New Treatments for Psoriasis: An Update on a Therapeutic Frontier

Natalia Pelet del Toro, MD; Jashin J. Wu, MD; George Han, MD, PhD

The landscape of psoriasis treatments has undergone rapid change within the last decade, and the dizzying speed of drug development has not slowed, with 4 notable entries into the psoriasis treatment armamentarium within the last year: tapinarof, roflumilast, deucravacitinib, and spesolimab. Several others are in late-stage development, and these therapies represent new mechanisms, pathways, and delivery systems, meaningfully broadening the spectrum of treatment choices for our patients. However, it can be quite difficult to keep track of all the medication options. This review aims to present the mechanisms and data on both newly available therapeutics for psoriasis and products in the pipeline that may have a notable impact on our treatment paradigm for psoriasis in the near future.

PRACTICE POINTS

- Roflumilast, a phosphodiesterase 4 inhibitor, and tapinarof, an aryl hydrocarbon receptor–modulating agent, are 2 novel nonsteroidal topical treatments safe for regular long-term use on all affected areas of the skin in adult patients with plaque psoriasis.
- Deucravacitinib is an oral selective tyrosine kinase 2 allosteric inhibitor that has demonstrated a favorable safety profile and greater levels of efficacy than other available oral medications for plaque psoriasis.
- The dual inhibition of IL-17A and IL-17F with bimekizumab provides faster responses and greater clinical benefits for patients with moderate to severe plaque psoriasis than inhibition of IL-17A alone, achieving higher levels of efficacy than has been reported with any other biologic therapy.
- Spesolimab, an IL-36 receptor inhibitor, is an effective, US Food and Drug Administration–approved treatment for patients with generalized pustular psoriasis.

The landscape of psoriasis treatments has undergone rapid change within the last decade, and the dizzying speed of drug development has not slowed, with 4 notable entries into the psoriasis treatment armamentarium within the last year: tapinarof, roflumilast, deucravacitinib, and spesolimab. Several others are in late-stage development, and these therapies represent new mechanisms, pathways, and delivery systems, meaningfully broadening the spectrum of treatment choices for our patients. However, it can be quite difficult to keep track of all the medication options. This review aims to present the mechanisms and data on both newly available therapeutics for psoriasis and products in the pipeline that may have a notable impact on our treatment paradigm for psoriasis in the near future.

Cutis. 2023;111:101-104.
choices for our patients. However, it can be quite difficult to keep track of all of the medication options. This review aims to present the mechanisms and data on both newly available therapeutics for psoriasis and products in the pipeline that may have a major impact on our treatment paradigm for psoriasis in the near future.

**Topical Treatments**

Tapinarof—Tapinarof is a topical aryl hydrocarbon receptor (AhR)–modulating agent derived from a secondary metabolite produced by a bacterial symbiont of entomopathogenic nematodes. Tapinarof binds and activates AhR, inducing a signaling cascade that suppresses the expression of helper T cells T_{H}17 and T_{H}22, upregulates skin barrier protein expression, and reduces epidermal oxidative stress. This is a familiar mechanism, as AhR agonism is one of the pathways modulated by coal tar. Tapinarof’s overall effects on immune function, skin barrier integrity, and antioxidant activity show great promise for the treatment of plaque psoriasis.

Two phase 3 trials (N=1025) evaluated the efficacy and safety of once-daily tapinarof cream 1% for plaque psoriasis. A physician global assessment (PGA) score of 0/1 occurred in 35.4% to 40.2% of patients in the tapinarof group and in 6.0% of patients in the vehicle group. At week 12, 36.1% to 47.6% of patients treated with daily applications of tapinarof cream achieved a 75% reduction in their baseline psoriasis area and severity index (PASI 75) score compared with 6.9% to 10.2% in the vehicle group. In a long-term extension study, a substantial improvement in PASI 75 was observed in patients who achieved complete clearance (PGA=0). Use of tapinarof cream was associated with folliculitis in up to 23.5% of patients.

Roflumilast—Phosphodiesterase 4 (PDE-4) is an intracellular enzyme involved in the regulation of cell proliferation, differentiation, and immune responses. The inhibition of PDE-4 decreases the expression of proinflammatory cytokines implicated in the pathogenesis of plaque psoriasis, such as tumor necrosis factor α, IFN-γ, and IL-2, IL-12, and IL-23. Phosphodiesterase 4–targeted therapies have been thoroughly explored to treat various inflammatory conditions, including atopic dermatitis and plaque psoriasis. The oral PDE-4 inhibitor apremilast was shown to achieve PASI 75 in approximately 30% of 562 patients, accompanied by severe gastrointestinal adverse events (AEs) including diarrhea and nausea associated with treatment. Local irritation from the topical PDE-4 inhibitor crisaborole for atopic dermatitis and psoriasis (where it only completed phase 2 trials) limits its widespread use. The lack of tolerable and effective treatment alternatives for psoriasis prompted the investigation of new PDE-4–targeted therapies.

Topical roflumilast is a selective, highly potent PDE-4 inhibitor with greater affinity for PDE-4 compared to crisaborole and apremilast. Two phase 3 trials (N=881) evaluated the efficacy and safety profile of roflumilast cream for plaque psoriasis, with a particular interest in its use for intertriginous areas. At week 8, 37.5% to 42.4% of roflumilast-treated patients achieved investigator global assessment (IGA) success compared with 6.1% to 6.9% of vehicle-treated patients. Intertriginous IGA success was observed in 68.1% to 71.2% of patients treated with roflumilast cream compared with 13.8% to 18.5% of vehicle-treated patients. At 8-week follow-up, 39.0% to 41.6% of roflumilast-treated patients achieved PASI 75 vs 5.3% to 7.6% of patients in the vehicle group. Few sting- ing, burning, or application-site reactions were reported with roflumilast, along with rare instances of gastrointestinal AEs (<4%).

**Oral Therapy**

Deucravacitinib—Tyrosine kinase 2 (TYK2) mediates the intracellular signaling of the T_{H}17 and T_{H}1 inflammatory cytokines IL-12/IL-23 and type I interferons, respectively, the former of which are critical in the development of psoriasis via the Janus kinase (JAK) signal transducer and activator of transcription pathway. Deucravacitinib is an oral selective TYK2 allosteric inhibitor that binds to the regulatory domain of the enzyme rather than the active catalytic domain, where other TYK2 and JAK2, and JAK3 inhibitors bind. This unique inhibitory mechanism accounts for the high functional selectivity of deucravacitinib for TYK2 vs the closely related JAK1, JAK2, and JAK3 kinases, thus avoiding the pitfall of prior JAK inhibitors that were associated with major AEs, including an increased risk for serious infections, malignancies, and thrombosis. The selective suppression of the inflammatory TYK2 pathway has the potential to shift future therapeutic targets to a narrower range of receptors that may contribute to favorable benefit-risk profiles.

Two phase 3 trials (N=1686) compared the efficacy and safety of deucravacitinib vs placebo and apremilast in adults with moderate to severe plaque psoriasis. At week 16, 53.0% to 58.4% of deucravacitinib-treated patients achieved PASI 75 compared with 35.1% to 39.8% of apremilast-treated patients. At 16-week follow-up, static PGA response was observed in 49.5% to 53.6% of patients in the deucravacitinib group and 32.1% to 33.9% of the apremilast group. The most frequent AEs associated with deucravacitinib therapy were nasopharyngitis and upper respiratory tract infection, whereas headache, diarrhea, and nausea were more common with apremilast. Treatment with deucravacitinib caused no meaningful changes in laboratory parameters, which are known to change with JAK1, JAK2, and JAK3 inhibitors. A long-term extension study demonstrated that deucravacitinib had persistent efficacy and consistent safety for up to 2 years.

**Other TYK2 Inhibitors in the Pipeline**

Novel oral allosteric TYK2 inhibitors—VTX958 and ND1-034858—and the competitive TYK2 inhibitor PF-06826647 are being developed. Theoretically, these...
new allosteric inhibitors possess unique structural properties to provide greater TYK2 suppression while bypassing JAK1, JAK2, and JAK3 pathways that may contribute to improved efficacy and safety profiles compared with other TYK2 inhibitors such as deucravacitinib. The results of a phase 1b trial (ClinicalTrials.gov Identifier NCT04999839) showed a dose-dependent reduction of disease severity associated with NDI-034858 treatment for patients with moderate to severe plaque psoriasis, albeit in only 26 patients. At week 4, PASI 50 was achieved in 13%, 57%, and 40% of patients in the 5-, 10-, and 30-mg groups, respectively, compared with 0% in the placebo group. In a phase 2 trial of 179 patients, 46.5% and 33.0% of patients treated with 400 and 200 mg of PF-06826647, respectively, achieved PASI 90 at week 16. Conversely, dose-dependent laboratory abnormalities were observed with PF-06826647, including anemia, neutropenia, and increases in creatine phosphokinase. At high concentrations, PF-06826647 may disrupt JAK signaling pathways involved in hematopoiesis and renal functions owing to its mode of action as a competitive inhibitor. Overall, these agents are much farther from market, and long-term studies with larger diverse patient cohorts are required to adequately assess the efficacy and safety data of these novel oral TYK2 inhibitors for patients with psoriasis.

EDP1815—EDP1815 is an oral preparation of a single strain of *Prevotella histicola* being developed for the treatment of inflammatory diseases, including psoriasis. EDP1815 interacts with host intestinal immune cells through the small intestinal axis (SINTAX) to suppress systemic inflammation across the Th1, Th2, and Th17 pathways. Therapy triggers broad immunomodulatory effects without causing systemic absorption, colonic colonization, or modification of the gut microbiome. In a phase 2 study (NCT04603027), the primary end point analysis, mean percentage change in PASI between treatment and placebo, demonstrated that at week 16, EDP1815 was superior to placebo with 80% to 90% probability across each cohort. At week 16, 25% to 32% of patients across the 3 cohorts treated with EDP1815 achieved PASI 50 compared with 12% of patients receiving placebo. Gastrointestinal AEs were comparable between treatment and placebo groups. These results suggest that SINTAX-targeted therapies may provide efficacious and safe immunomodulatory effects for patients with mild to moderate psoriasis, who often have limited treatment options. Although improvements may be mild, SINTAX-targeted therapies can be seen as a particularly attractive adjunctive treatment for patients with severe psoriasis taking other medications or as part of a treatment approach for a patient with milder psoriasis.

**Biologics**

*Bimekizumab*—Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits IL-17A and IL-17F. Although IL-17A is a more potent cytokine, IL-17F may be more highly expressed in psoriatic lesional skin and independently contribute to the activation of proinflammatory signaling pathways implicated in the pathophysiology of psoriasis. Evidence suggests that dual inhibition of IL-17A and IL-17F may provide more complete suppression of inflammation and improved clinical responses than IL-17A inhibition alone.

Prior bimekizumab phase 3 clinical studies have shown both rapid and durable clinical improvements in skin clearance compared with placebo. Three phase 3 trials—BE VIVID (N=567), BE SURE (N=478), and BE RADIANT (N=743)—assessed the efficacy and safety of bimekizumab vs the IL-12/IL-23 inhibitor ustekinumab, the tumor necrosis factor inhibitor adalimumab, and the selective IL-17A inhibitor secukinumab, respectively. At week 4, significantly more patients treated with bimekizumab (71%–77%) achieved PASI 75 than patients treated with ustekinumab (15%; P<.0001), adalimumab (31.4%; P<.001), or secukinumab (47.3%; P<.001). After 16 weeks of treatment, PASI 90 was achieved by 85% to 86.2%, 50%, and 47.2% of patients treated with bimekizumab, ustekinumab, and adalimumab, respectively. An IGA response (score of 0/1) at week 16 was achieved by 84% to 85.5%, 53%, 57.2%, and 78.6% of patients receiving bimekizumab, ustekinumab, adalimumab, and secukinumab, respectively. The most common AEs in bimekizumab-treated patients were nasopharyngitis, oral candidiasis, and upper respiratory tract infection. The dual inhibition of IL-17A and IL-17F suppresses host defenses against *Candida* at the oral mucosa, increasing the incidence of bimekizumab-associated oral candidiasis. Despite the increased risk of *Candida* infections, these data suggest that inhibition of both IL-17A and IL-17F with bimekizumab may provide faster and greater clinical benefit for patients with moderate to severe plaque psoriasis than inhibition of IL-17A alone and other biologic therapies, as the PASI 100 clearance rates across the multiple comparator trials and the placebo-controlled pivotal trial are consistently the highest among any biologic for the treatment of psoriasis.

*Sespolimab*—The IL-36 pathway and IL-36 receptor genes have been linked to the pathogenesis of generalized pustular psoriasis. In a phase 2 trial, 19 of 35 patients (54%) receiving an intravenous dose of sespolimab, an IL-36 receptor inhibitor, had a generalized pustular psoriasis PGA psutilation subscore of 0 (no visible pustules) at the end of week 1 vs 6% of patients in the placebo group. A generalized pustular psoriasis PGA total score of 0 or 1 was observed in 43% (15/35) of sespolimab-treated patients compared with 11% (2/18) of patients in the placebo group. The most common AEs in patients treated with sespolimab were minor infections.
Two open-label phase 3 trials—NCT05200247 and NCT05239039—are underway to determine the long-term efficacy and safety of spesolimab in patients with generalized pustular psoriasis.

Conclusion

Although we have seen a renaissance in psoriasis therapies with the advent of biologics in the last 20 years, recent evidence shows that more innovation is underway. Just in the last year, 2 new mechanisms for treating psoriasis topicaly without steroids have come to fruition, and there have not been truly novel mechanisms for treating psoriasis topicaly since approvals for tazarotene and calcipotriene in the 1990s. An entirely new class—TYK2 inhibitors—was developed and landed in psoriasis first, greatly improving the efficacy measures attained with oral medications in general. Finally, an orphan diagnosis got its due with an ambitiously designed study looking at a previously unheard-of 1-week end point, but it comes for one of the few true dermatologic emergencies we encounter, generalized pustular psoriasis. We are fortunate to have so many meaningful new treatments available to us, and it is invigorating to see that even more efficacious biologics and treatments are coming, along with novel concepts such as a treatment affecting the microbiome. Now, we just need to make sure that our patients have the access they deserve to the wide array of available treatments.

REFERENCES