Oral small molecules for psoriasis
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Abstract
Psoriasis is a chronic inflammatory skin condition that imposes a significant physical and psychosocial burden on patients. Moderate to severe psoriasis often requires systemic treatments, including oral systemic therapies and biologics. Among these medications, apremilast, tofacitinib, and ponesimod have demonstrated clinical efficacy in treating psoriasis; however, further studies are required to understand the benefit-risk profile of these medications in psoriasis patients.

Psoriasis is a chronic condition mediated by immune dysregulation, and it can affect the skin, nails, and joints. The prevalence of psoriasis is thought to be 2% to 4%, and psoriasis may affect as many as 125 million people worldwide.¹,² It is associated with various cardiometabolic disorders and may have a significant psychosocial burden on patients.³,⁴ The pathophysiology of psoriasis is complex and involves an interplay of multiple pro-inflammatory cytokines and signaling pathways.⁵ While topical steroids remain the first-line treatment for patients with limited disease, those with moderate to severe psoriasis often require systemic treatments, including oral systemic therapies and biologics.

Oral systemic therapies for psoriasis encompass traditional oral therapies such as methotrexate, acitretin, and cyclosporine as well as advanced oral small molecules for psoriasis. In this article, we will focus on 3 types of advanced oral small molecules that have been approved or are in development to treat psoriatic diseases: apremilast (a phosphodiesterase-4 [PDE-4] inhibitor), tofacitinib (a Janus kinase [JAK] inhibitor), and ponesimod (a sphingosine-1-phosphate receptor 1 [S1PR1] antagonist; Table). Of the 3 medications, apremilast is approved for the treatment of psoriasis and psoriatic arthritis.

Efficacy
Two multicenter, randomized, double-blind placebo-controlled studies assessed the efficacy and safety of apremilast for up to 52 weeks in 1,255 subjects (ESTEEM 1 and ESTEEM 2).⁸,⁹ The patients had moderate to severe plaque psoriasis—defined as Psoriasis Area and Severity Index (PASI) score ≥12, body surface area involvement (BSA) ≥10%, and Static Physician’s Global Assessment (sPGA) score ≥3 (moderate to severe)—and were candidates for phototherapy or systemic therapy. The primary efficacy endpoint was the proportion of patients achieving PASI 75 from baseline at week 16. For the second phase of the study, during weeks 16 to 32, placebo patients were switched to apremilast. For weeks 32 to 52, the treatment withdrawal phase, patients initially randomized to apremilast who achieved PASI 75 were rerandomized to continue apremilast or switch to placebo.

Across both studies, patients on apremilast showed greater treatment response at week 16 compared with placebo (PASI 75 33.1% versus 5.3%).⁸ Of the patients rerandomized to placebo at week 32, 83.1% lost PASI 75 response. Patients on apremilast also had greater improvements on the following measures compared with placebo: BSA, PASI 50, Nail Psoriasis Severity Index, Scalp PGA, Pruritus Visual Analog Scale, and Dermatology Life Quality Index (DLQI). Similarly, in a phase 4 apremilast efficacy and safety trial (UNVEIL), patients on apremilast had greater percent improvement in PGA X BSA scores compared with placebo (48.1% versus 10.2%, respectively).¹⁰

Safety
Across the trials discussed above, there were several notable adverse events, the most common being gastrointestinal symptoms.
During the placebo-controlled period of the ESTEEM trials, patients on apremilast had a higher prevalence of the following compared with placebo: diarrhea (18.8% versus 7.1%), upper respiratory tract infection (10.2% versus 7.4%), nausea (15.7% versus 6.7%), tension headache (7.3% versus 4.3%), and headache (5.5% versus 4.6%). A higher prevalence of depression was also noted in those treated with apremilast compared with placebo (1.4% versus 0.4%, respectively). Notably, diarrhea and nausea occurred within 2 weeks after the first dose of apremilast for most patients and resolved within 1 month.8,9

A pooled safety analysis of both the ESTEEM 1 and 2 trials assessed the long-term safety of apremilast in patients receiving the medication for up to 156 weeks.11 From weeks 0 to 156, the most common reasons for study discontinuation were lack of efficacy (34.7%), withdrawal by patient (18.8%), and adverse events (11.2%). Commonly reported adverse events included diarrhea, nausea, nasopharyngitis, tension headache, and headache.6 Importantly, the rates of serious adverse events did not increase with long-term apremilast exposure.

Apremilast has been shown to be efficacious in treating patients with psoriasis compared with placebo when assessed using disease severity and health-related quality of life measures.7-9,12-14 Additionally, the safety profile of apremilast has been reported as tolerable in most cases.11 While patients tend to experience gastrointestinal discomfort upon initiating apremilast, this discomfort tends to resolve within a month. Based on clinical trial data, indirect comparisons of apremilast to methotrexate have shown comparable efficacy; however, head-to-head comparisons are lacking between apremilast and other oral systemic medications to help inform clinical decisions.15

### Patient selection
Apremilast is approved for patients with moderate to severe psoriasis and for those with psoriatic arthritis. In clinical practice, due to its modest efficacy, apremilast is best reserved for those with moderate psoriasis. Patients with severe psoriasis likely need biologics for greater disease control. In addition to being a good option for those with moderate psoriasis, apremilast is also appropriate for patients who are particularly adverse to needles. However, clinicians should explain the possible trade-off between avoiding injections versus the risk of not achieving optimal disease control. Finally, it is important to understand in which populations we should take precaution with apremilast. Given the warning on depression in its label, clinicians need to counsel patients with a history of psychiatric disorders prior to initiation. In addition, apremilast needs to be dose-adjusted in those with renal impairment. Finally, while apremilast is thought to minimally affect the immune system, data demonstrating its safety in severely immunosuppressed populations are lacking. Therefore, apremilast use in severely immunocompromised patients should be carefully monitored.

### Tofacitinib
Tofacitinib is an oral, selective JAK 1 and 3 inhibitor that blocks cellular signaling through the common gamma chain-containing receptors for cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. This signaling blockade is thought to disrupt the activation and proliferation of T cells, thus blocking the inflammatory mediators that can lead to psoriasisform skin lesions.16,17 Tofacitinib is currently approved for the treatment of psoriatic arthritis and not psoriasis.

### Indication and dosage
Tofacitinib is currently approved for the treatment of adults with moderate to severe rheumatoid arthritis and psoriatic arthritis who do not respond to methotrexate or other disease-modifying anti-rheumatic drugs (DMARDs). It may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs. For the treatment of rheumatoid and psoriatic arthritis, standard dosing is 5 mg twice daily. For extended-release formulations of tofacitinib, dosing is 11 mg once daily. Phase 2 and phase 3 studies have demonstrated the clinical efficacy of tofacitinib in the treatment of psoriasis.18-22

### Efficacy
Pivotal 1 and Pivotal 2 were similarly designed phase 3, placebo-controlled studies with a total of 1,861 patients randomized in a 2:2:1 ratio to twice-daily tofacitinib 10 mg, 5 mg, or placebo.22 Study endpoints assessed change in disease severity using PGA “clear” or “almost clear” and PASI 75 at week 16. In both studies, patients treated with tofacitinib demonstrated dose-dependent improvement in PASI 75 (29.9%, 59.2%, and 62.6% with 5 mg twice daily, 10 mg twice daily, and placebo, respectively). More patients on tofacitinib 10 mg twice daily achieved PGA and PASI 75 response compared with tofacitinib 5 mg, with a shorter time to response. A noninferiority trial comparing tofacitinib 5 mg or 10 mg twice daily to etanercept 50 mg twice weekly demonstrated that only tofacitinib 10 mg twice daily had comparable efficacy to etanercept.21

### Safety
In the phase 3 trials, the commonly reported adverse events associated with tofacitinib included mild nasopharyngitis, nausea,
and diarrhea. There were slightly higher rates of nasopharyngitis in those treated with tofacitinib 10 mg twice daily compared with placebo in PIVOTAL 2 (7.9% versus 5.6%, respectively). Rates of other adverse events were similar between patients treated with 5 mg, 10 mg, or placebo twice daily across both studies, and events were reported as mild to moderate. In both studies, there were a total of 12 cases of herpes zoster in the tofacitinib groups, leading 5 subjects to discontinue the study during the placebo-controlled period of the study (16 weeks); however, there were no cases of serious infections in the placebo groups. There were few reported malignancies, all of which were not thought to be medication related. Additionally, a pooled safety analysis from both trials demonstrated sustained efficacy of tofacitinib through 2 years. The efficacy was greater for 10 mg than 5 mg, which aligns with the dose-dependent efficacy seen in previous trials.24,25

Tofacitinib has shown clinical efficacy for psoriasis in multiple placebo-controlled trials and in one head-to-head comparison with etanercept.18,19,21-23,26 In addition to improving psoriasis lesions, it has also been shown to significantly improve health-related quality of life compared with placebo.27-30 Clinical data suggest that tofacitinib may be a safe alternative for patients who do not respond to conventional psoriasis treatments. Additional studies directly comparing tofacitinib to currently used psoriasis treatments are needed to highlight the benefit-risk profile of tofacitinib over currently approved therapies.

Ponesimod

Ponesimod is a selective, rapidly reversible S1PR1 modulator. S1PR1 expression on lymphocytes controls their egress from thymus and secondary lymphoid organs. Oral administration of this medication has been shown to lead to a reversible, dose-dependent reduction of blood lymphocyte counts in humans by up to 70%. In mouse models, it has been shown to reduce edema, protein extravasation, neutrophil activity, and skin levels of the proinflammatory cytokines IL-1β, IL-6, IFN-γ, and TNF-α at a dose of 30 mg/kg.31,32 Ponesimod is not currently Food and Drug Administration-approved for treating psoriasis.

Indication and dosage

Ponesimod is an investigational compound that was developed as a potential treatment for relapsing multiple sclerosis. Clinical data in multiple sclerosis have shown a dose-dependent therapeutic effect of ponesimod and defined 20 mg as a daily dose with desired efficacy and acceptable safety and tolerability.33 In addition to its role in multiple sclerosis, investigators have explored ponesimod’s role in other chronic inflammatory disorders. Investigators found that in animal models, it prevented cytokine release in the skin.34

Efficacy

In a phase 2 trial conducted from 2010 to 2012, 326 patients were randomized in a ratio of 1:2:2 to receive once-daily oral placebo, ponesimod 20 mg, or ponesimod 40 mg.35 The primary endpoint was PASI 75 at week 16. Additional endpoints included DLQI, short form-36, and percent change in blood lymphocyte counts. The study found a dose-dependent change in PASI and PGA scores. Of the patients randomized to ponesimod 20 mg, ponesimod 40 mg, and placebo, PASI 75 was achieved at week 16 in 46%, 48%, and 13%, respectively. A PGA score of 0/1 was seen at 16 weeks in 28% of patients on 20-mg ponesimod, 32% in the 40-mg-ponesimod group, and 4.5% of patients in the placebo group. Patients on ponesimod also had greater improvements in quality of life scores than those in the placebo group. These improvements persisted for those who continued ponesimod during the maintenance period from weeks 16 to 28.

Safety

Several important safety concerns have been noted in patients treated with ponesimod. Dyspnea was noted to be the most frequent and serious adverse event noted in patients on ponesimod, followed by increase in liver enzymes and headache. Most adverse events were reported as mild or moderate; however, dyspnea led to early medication discontinuation in the 40-mg group (n = 6; 4.5%) and the 20-mg group (n = 1; 0.8%). Dose-dependent decreases in lymphocyte counts were also reported. From baseline to week 16, mean percentage decreases in lymphocyte counts were 56%, 65%, and 2% with 20-mg ponesimod, 40-mg ponesimod, and placebo, respectively. Lymphocyte counts recovered in those who switched from ponesimod to placebo during the maintenance period. Rebound psoriasis was reported in 3 patients switching from ponesimod to placebo.

Ponesimod may modulate S1PR1 receptors in cardiac and respiratory tissue.35 In this study, patients being up-titrated on ponesimod experienced a mean heart rate decrease of around 13 beats per minute within 2 hours of receiving 10 mg of ponesimod. Four patients discontinued treatment with ponesimod because of transient second-degree atrioventricular block after receiving 10 mg of ponesimod on day 1. Patients on 40 mg of ponesimod experienced up to a 10% decrease in respiratory Forced Expiratory Volume In 1 (FEV1) from baseline compared with 0.1% in the placebo group; however, the effects were reversed in patients who switched to placebo.

The findings of this study suggest that ponesimod may be beneficial for patients with moderate to severe plaque psoriasis; however, further studies must be done to better understand the benefit-risk profile of ponesimod in this patient population.

Conclusion

Small-molecule medications offer an additional therapeutic option for patients who may not respond to conventional psoriasis treatments. Of the 3 small-molecule medications discussed, only apremilast is currently approved for psoriasis. Although tofacitinib was found to be efficacious in treating psoriasis, it is not currently approved for psoriasis. Ponesimod has been studied for relapsing multiple sclerosis; however, additional studies need to be done to determine its efficacy and safety profile in treating psoriasis. Additionally, ponesimod’s safety profile in psoriasis patients need to be further examined due to the medication’s cross-reactivity with its target receptors in cardiac and respiratory tissues. These exciting advancements in small-molecule medications have led to an increased understanding of psoriasis pathophysiology and are expanding the treatment options for psoriasis patients.
16. O’Shea JJ. Targeting the Jak/STAT pathway for immunosuppression.


References