Systemic Therapies in Psoriasis: An Update on Newly Approved and Pipeline Biologics and Oral Treatments

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PRACTICE **POINTS**

- New systemic options for the treatment of psoriasis continue to emerge.
- With more choices, we can now tailor therapeutic approaches to the patient rather than base treatment choices purely on efficacy.
- New and upcoming biologics may offer improved skin clearance in line with the National Psoriasis Foundation's treat-to-target approach, while others may offer increased efficacy in treating psoriatic arthritis.
- Novel small-molecule oral medications are in development and may have improved efficacy over current options.

Although there are numerous biologics and several oral treatments for psoriasis, a number of promising systemic therapies are on the horizon. Knowledge of these medications might help guide our treatment approach to the patient with psoriasis. This article provides an update on the most recent (as of 2019) approved therapies and medications in the pipeline for moderate to severe plaque psoriasis, with a focus on systemic agents in phase 3 clinical trials.

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Recent advances in our understanding of psoriatic immune pathways have led to new generations of targeted therapies developed over the last 5 years. Although the pathogenesis of psoriasis remains to be fully elucidated, the success of these targeted therapies has confirmed a critical role of the IL-23/helper T cell (T_H17) axis in maintaining the psoriatic immune cascade, a positive feedback loop in which IL-17, IL-12, and IL-23 released from myeloid dendritic cells lead to activation of helper T cells. Activated helper T cells—namely T_H1, T_H17, and T_H22—release IL-17, IL-22, and other proinflammatory cytokines, amplifying the immune response and leading to keratinocyte proliferation and immune cell migration to psoriatic lesions. Inhibition of IL-17 and IL-23 by several biologics disrupts this aberrant inflammatory cascade and has led to dramatic improvements in outcomes, particularly among patients with moderate to severe disease.

Numerous biologics targeting these pathways and several oral treatments have been approved by the US Food and Drug Administration (FDA) for the treatment of psoriasis; in addition, a number of promising therapies are on the horizon, and knowledge of these medications might help guide our treatment approach to the patient with psoriasis. This article provides an update on the most

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recent (as of 2019) approved therapies and medications in the pipeline for moderate to severe plaque psoriasis, with a focus on systemic agents in phase 3 clinical trials. (Medications targeting psoriatic arthritis, biosimilars, and existing medications approved by the FDA prior to 2019 will not be discussed.)

Risankizumab

Risankizumab-rzaa (formerly BI 655066) is a humanized IgG1 monoclonal antibody that targets the p19 subunit of IL-23, selectively inhibiting the role of this critical cytokine in psoriatic inflammation.

Phase 1 Trial—In a phase 1 proof-of-concept study, 39 patients with moderate to severe plaque psoriasis received varying dosages of intravenous or subcutaneous risankizumab or placebo.[1] At week 12, the percentage of risankizumab-treated patients achieving reduction in the psoriasis area and severity index (PASI) score by 75% (PASI 75), 90% (PASI 90), and 100% (PASI 100) was 87% (27/31; $P<.001$ vs placebo), 58% (18/31; $P=.007$ vs placebo), and 16% (5/31; $P=.590$ vs placebo), respectively. Improvements in PASI scores were observed as early as week 2. Adverse events (AEs) were reported by 65% of the risankizumab group and 88% of the placebo group. Serious AEs were reported in 4 patients receiving risankizumab, none of which were considered related to the study medication.[1]

Phase 2 Trial—A phase 2 comparator trial demonstrated noninferiority at higher dosages of risankizumab in comparison to the IL-12/IL-23 inhibitor ustekinumab.[2] Among 166 participants with moderate to severe plaque psoriasis, PASI 90 at week 12 was met by 77% of participants receiving 90 or 180 mg of risankizumab compared to 40% receiving ustekinumab ($P<.001$). Onset of activity with risankizumab was faster and the duration of effect longer vs ustekinumab; by week 8, at least PASI 75 was achieved by approximately 80% of participants in the 90-mg and 180-mg risankizumab groups compared to 60% in the ustekinumab group; PASI score reductions generally were maintained for as long as 20 weeks after the final dose of risankizumab was administered.[2]

Phase 3 Trials—The 52-week UltIMMa-1 and UltIMMa-2 phase 3 trials compared subcutaneous risankizumab (150 mg) to ustekinumab (45 or 90 mg [weight-based dosing]) or placebo administered at weeks 0, 4, 16, 28, and 40 in approximately 1000 patients with moderate to severe plaque psoriasis.[3] Patients initially assigned to placebo switched to risankizumab 150 mg at week 16. At week 16, PASI 90 was achieved by 75.3% of risankizumab-treated patients, 42.0% of ustekinumab-treated patients, and 4.9% of placebo-treated patients in UltIMMa-1, and by 74.8% of risankizumab-treated patients, 47.5% of ustekinumab-treated patients, and 2.0% of placebo-treated patients in UltIMMa-2 ($P<.0001$ vs placebo and ustekinumab for both studies). Achievement of a static physician's global assessment (sPGA) score of 0 or 1 at week 16 similarly favored risankizumab, with 87.8%, 63.0%, and 7.8% of patients in UltIMMa-1 meeting an sPGA score of 0 or 1 in the risankizumab, ustekinumab, and placebo groups, respectively, and 83.7%, 61.6%, and 5.1% in UltIMMa-2 meeting an sPGA score of 0 or 1 in the risankizumab, ustekinumab, and placebo groups, respectively ($P<.0001$ vs placebo and ustekinumab for both studies). Among patients initially assigned to risankizumab, improvements in PASI and sPGA continued to increase until week 52, with 81.9% achieving PASI 90 at week 52 compared to 44.0% on ustekinumab in UltIMMa-1, and 80.6% achieving PASI 90 at week 52 compared to 50.5% on ustekinumab in UltIMMa-2 ($P<.0001$ vs ustekinumab for both studies). Treatment-emergent AE profiles were similar for risankizumab and ustekinumab in both studies, and there were no unexpected safety findings.[3]

Risankizumab received FDA approval for the treatment of moderate to severe plaque psoriasis in April 2019.

Bimekizumab

Bimekizumab (UCB4940), a humanized IgG1 monoclonal antibody, selectively neutralizes the biologic functions of IL-17A and IL-17F, the latter of which has only recently been implicated in contributing to the psoriatic immune cascade.[4]

First-in-Human Study—Thirty-nine participants with mild psoriasis demonstrated efficacy after single-dose intravenous bimekizumab, with maximal improvements in all measures of disease activity observed between weeks 8 and 12 in participants receiving 160 to 640 mg.[5]

Proof-of-Concept Phase 1b Study—A subsequent trial of 53 participants with psoriatic arthritis demonstrated sustained efficacy to week 20 with varying dosages of intravenous bimekizumab.[6] At week 8, PASI 100 was met by 86.7% of participants receiving the top 3 dosages of bimekizumab compared to none of the placebo-treated participants. Treatment-emergent AEs, including neutropenia and elevation of liver transaminases, were mostly mild to moderate and resolved spontaneously. There were 3 severe AEs and 3 serious AEs, none of which were related to treatment.[6]

Importantly, bimekizumab was shown in this small study to have the potential to be highly effective at treating psoriatic arthritis. American College of Rheumatology ACR20, ACR50, and ACR70 response criteria were very high, with an ACR20 of 80% and an ACR50 of 40%.[6] Further trials are necessary to gather more data and confirm these findings; however, these levels of response are higher than those of any other biologic on the market.

Phase 2b Dose-Ranging Study—In this trial, 250 participants with moderate to severe plaque psoriasis received either 64 mg, 160 mg with a 320-mg loading dose, 320 mg, or 480 mg of subcutaneous bimekizumab or placebo at weeks 0, 4, and 8.[7] At week 12, PASI 90 was achieved by significantly more patients in all bimekizumab-treated groups compared to the placebo group (46.2%–79.1% vs 0%; $P<.0001$ for all dosages); PASI 100 also was achieved by significantly more bimekizumab-treated

patients (27.9%–60.0% vs 0%; $P \leq .0002$). Improvement began as early as week 4, with clinically meaningful responses observed in all bimekizumab groups across all measures of disease activity. Treatment-emergent AEs occurred more frequently in bimekizumab-treated participants (61%) than in placebo-treated participants (36%); the most common AEs were nasopharyngitis and upper respiratory tract infection. Of note, fungal infections were reported by 4.3% of participants receiving bimekizumab; all cases were localized superficial infection, and none led to discontinuation. Three serious AEs were reported, none of which were considered related to the study treatment.[7]

Mirikizumab

Mirikizumab (LY3074828) is a humanized IgG4 monoclonal antibody that selectively binds and inhibits the p19 subunit of IL-23, with no action on IL-12.

Phase 1 Trial—Mirikizumab was shown to improve PASI scores in patients with plaque psoriasis.[8]

Phase 2 Trial—Subsequently, a trial of 205 participants with moderate to severe plaque psoriasis compared 3 dosing regimens of subcutaneous mirikizumab—30, 100, or 300 mg—at weeks 0 and 8 compared to placebo.[9] Primary end point results at week 16 demonstrated PASI 90 response rates of 0%, 29% ($P=.009$), 59% ($P<.001$), and 67% ($P<.001$) in the placebo, 30-mg, 100-mg, and 300-mg mirikizumab groups, respectively. Complete clearance of psoriasis, measured by PASI 100 and sPGA 0, was achieved by 0%, 16%, 31%, and 31%, respectively ($P=.039$ for 30 mg vs placebo; $P=.007$ for the higher dosage groups vs placebo). Response rates for all efficacy outcomes were statistically significantly higher for all mirikizumab treatment groups compared to placebo and were highest in the 100-mg and 300-mg treatment groups. Frequencies of participants reporting AEs were similar across treatment and placebo groups.[9]

Oral Medications

Only a few small-molecule, orally bioavailable therapies are on the market for the treatment of psoriasis, some of which are associated with unfavorable side-effect profiles that preclude long-term therapy.

BMS-986165—The intracellular signaling enzyme tyrosine kinase 2 is involved in functional responses of IL-12 and IL-23. BMS-986165, a potent oral inhibitor of tyrosine kinase 2 with greater selectivity than other tyrosine kinase inhibitors, demonstrated efficacy in a phase 2 trial of 267 participants with moderate to severe plaque psoriasis receiving any of 5 dosing regimens—3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, and 12 mg daily—compared to placebo.[10] At week 12, the percentage of patients with a 75% or greater reduction in PASI was 7% with placebo, 9% with 3 mg every other day ($P=.49$ vs placebo), 39% with 3 mg daily ($P<.001$ vs placebo), 69% with 3 mg twice daily ($P<.001$ vs placebo), 67% with 6 mg twice daily ($P<.001$ vs placebo), and 75% with 12 mg once daily ($P<.001$ vs placebo). Adverse events occurred in 51% of patients in the placebo group and in 55% to 80% of BMS-986165–treated patients; the most common AEs were nasopharyngitis, headache, diarrhea, nausea, and upper respiratory tract infection.[10]

A phase 3 trial comparing BMS-986165 with placebo and apremilast is underway (ClinicalTrials.gov Identifier NCT03611751).

Piclidenoson (CF101)—A novel small molecule that binds the Gi protein–associated A_3 adenosine receptor piclidenoson induces an anti-inflammatory response via deregulation of the Wnt and nuclear factor κB signal transduction pathways, leading to downregulation of proinflammatory cytokines, including IL-17 and IL-23.[11]

In a phase 2 dose-ranging study, 75 patients with moderate to severe plaque psoriasis received varying dosages—1, 2, or 4 mg—of oral piclidenoson or placebo twice daily for 12 weeks.[12] Progressive improvement in the mean change from baseline PASI score was observed in the 2-mg group, with statistically significant differences at weeks 8 and 12 compared to placebo ($P=.047$ and $P=.031$, respectively). At week 12, 35.3% of the 2-mg group achieved at least PASI 50. Improvements in PASI were less pronounced in the 4-mg group, and no therapeutic benefit was observed in the 1-mg group. Of the 20 AEs reported, 15 possibly were related to the study drug; 1 AE was severe.[12]

In a subsequent phase 2/3 trial, patients with moderate to severe plaque psoriasis received piclidenoson—1 or 2 mg—or placebo twice daily.[13] At week 12, PASI 75 was achieved by 8.5% of patients in the 2-mg group and by 6.9% of patients receiving placebo ($P=.621$), thereby not meeting the primary study end point. Results at week 32 were more encouraging. In the 2-mg group, PASI mean percentage improvement was 57% ($P<.002$) compared to baseline, with linear improvements observed in PASI 50 (63.5%), PASI 75 (35.5%), PASI 90 (24.7%), and PASI 100 (10.6%).[13]

A phase 3 trial comparing piclidenoson 2 and 3 mg to apremilast and placebo is in progress (ClinicalTrials.gov Identifier NCT03168256).

Future Directions

Despite abundant options for treating moderate to severe plaque psoriasis and psoriatic arthritis, the pipeline remains rich. Novel treatments might have improved efficacy, favorable safety profiles, and different modes of administration compared to current medications. In addition to the novel therapeutics covered here, several treatments are in development further down the pipeline, with only phase 1 or 2 data available. Remtolumab (ABT-122), a tumor necrosis factor α– and IL-17A–targeted immunoglobulin, is unique among biologics, given its dual inhibition of tumor necrosis factor α and IL-17A.[14] M1095 (ALX-0761), a novel trivalent bispecific nanobody, is another intriguing candidate. This dual inhibitor of IL-17A/F might exhibit a number of

advantages over conventional antibodies, including better tissue penetration, reduced immunogenicity, and a longer half-life (ClinicalTrials.gov Identifier NCT03384745).[15,16]

As always with drug development, numerous medications that were under development failed to meet primary end points in phase 2 trials and have therefore been discontinued, including namilumab and prurisol. It is reassuring that the pace of drug discovery and development in psoriasis does not seem to be slowing; to our patients' benefit, we will have an array of treatments available to tailor therapy to the individual.

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