Apremilast for the treatment of psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy that affects joints and entheses and is associated with psoriasis (PsO). There are five clinical patterns of PsA: symmetrical polyarthritis, distal interphalangeal arthropathy, asymmetrical oligoarthritis, arthritis mutilans, and spondylitis, with or without sacroiliitis. Concerning PsA, the goals of therapy are to control inflammation, prevent articular damage, and reduce discomfort in the affected joints. Although there are many therapeutic options for the treatment of PsAs, physicians most often begin with nonsteroidal anti-inflammatory drugs (NSAIDs) for mild disease. Disease-modifying anti-rheumatic drugs (DMARDS) are reserved for moderate to severe disease. Apremilast may be a useful option for some patients.

Keywords: apremilast; psoriatic arthritis; psoriasis

Introduction

Apremilast (Otezla©) is an orally administered phosphodiesterase-4 inhibitor that was FDA approved for the treatment of PsA in March 2014. This novel medication suppresses many pro-inflammatory mediators and cytokines released in the innate and adaptive immune responses. Apremilast's mechanism of action allows for targeting the inflammatory cascade at an earlier point to interrupt and modulate the pro-inflammatory response. This allows for a potential benefit compared to currently available biologic therapies that are aimed at curtailing the production of specific single inflammatory mediators within the inflammatory signaling cascade. Recent studies show that apremilast has a low side effect profile and have been classified as "mild to moderate" by most investigators. Apremilast is orally available, slightly lower-priced, with fewer side effects compared to biologic therapy. Apremilast appears to be well-tolerated and effective when used for treatment of psoriatic arthritis. Apremilast is also currently approved for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy. Apremilast may be particularly useful in patients who are unwilling to self-inject or undergo infusion therapy, while requiring the need for a systemic therapy. It may be especially useful for patients who have failed other therapies as a result of side effects, toxicity, or lack or efficacy. Routine laboratory monitoring is not required for patients who are treated with apremilast. Owing to a half-life of 6-9 hours, side effects, when they occur, can resolve more rapidly in those taking apremilast. Apremilast's convenience and low side-effect profile, including no association of increased risk for infections or malignancies, warrant its consideration before starting biologic therapy following unsuccessful topical and DMARD treatment.

Review and Discussion

Psoriatic arthritis is a chronic inflammatory arthropathy that affects joints and entheses and is associated with psoriasis. The global prevalence of psoriasis ranges from 0.91 to 8.5% among adults. As many as 30% of patients with psoriasis will proceed to develop arthritic manifestations [1,2,3].

Eighty-four percent of patients with psoriatic arthritis have psoriasis at presentation [4]. One study revealed that only six percent of 129 patients diagnosed with psoriatic arthritis did not have psoriasis at presentation [5]. Furthermore, another study showed that arthritis preceded skin disease in 13 to 17% of all patients. Importantly, 15% of patients who have not been previously diagnosed with skin disease prior to

presentation will be found to actually have psoriasis when they are thoroughly examined [6].

Symptoms of psoriatic arthritis usually begin between the ages of 30 and 50 with joint involvement typically beginning in an indolent manner. Psoriatic arthritis causes erosive changes of joints (**Figure 1**). A classic boney presentation of psoriatic arthritis on plain radiograph is pencil-in-cup deformity (**Figure 2**). There are five clinical patterns of psoriatic arthritis (**Table 1**): symmetrical polyarthritis, distal interphalangeal arthropathy, asymmetrical oligoarthritis, arthritis mutilans, and spondylitis, with or without sacroiliitis [7].

Although the pattern of joint involvement is diverse, it usually affects the distal interphalangeal joints of the hands and feet first in an asymmetric distribution.

Psoriatic arthritis is in the family of seronegative spondyloarthopathies, a group of several related but phenotypically distinct disorders including psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis [10]. Two hallmarks of psoriatic arthritis are pain and stiffness in the affected joints, with pain commonly lasting longer than 30 minutes and alleviated by physical activity. It is also characterized by enthesitis (inflammation of the tendon or ligament insertion sites on the bone), dactylitis (sausage-like digits), and spinal involvement. Nail disease showed an odds ratio of three with the subsequent arrival of arthritic manifestations [11]. Nail disease and arthritic manifestations are intimately linked through a network of entheses fibers possibly linking enthesopathy as the tissue specific factor linking these two entities [12-15].

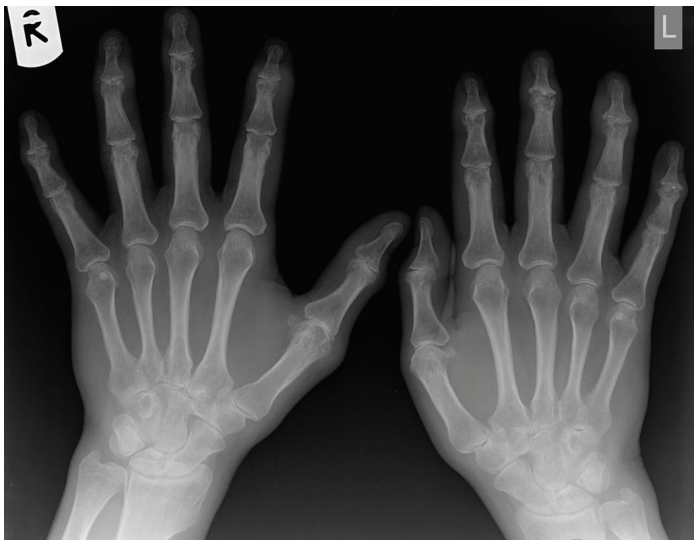


Figure 1. *The hallmark of psoriatic arthritis is the combination of erosive change with bone proliferation leading to the destruction of and fusion of joints and subsequent deviation and displacement of digits. The disease most commonly involves the hands, followed by feet. It can also affect sacroiliac joints and the spine [8]. Case courtesy of Dr Jeremy Jones, Radiopaedia.org, rID: 8798*

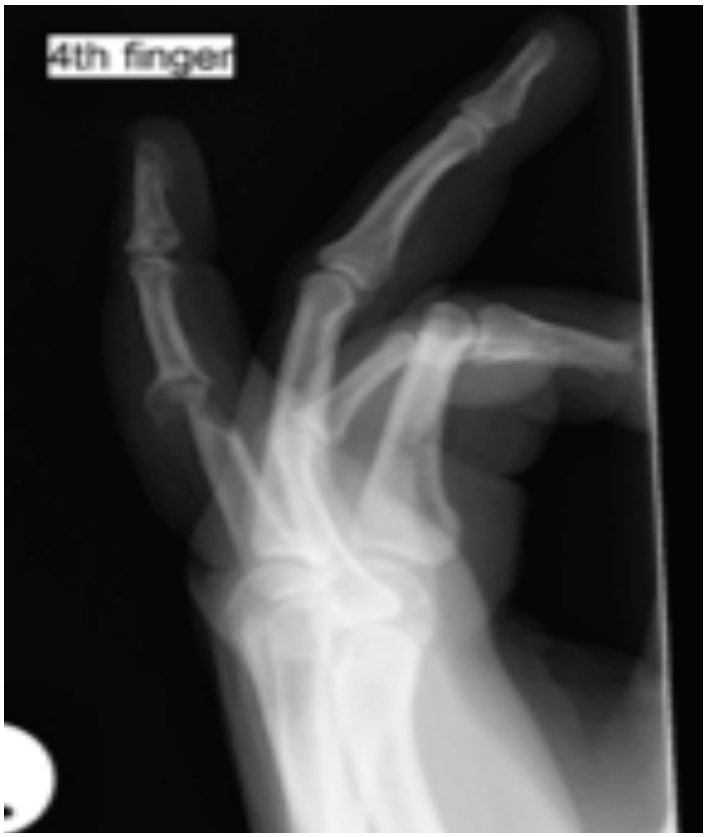


Figure 2. *Pencil-in-cup deformity is the description given to one of the appearances on plain radiograph in psoriatic arthritis. The appearance results from gradual periarticular erosions and bone resorption giving the ultimate appearance of a pencil in a cup. Case courtesy of RMH Key Conditions, Radiopaedia.org, rID: 33845*

Psoriatic arthritis is classified according to the Classification Criteria for Psoriatic Arthritis (CASPAR, **Table 2**), which requires a minimum three points from the following features, in addition to inflammatory articular disease [16].

Currently there is no serologic test for psoriatic arthritis. Laboratory abnormalities in affected patients include an elevated C-reactive protein and erythrocyte sedimentation rate, typical of systemic

Table 1. *Moll and Wright Classification of Psoriatic Arthritis.*

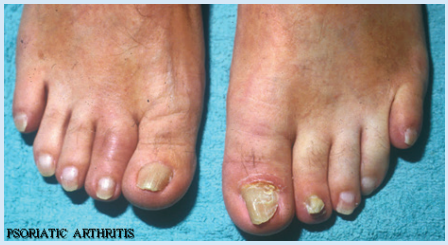
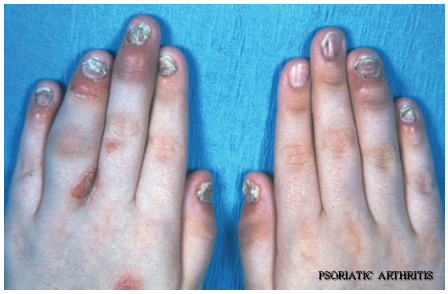
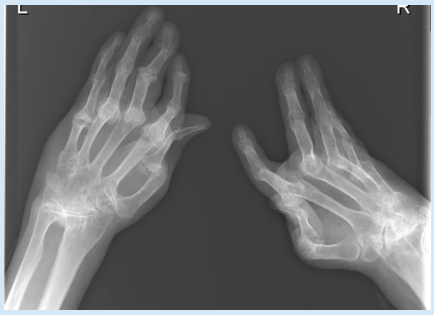
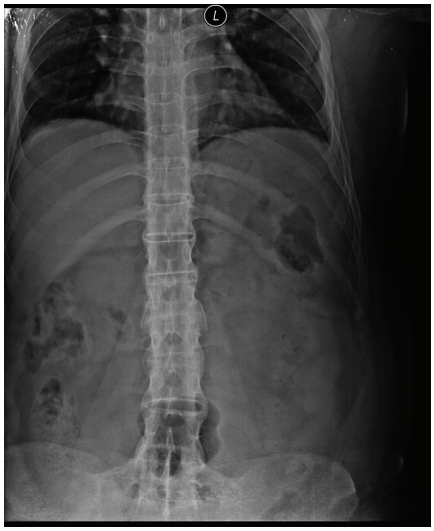
Clinical presentation	Image	Percentage of patients with symptoms (Percentages overlapping) [9]
Asymmetrical oligoarthritis: This causes a painful, sausage-like swelling of the fingers and toes.	 Case courtesy of Dr George V Lawry MD	50%
Distal interphalangeal arthritis: The most typical pattern of joint involvement in psoriasis. Associated with nail dystrophy.	 Case courtesy of Dr George V Lawry MD	5%
Arthritis mutilans: An erosive and painful arthritis that affects fingers and toes and can cause a deformity.	 Case courtesy of Dr Jan Frank Gerstenmaier, Radiopaedia.org, rID: 25200	5%
Spinal column involvement: Spondylitis is an inflammation of the joints between the vertebrae of the spine, causing lower back pain.	 Case courtesy of Dr Neel Raithatha, Radiopaedia.org, rID: 28355	40%

Table 2. *CASPAR Criteria.*

Current evidence of psoriasis (2 points)
Family history of psoriasis, in the absence of current or history of psoriasis (1 point)
Negative rheumatoid factor (1 point)
Dactylitis (1 point)
Nail dystrophy (1 point)

inflammation. A negative rheumatoid factor, seen in about 95% of affected patients, illustrates the disease as a seronegative process [17].

Factors Associated with Development of Psoriatic Arthritis

The early phases of the disease are likely mediated through both tissue-specific factors and innate immune mechanisms (**Table 3**). As the disease progresses, additional abnormalities suggest an immunologic pathogenesis [18]. However, the precise cause(s) of psoriatic arthritis is unknown but is likely the result of a confluence of genetic, immunologic, and environmental factors.

Immunologic Abnormalities of Psoriatic Arthritis

Activated T cells appear to play a major role in the pathogenesis of psoriasis and psoriatic arthritis [18]. Current literature suggests that Th17 and IL-17 play a key role in pathogenesis. The effects of IL-1β and TNF-α have influenced joint pathology. In psoriatic disease, Th17 cells produce IL-22, which has potent capacity in inducing keratinocyte proliferation [19]. IL-17 plays an important role in the development of psoriasis and psoriatic arthritis, and, therefore, it has become a sought after target in the treatment of psoriatic disease [20].

Treatment of Psoriatic Arthritis

Psoriatic arthritis can be a severe and progressive disease. Therapy is directed at both skin and musculoskeletal aspects of this psoriatic disease. Concerning psoriatic arthritis, the goals of therapy are to control inflammation, prevent articular damage, and reduce discomfort in the affected joints. Although there are many therapeutic options for the treatment of psoriatic arthritis (**Figure 3**), physicians most often begin with nonsteroidal

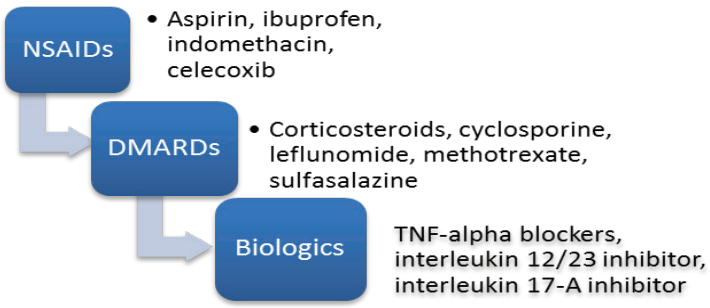


Figure 3. *Typical Treatment Pattern for Psoriatic Arthritis [22]*

anti-inflammatory drugs (NSAIDs) for mild disease. Disease-modifying anti-rheumatic drugs (DMARDS) are reserved for moderate to severe disease [21].

NSAIDs used to treat psoriatic arthritis include selective and non-selective cyclooxygenase inhibitors and are used in the treatment of mild

Table 3. *Immunologic Response.*

Elevated plasma levels of:
Immunoglobulins Antinuclear antibodies
Elevated synovial levels of:
Cytokines including IL-1-beta, IL-6, IL-8, TNF-a Platelet-derived growth factors

disease. Comparative studies have not shown any difference among NSAIDs in the improvement of symptoms of psoriatic arthritis [1,21].

A DMARD is typically the first line of treatment when patients present with moderate disease, although none are FDA approved for this indication. DMARDs include methotrexate, leflunomide, cyclosporine, and sulfasalazine. Methotrexate (MTX) is typically the first DMARD initiated and leflunomide (LEF) is reserved for situations in which patients do not respond to MTX or have adverse effects. MTX and LEF are indicated in patients with five or more swollen joints. These drugs, particularly MTX, are used primarily to relieve the pain and reduce joint inflammation. They are titrated to increase patient tolerance to the maximum recommended dosage [21].

Tumor necrosis factor (TNF) inhibitors are FDA approved and effective in treatment of psoriatic arthritis including certolizumab pegol (Cimzia©), etanercept (Enbrel©), adalimumab (Humira©), infliximab (Remicade©), and golimumab (Simponi©). They appear to be the most effective treatment of psoriatic arthritis currently and have been shown to reduce joint disease activity, prevent structural damage, and improve function. There are no head to head trials but there appears to be no statistically significant difference between the TNF inhibitors [21].

Newer medications include secukinumab (Cosentyx©) and ustekinumab (Stelara©), which are biologic medications that target other modulators of the immune system. Ustekinumab (Stelara©) is FDA approved for the treatment of psoriatic arthritis and is an IL-12/IL-23 antagonist. Direct comparisons with the TNF inhibitors are lacking, but response rates appear to be slightly lower based on comparisons. In significant arthritis, rheumatologists prefer to use TNF inhibitors compared to Ustekinumab (Stelara©). Secukinumab (Cosentyx©) is under investigation for the treatment of psoriatic arthritis and is an IL-17A inhibitor. Further data needs to be collected to assess efficacy in psoriatic arthritis [21].

Apremilast (Otezla©) is an orally administered phosphodiesterase-4 inhibitor that was FDA approved for the treatment of psoriatic arthritis in March 2014. This novel medication suppresses many pro-inflammatory mediators and cytokines released in the innate and adaptive immune responses. In October 2014 apremilast was also approved for the treatment of moderate to severe plaque psoriasis for patients who are candidates for systemic therapy or phototherapy.

Mechanism of Action

Apremilast is an orally available compound that inhibits phodiesterase 4 (PDE4). It is absorbed orally and thus represents an improvement over the current biologic therapies that are only available in injectable forms. Apremilast is metabolized in the liver, primarily through CYP34A. The drug has a half-life elimination of 6 to 9 hours. PDE4 inhibitors are used to treat other conditions such as inflammation in asthma, lung neutrophilia, arthritis, inflammatory bowel disease and a variety of other conditions [23].

Apremilast's mechanism of action allows for targeting the inflammatory cascade at an earlier point to interrupt and modulate the pro-inflammatory response. This allows for a potential benefit compared to currently available biologic therapies that are aimed at curtailing the production of specific single inflammatory mediators within the inflammatory signaling cascade. Over-activity of T cells with subsequent production of pro-inflammatory cytokines is significantly associated psoriatic arthritis.

PDE4 hydrolyzes cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP) and it is the predominant form of phosphodiesterase found in keratinocytes, macrophages, lymphocytes, and neutrophils [24,25]. cAMP is a second messenger that regulates inflammatory responses. Elevation of cAMP by the inhibition of PDE4 suppresses TNF production and the immune response. TNF is involved in up-regulation of cartilage degradation and collagen in the joints, and the TNF inhibitors may suppress these actions in the synovium [26].

As a broad-spectrum anti-inflammatory agent [27], apremilast also inhibits the response of polymorphonuclear cells (PMN) and the production of TNF by NK cells and keratinocytes. Both are implicated in the pathophysiology of psoriasis [27]. Apremilast also modulates the anti-inflammatory

mediators involved in inflammatory homeostasis, which results in a reduction of clinical symptoms and reversal of the inflammatory pathophysiology of skin and joints associated with psoriatic arthritis/psoriasis [28].

Results of Clinical Trials

There have been 42 clinical trials to date that involve apremilast. Small Phase I trials and pilot studies analyzed the drug's efficacy in the treatment of a wide variety of conditions, such as acute gout and rosacea [29]. Since 2008, nine of these studies have published results and four have assessed the efficacy of apremilast in the treatment of psoriasis and psoriatic arthritis [30].

There are a number of Phase III trials underway and most are due for completion in 2015 or 2016. These studies aim to test the effectiveness of apremilast in the treatment of psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, and sarcoidosis.

An ongoing study of patients with psoriasis this year randomized patients to apremilast 30 mg twice daily for 32 weeks, and at week 32, responders were re-randomized to apremilast 30 mg twice daily or placebo. The primary outcome measure is a 75% improvement in the PASI 75* from week 16 to baseline, in addition to other outcome measures such as participants receiving a Static Physician Global Assessment score of Clear (0) or Almost Clear (1) with a 2 point reduction from baseline by week 16, a 48 % reduction in affected body surface area by week 16, and other improvements in PASI scores [31]. The time to loss of effect during the randomized treatment withdrawal phase was also measured, but the results have not yet been published.

* Psoriasis Area and Severity Index (PASI). Measurement of psoriasis disease severity; treatment is characterized by PASI reduction. PASI 75 reflects 75% reduction in severity.

Another Phase III trial of 844 patients revealed a 50% improvement in symptoms of psoriasis (PASI 50) at 16 weeks of treatment compared to 17 percent of subjects randomized to a placebo. Thirty-three percent of patients achieved PASI 75 [32].

The Phase III psoriatic arthritis long-term assessment of clinical efficacy (PALACE, **Table 4**) program consists of four independent, Phase III trials with treatment periods of 12 weeks followed by an extension period of 52 weeks. PALACE-1, 2 and 3 are currently underway and are evaluating the efficacy and safety of an apremilast 20 and 30 mg dose twice daily in 1500 biologic-naive and biologic-experienced psoriatic arthritis patients. Patients taking concurrent DMARDs were allowed to continue stable doses (methotrexate, sulfasalazine, leflunomide, or a combination). Preliminary reports summarized below reveal apremilast to be significantly superior to placebo. Apremilast displayed a lower efficiency of the drug in patients who had received biological agents in the past [33]. PALACE-4 found consistent rates of response among patients naive to DMARD therapy. The study included 501 patients with a history of psoriasis and active psoriatic arthritis [33].

Adverse Effects

Recent studies show that apremilast has a low side effect profile and have been classified as "mild to moderate" by most investigators [29,36,37,38]. Before the advent of apremilast, primary adverse effects of the early PDE4 inhibitors are classified into mild effects such as gastrointestinal distress including nausea and emesis, and headaches, and severe side effects such as arrhythmias and heart failure [39,40]. Pooled data from three multi-center randomized controlled trials with 1493 adults with active psoriatic arthritis randomized to apremilast 20 mg BID, apremilast 30 mg BID or placebo revealed weight loss, drug-drug interactions, depression, diarrhea, and nausea. The incidence of diarrhea has been reported at 8% to 17%, with an incidence of nausea between 7% and 17% [41]. GI side effects appear to occur predominantly during initiation of the medication, so a 5- day dose escalation schedule is advised. A dose escalation recommended by the manufacturers is:

Day 1: 10 mg in morning

Day 2: 10 mg in morning and 10 mg in evening

Day 3: 10 mg in morning and 20 mg in evening

Day 4: 20 mg in morning and 20 mg in evening

Day 5: 20 mg in morning and 30 mg in evening

Day 6 and thereafter: 30 mg twice daily

One % of patients with apremilast reported depression (**Table 5**), compared to 0.8% of patients randomized to placebo, so an assessment for depression and suicidal ideation should be undertaken before and during continued therapy with apremilast [42]. Ten to 12 % of patients randomized to apremilast 30 mg BID were found to lose 5-10% of their body weight, compared to 3.3% of patients taking a placebo [43,44].

The adverse effects of most early PDE4 inhibitors appear to result from the inhibition of the PDE4D isoform [45]. However, apremilast does not selectively inhibit that specific isoform, and so does not result in severe side effects [39].

Apremilast is metabolized by the cytochrome P450 pathway, so drugs that induce or inhibit that pathway should be used with caution with apremilast [43]. CYP3A4 inducers (**Table 6**) may decrease the serum concentration of apremilast.

Table 4. *PALACE Trials Summary.*

Trial	Drug	Indication	Primary Outcome Measure	Result (Percentage of patients to achieve ACR20*)
PALACE-1 N=504	Apremilast 20 mg BID	Psoriatic Arthritis	ACR20* at week 16	19.0 placebo, 31 Apremilast 20 mg [34, 33]
PALACE-1 N=504	Apremilast 30 mg BID	Psoriatic Arthritis	ACR20* at week 16	19.0 placebo, 40 Apremilast 30 mg [34, 33]
PALACE-2 N=488	Apremilast 20 mg BID	Psoriatic Arthritis	ACR20* at week 52	19.5 placebo, 52.9 Apremilast 20 mg [34]
PALACE-2 N=488	Apremilast 30 mg BID	Psoriatic Arthritis	ACR20* at week 52	19.5 placebo, 52.6 Apremilast 30 mg [34]
PALACE-3 N=505	Apremilast 20 mg BID	Psoriatic Arthritis	ACR20* at week 16	18.9 placebo, 29.4 Apremilast 20 mg [34]
PALACE-3 N=505	Apremilast 30 mg BID	Psoriatic Arthritis	ACR20* at week 16	18.9 placebo, 42.8 Apremilast 30 mg [34]
PALACE-4 N=527	Apremilast 20 mg BID	Psoriatic Arthritis	ACR20* at week 16	16.9 placebo, 29.2 Apremilast 20 mg [34]
PALACE-4 N=527	Apremilast 30 mg BID	Psoriatic Arthritis	ACR20* at week 16	16.9 placebo, 32.3 Apremilast 30 mg [34]

** American College of Rheumatology (ACR) Criteria. Measurement of arthritis improvement, ACR20 is equivalent to 20% improvement of arthritic joint parameters [35]. Although a useful measurement in arthritis, an ACR20 is a smaller improvement compared to normal parameters established for psoriasis improvement (PASI75).*

Table 5. *Apremilast Most Common Side Effects.*

Most Common Side Effects (Percentage of subjects with side effect that took 30mg of apremilast BID) [46]
Diarrhea (17%)
Nausea (17%)
Upper respiratory tract infection/nasopharyngitis (9%)
Vomiting (4%)
Abdominal pain (4%)
Decreased appetite (3%)
Migraine headache (2%)
Depression (1%)
Rebound worsening of psoriasis (0.3%)

The drug is categorized as Pregnancy Risk Factor C and excretion in breast milk is unknown [43]. Dose reduction of apremilast is recommended in patients with severe renal impairment, or a creatinine clearance of <30 mL/minute.

There is a mild association with infection rates on apremilast with nasopharyngitis and upper respiratory infections seen in 2.6% and 3.9% of patients [45,47]. Infections resolved with antibiotics and patients resumed treatment. It is worth noting that apremilast has yet to be associated with increased risks of infection or malignancy [48].

Comparison of Biologic Therapies for Treatment of Psoriatic Arthritis

Treatment of patients with psoriatic arthritis is targeted at the control of pain and inflammation of the affected joints. The ultimate goal of therapy is to slow joint destruction. Prior to oral apremilast, oral DMARDs (**Table 7**) were the only available treatment of psoriatic arthritis. There is no expert consensus comparing the effectiveness of different drug classes in the treatment of psoriatic arthritis. The treatment of psoriatic arthritis includes agents used to treat cutaneous psoriasis and other types of inflammatory arthritis [49].

There are five biologics available currently (**Table 8**), which target tumor necrosis factor in patients with psoriatic arthritis. Apremilast may be compared (**Table 9**). There is also evidence from trials of other biologics approved for the treatment of rheumatoid arthritis, but this discussion will focus on the drugs approved by the United States Food and Drug Administration (FDA) for use in patients with psoriatic arthritis. These anti-TNF drugs are adalimumab, etanercept, golimumab, infliximab and certolizumab.

Table 6. *CYP3A4 Inducers.*

Drug
Carbamazepine
Nevirapine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
St. John's Wort

Table 7. *Summary of TNF inhibitors.*

Drug	Therapeutic Regimen	Mechanism of Action	Efficacy	Safety	Cost [76]
Adalimumab (Humira®)	40 mg SC every other week	Human monoclonal antibody	PASI-75: 59% ACR20 at week 12: 39%	Increased prevalence of bacterial, viral, fungal infections, reactivation of HBV; reactivation of latent TB [8]	$2073 40mg/0.8 mL pen
Etanercept (Enbrel®)	25 mg SQ twice a week	Fusion protein links TNF receptor to Fc component of human IgG	PASI-75: 26% [8] Mean PASI Score Increase: 42 ACR20 response at 12 weeks: 59%	Lower rate of withdrawal than infliximab due to adverse effects.	$518 25 mg 1 kit
Golimumab (Simponi®)	50 mg SQ every month	Human monoclonal antibody	PASI-75: 57% [8] ACR20 week 14: 51%	Increased URI, sepsis, ALT, AST, tuberculosis, anemia, and various malignancies, particularly	$4199 50 mg/0,5 mL pen
Infliximab (Remicade®)	5 mg/kg week 0, 2, 6, and every 8 weeks afterward [8]	Mouse-human monoclonal antibody (Chimeric monoclonal antibody)	PASI-75: 65% ACR20 at 14 weeks: 58%	Infusion related reactions, infection, CMV, TB, heart failure, lymphoma, other malignancies, hepatic injury	$1225 100 mg vial
Certolixumab (Cimzia ®)	400 mg D1, week 2 and week 4, then 200 mg every other week	Recombinant antibody	ACR20 week 12 58% (placebo 24.3%)	Infections, malignancies, heart failure; upper respiratory infections, rash and urinary tract infection. Tuberculosis, lupus-like syndromes, opportunistic infections	$3651 200 mg/mL

Table 8. *Summary of Biologic DMARDs: Interleukin 12/23 inhibitors.*

Drug	Therapeutic Regimen	Mechanism of Action	Efficacy	Safety	Cost
Ustekinemab (Stelara ®)	SQ Injection: 45 mg at week0, week 4, and every 12 weeks.	Human monoclonal antibody anti-p40 subunit	PASO-75: 67% ACR20 week 12: 42%	Headache, myocardial infarction, stroke [51].	$9,827 45 mg/0.5mL syringe

Table 9. *Summary of New Oral Treatments.*

Drug	Therapeutic Regimen	Mechanism of Action	Efficacy	Safety	Cost
Apremilast (Otezla ®)	30 mg po BID	PDE4 inhibition	ACR20 at week 16: 34-43% [52]	Diarrhea, nausea, headache [41]	$2250 30 mg 60 pills

Randomized controlled trials that directly compare the efficacy of apremilast with other biologics for the treatment of psoriatic arthritis are not yet available [50].

Apremilast has multiple advantages over the biologics including TNF inhibitors, including ease of use, low side-effect profile, and cost. Apremilast reduces cost because it does not require continuous laboratory monitoring like other treatments for psoriatic arthritis. Although the drug is less effective than some biologics, reflected in PASI and ACR scores, it has proven effective in many patients, and has very few significant side effects, particularly in comparison to other drugs on the market currently for the treatment of psoriatic arthritis.

Conclusion

Apremilast is orally available, slightly lower-priced, with fewer side effects compared to biologic therapy. Apremilast appears to be well-tolerated and effective when used for treatment of psoriatic arthritis. Apremilast may be particularly useful in patients who are unwilling to self-inject or undergo infusion therapy, while requiring the need for a systemic therapy. It may be especially useful for patients who have failed other therapies as a result of side effects, toxicity, or lack or efficacy. Routine laboratory monitoring is not required for patients who are treated with apremilast. In clinical trials, most adverse reactions were mild and resolved with continuation of the drug. The effectiveness of apremilast is dose dependent, and further research is needed to determine if the benefits of a higher dose exceed any increased adverse effects. Other TNF blockers have half-lives that range from 5 days (etanercept) to 14 days (adalimumab) in contrast to apremilast's terminal elimination half-life of 6-9 hours [53]. As a result, side effects, when they occur, can resolve more rapidly in those taking apremilast.

Apremilast is also currently approved for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy, but success rates are slightly lower than those seen with the other anti-TNF biologics, ustekinumab, and cyclosporine. Apremilast should also be considered in patients who have psoriasis with or without mild joint involvement whose disease does not improve with topical treatment. Studies are still needed to compare the efficacy and safety of apremilast in head to head studies against current biologics.

In summary, apremilast is recommended for the treatment of psoriatic arthritis in patients who have failed other drug therapies, prefer an orally administered drug, and in those with mild psoriatic arthritis with or without skin manifestations. It is of moderate efficacy and is recommended as a second line drug in patients who are refractory to initial therapy. Given its safety, oral bioavailability, overall reduction of drug laboratory monitoring, and efficacy in suppression of proinflammatory mediators and cytokines in both innate and adaptive immunity, apremilast is another proven therapeutic option for the treatment of psoriatic arthritis.

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