between treatment groups not performed). Secondary: At week 16, apremilast was associated with significantly greater reductions in HAQ-DI compared to placebo. The mean (SE) changes from baseline were -0.20 (0.04) for the apremilast 20 mg twice daily group; P=0.0252 vs placebo), -0.25 (0.04) for the apremilast 30 mg twice daily group; P=0.0015 vs placebo) and -0.09 (0.04) for the placebo group. The intent to treat analysis demonstrated consistent results for the mean changes (SD) from baseline in the HAQ-DI among the apremilast 20 mg twice daily group; -0.20 (0.04; P=0.0252); the apremilast 30 mg twice daily group; -0.24 (0.04; P=0.0017); and placebo group; -0.09 (0.04). At week 16, a significantly greater proportion of patients in the apremilast 30 mg twice daily group achieved minimal clinically important differences of ≥0.13 and ≥0.30 on the HAQ-DI compared to placebo. The differences between apremilast 20 mg twice daily and placebo did not reach statistical significance. Minimal clinically important differences ≥0.13 was achieved by

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				44.8% of patients treated with apremilast 20 mg twice daily, 50.3% of patients treated with apremilast 30 mg twice daily (P=0.0334 vs placebo); and 38.8% of patients treated with placebo. Minimal clinically important differences ≥0.30 was achieved by 33.7% of patients treated with apremilast 20 mg twice daily; 39.8% of patients treated with apremilast 30 mg twice daily (P=0.0149 vs placebo); and 27.3% patients treated with placebo. A significantly greater proportion of patients receiving either dose of apremilast 20 mg twice daily and 30 mg twice daily achieved ACR20, ACR50 and ACR70 vs placebo, or the response rates among those in the active treatment groups were maintained. An ACR20 response of 45.3% was observed at week 24 in patients treated with apremilast 30 mg twice daily independent of their response at week 16. A statistically significant improvement in physical function was observed with apremilast, as measured by changes from baseline in HAQ-DI score and the 36-Item Short-Form Health Survey Physical Functioning domain score. Significant improvements in most ACR component scores, particularly swollen and tender joint counts and patient assessment of pain, were also reported. In patients with baseline enthesitis, the mean change from baseline in Maastricht Ankylosing Spondylitis Enthesitis Score was significantly higher for apremilast 30 mg twice daily vs placebo (P=0.0334). A significantly greater proportions of patients receiving apremilast 20 mg twice daily (32.0%; P=0.0037) and 30 mg twice daily (33.6%; P=0.0013) achieved a Maastricht Ankylosing Spondylitis Enthesitis Score of 0 at week 24 compared to patients receiving placebo (14.4%). In patients with baseline dactylitis, the mean change from baseline in dactylitis severity score was higher with apremilast vs placebo and resulted in greater proportions of patients with dactylitis scores achieving 0 at week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				24 (apremilast 20 mg twice daily group; 50.9%; apremilast 30 mg twice daily group; 47.7%; placebo [40.9%]). The differences did not reach statistical significance at week 24, however. In patients with baseline psoriasis affecting ≥3% of the BSA, significantly greater proportions of patients receiving either dose of apremilast achieved ≥50% improvement in the PASI score (PASI-50) compared to placebo [apremilast 20 mg twice daily group; 33.8% (P=0.0439); apremilast 30 mg twice daily group; 50.6% (P=0.0001); and 18.5%, respectively]. Similar results were also observed among the PASI-75 score for those treated with apremilast 20 mg twice daily, apremilast 30 mg twice daily, and placebo (17.6%; P=0.0180, 21.0%; P=0.0040, and 4.6%, respectively). During the 24-week placebo-controlled phase, adverse events occurring in ≥5% of any treatment group included diarrhoea, nausea, headache and upper respiratory tract infection, most of which were mild to moderate in severity. Discontinuations due to adverse events were comparable across groups; including 6.0% among the apremilast 20 mg twice daily group; 7.1% among the apremilast 30 mg twice daily group; and 4.8% among the placebo group.

Study abbreviations: DB=double-blind, IN=international, MC=multicenter, PC=placebo-controlled, RCT=randomized-controlled trial, SD=standard deviation
Miscellaneous abbreviations: ACR20= American College of Rheumatology Classification of Improvement in Functional Status of Rheumatoid Arthritis, BSA=body surface area, DMARD=disease modifying anti-rheumatic drugs, HAQ-DI=Health Assessment Questionnaire-Disability Index, NSAIDs=non-steroidal anti-inflammatory drugs, PASI=Psoriasis Area and Severity Index, SD=standard deviation

Special Populations

Table 5. Special Populations[6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Apremilast	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children <18 years have not been established.	No dose adjustments provided for mild (CrCl 60 to 80 mL/minute) or moderate (CrCl 30 to 59 mL/minute) renal impairment. Reduce dose to 30 mg once daily in patients with severe (CrCl <30 mL/minute) renal impairment.	No dose adjustments required in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.	C	Unknown; use with caution.

CrCl=creatinine clearance estimated by Cockroft-Gault equation

Adverse Drug Events

The adverse events in clinical trials reported in ≥2% of patients receiving apremilast 30 mg twice daily and ≥1% than the rate reported by patients receiving placebo for up to 16 weeks are outlined in Table 6.

Table 6. Adverse Drug Events* (%)[6]

Adverse Event	Apremilast Day 1 to 5 (N=497)	Apremilast Day 6 to 112 (N=493)	Placebo Day 1 to 5 (N=495)	Placebo Day 6 to 112 (N=490)
Abdominal pain, upper	0.6	2.0	0.0	0.2
Diarrhea	9.3	7.7	1.2	1.6
Headache	4.8	5.9	1.8	2.2
Nasopharyngitis	0.2	2.6	0.2	1.6
Nausea	7.4	8.9	1.4	3.1
Upper respiratory tract infection	0.6	3.9	0.6	1.8
Vomiting	0.8	3.2	0.4	0.4

Contraindications/Precautions

Table 7. Contraindications[6]

Contraindication(s)	Apremilast
Hypersensitivity to the active agent or any excipient within the formulation	✔

Table 8. Warnings and Precautions[6]

Warning/Precaution	Apremilast
Depression; there is an increased risk of depression as well as suicidal thoughts and behavior; monitor closely for the emergence of worsening depression, suicidal thoughts, or mood changes	✔
Weight decreased; a reduction in weight by 5 to 10% of body weight was observed in clinical trials; body weight should be monitored routinely and if unexplained or significant weight loss occurs consider discontinuing therapy	✔

Drug Interactions

Table 9. Drug Interactions[6]

Generic Name	Interacting Medication or Disease	Potential Result
Apremilast	Strong CYP 450 inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin, etc.)	Co-administration may result in reduced systemic exposure of apremilast, resulting in decreased efficacy.

Dosing and Administration

The recommended initial dose of apremilast involves a taper of the course of five days to reduce the gastrointestinal adverse events associated with initial therapy. Following the five day titration phase, the recommended maintenance dose is 30 mg twice daily by mouth beginning on day six.[6]

Table 9. Dosing and Administration[6]

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Apremilast	Treatment of adult patients with psoriatic arthritis: Tablet: initial, titration over five days according to the following schedule: day 1, 10 mg once daily in the morning; day 2, 10 mg twice daily; day 3, 10 mg once daily in the morning and 20 mg once daily in the evening; day 4, 20 mg twice daily; day 5, 20 mg once daily in the morning and 30 mg once daily in the evening; maintenance; 30 mg twice daily beginning on day six and thereafter	Safety and efficacy in children <18 years have not been established.	Tablet: 30 mg*† Starter pack‡

* Supplied in 60-count bottles.
† Supplied as a 28-count carton, consisting of two-30 mg blister cards containing fourteen 30 mg tablets.
‡ Supplied in a two-week starter pack consisting of 13 tablets of 10 mg, 20 mg, and 30 mg tablets with an additional 14 tablets of 30 mg.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3 and 4 (2008-2009)[1-3]**	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 Food and Drug Administration (FDA) indication.

Clinical Guideline	Recommendations
	• 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 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. Biologics • Three tumor necrosis factor alpha (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. • Non-steroidal antiinflammatory drugs (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 disease modifying anti-rheumatic drugs (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

Clinical Guideline	Recommendations
	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 Academy of Dermatology: **Position Statement on Treatment of Psoriatic Patients (2013)**[8]	• Therapeutic options in the treatment of chronic plaque psoriasis should be tailored to meet individual patients' needs. • The "stepwise-therapy" (i.e., first phototherapy, then oral systemic therapies, followed by biologic therapies) in ascending order is not required. • Patients with moderate-to-severe psoriasis are candidates for systemic therapy (i.e., phototherapy, or systemic therapy including biologic therapy). • The decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[9]	<u>Recommendations for treatment</u> • 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.

Conclusions

Psoriasis is an autoimmune inflammatory disease that has significant medical, psychological, and quality of life implications. Psoriasis affects approximately 1 to 3% of the population, with approximately 15 to 30% of those afflicted with the condition developing psoriatic arthritis, a chronic, inflammatory spondyloarthropathy.[1-3] The condition is characterized by stiffness, pain, swelling, and tenderness of the joints as well as the surrounding ligaments and tendons (i.e., enthesitis). In addition, peripheral arthritis, axial involvement, dactylitis, uveitis may also develop.[4,5]

The course of psoriatic arthritis is variable and unpredictable; it may range from a mild non-destructive disease to debilitating arthropathy. Mild forms of psoriatic arthritis typically have minimal impact on quality of life and generally respond to non-steroidal anti-inflammatory drugs. Moderate disease severity impacts activities of daily living as well as physical and/or mental function. These forms tend to be unresponsive to non-steroidal anti-inflammatory drugs and require treatment with disease-modifying antirheumatic drugs or tumor necrosis factor-alpha inhibitors. Severe disease typically requires both disease-modifying antirheumatic drugs and tumor necrosis factor-alpha inhibitors or other biologic therapies and have a significant impact on quality of life. Patients with severe disease may not be able to perform the majority of routine activities of daily living without significant pain or dysfunction, which often further impacts their physical and emotional well-being.[1-5] Overall, the disease course is characterized by flares and remissions, leading to chronic joint damage, especially if not properly treated.[4,5]

Apremilast (Otezla®) is a phosphodiesterase 4 inhibitor approved by the Food and Drug Administration (FDA) for the treatment of adults with active psoriatic arthritis.[6] It is a small-molecule inhibitor of phosphodiesterase 4, specific for cyclic adenosine monophosphate (cAMP). The inhibition of phosphodiesterase 4 results in increased intracellular cAMP levels, helping to regulate the inflammatory mediators involved in the pathophysiology of psoriatic arthritis. It is the first, in-class, oral therapy for the management of psoriatic arthritis and does not require routine laboratory monitoring.[6,7] It is administered over a five-day titration period, to minimize gastrointestinal symptoms, to a target dose of 30 mg twice daily.

The FDA-approval of apremilast was based upon the safety and efficacy results from three multi-center, randomized, double-blind, placebo-controlled trials (PALACE 1 through 3); however, only the PALACE 1 trial is currently available in the published literature.[7,11] The PALACE 1 trial demonstrated the efficacy of apremilast across patients with varying treatment experience, and found that at 16 weeks, significantly more patients receiving either apremilast 20 mg twice daily or apremilast 30 mg twice daily achieved an American College of Rheumatology 20 Response (ACR20) response vs placebo. At week 16, apremilast was associated with significantly greater reductions in Health Assessment Questionnaire Disability Index compared to placebo and a greater proportion of patients receiving either dose of apremilast also achieved ACR50 and ACR70 vs placebo. Overall, the drug was well tolerated.[11]

According to current clinical guidelines for the management of psoriasis and psoriatic arthritis, the decision for treatment should be based on efficacy, potential adverse effects, prior treatments, patient preference, duration and severity of disease, medical risk factors**,** co-morbidities, and potential impact on quality of life.[1-3,8] non-steroidal anti-inflammatory drugs and/or intra-articular injections of corticosteroids are appropriate treatment options in patients with mild, localized disease. Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that has significantly impacted quality of life should be treated with methotrexate, a tumor necrosis factor-alpha inhibitor, or both. Other effective disease-modifying antirheumatic drugs include leflunomide and sulfasalazine. The currently available clinical guidelines note a relatively comparable efficacy profile for the biologics approved by the FDA and do not recommend any one particular biologic agent over another. In addition, they also do not currently include recommendations for the use of apremilast in the management of psoriatic arthritis.[1-3,8,9]

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