New Biologics in Psoriasis: An Update on IL-23 and IL-17 Inhibitors

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PRACTICE **POINTS**

- The newest biologics for treatment of moderate to severe plaque psoriasis are IL-23 and IL-17 inhibitors with unprecedented efficacy of complete skin clearance compared to older biologics.
- Risankizumab, guselkumab, and tildrakizumab are new IL-23 inhibitors currently in phase 3 trials with promising early efficacy and safety results.
- Ixekizumab, which recently was approved, and brodalumab, which is pending US Food and Drug Administration review, are new IL-17 inhibitors that achieved total skin clearance in more than one-quarter of phase 3 participants after 12 weeks of treatment.

As immune-related pathways involved in the pathogenesis of psoriasis are elucidated, new biologic treatments targeting these steps of the psoriatic immune cascade are developed. In this article, we review the literature on IL-23 and IL-17 inhibitors in the pipeline for use in moderate to severe psoriasis. Numerous pipeline biologic therapies, including risankizumab, guselkumab, tildrakizumab, ixekizumab, and brodalumab, are being investigated in phase 2 and 3 studies to establish the efficacy and safety of these new agents. Of these newest biologics being studied for psoriasis, ixekizumab has been approved and brodalumab is pending approval by the US Food and Drug Administration.

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The role of current biologic therapies in psoriasis predicates on the pathogenic role of upregulated, immune-related mechanisms that result in the activation of myeloid dendritic cells, which release IL-17, IL-23, and other cytokines to activate T cells, including helper T cell T_H17. Along with other immune cells, T_H17 produces IL-17. This proinflammatory cascade results in keratinocyte proliferation, angiogenesis, and migration of immune cells toward psoriatic lesions.[1] Thus, the newest classes of biologics target IL-12, IL-23, and IL-17 to disrupt this inflammatory cascade.

We provide an updated review of the most recent clinical efficacy and safety data on the newest IL-23 and IL-17 inhibitors in the pipeline or approved for psoriasis, including risankizumab, guselkumab, tildrakizumab, ixekizumab, and brodalumab (Table). Ustekinumab and adalimumab, which have been previously approved by the US Food and Drug Administration (FDA), will be discussed here only as comparators.

IL-23 Inhibitors

Risankizumab—Risankizumab (formerly known as BI 655066)(Boehringer Ingelheim) is a selective human monoclonal antibody targeting the p19 subunit of IL-23 and currently is undergoing phase 3 trials for psoriasis. A proof-of-concept phase 1 study of 39 participants demonstrated efficacy

New Biologics for Psoriasis

Drug	Mechanism of Action	Phase 2 or Phase 3 Dosage and Administration	AEs of Specific Interest	Advantages	Disadvantages
Risankizumab	IL-23 inhibition	90 or 180 mg subcutaneously at weeks 0, 4, and 16[2]	N/A	Noninferior to ustekinumab,[2] few injections necessary	N/A
Guselkumab	IL-23 inhibition	100 mg subcutaneously at weeks 0 and 4, then every 8 weeks[3]	N/A	Long-term superiority to adalimumab[3,4]	N/A
Tildrakizumab	IL-23 inhibition	100 or 200 mg subcutaneously at weeks 0 and 4, then every 12 weeks[5,6]	N/A	High rates of total skin clearance[5]	N/A
Ixekizumab	IL-17A inhibition	160 mg subcutaneously at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks[7,8]	Cardiovascular and cerebrovascular events, inflammatory bowel disease, malignancy, neutropenia[7]	High rates of total skin clearance[7,8]	Frequent injection schedule
Brodalumab	IL-17A inhibition	140 or 210 mg subcutaneously every 2 weeks with an extra dose at week 1[9,10]	Neutropenia, candidal infections, depression and suicide[9,10]	High rates of total skin clearance[9,10]	Frequent injection schedule

Abbreviations: AE, adverse event; N/A, not applicable.

after 12 weeks of treatment at varying subcutaneous and intravenous doses with placebo control.[11] At week 12, 87% (27/31)($P<.001$) of all risankizumab-treated participants achieved 75% reduction in psoriasis area and severity index (PASI) score compared to 0% of 8 placebo-treated participants. Common adverse effects (AEs) occurred in 65% (20/31) of risankizumab-treated participants, including non–dose-dependent upper respiratory tract infections, nasopharyngitis, and headache. Serious adverse events (SAEs) that occurred were considered unrelated to the study medication.[11]

A phase 2 trial of 166 participants compared 3 dosing regimens of subcutaneous risankizumab (single 18-mg dose at week 0; single 90-mg dose at weeks 0, 4, and 16; or single 180-mg dose at weeks 0, 4, and 16) and ustekinumab (weight-based single 45- or 90-mg dose at weeks 0, 4, and 16), demonstrating noninferiority at higher doses of risankizumab.[2] Preliminary primary end point results

at week 12 showed PASI 90 in 32.6% (P=.4667), 73.2% (P=.0013), 81.0% (P<.0001), and 40.0% of the treatment groups, respectively. Participants in the 180-mg risankizumab group achieved PASI 90 eight weeks faster than those on ustekinumab, lasting more than 2 months longer. Adverse effects were similar across all treatment groups and SAEs were unrelated to the study medications.[2]

Guselkumab—Guselkumab (Janssen Biotech, Inc) is a selective human monoclonal antibody against the p19 subunit of IL-23. The 52-week phase 2 X-PLORE trial compared dose-ranging subcutaneous guselkumab (5 mg at weeks 0 and 4, then every 12 weeks; 15 mg every 8 weeks; 50 mg at weeks 0 and 4, then every 12 weeks; 100 mg every 8 weeks; or 200 mg at weeks 0 and 4, then every 12 weeks), adalimumab (80-mg loading dose, followed by 40 mg at week 1, then every other week), and placebo in 293 randomized participants.[4] At week 16, 34% (P=.002) of participants in the 5-mg guselkumab group, 61% (P<.001) in the 15-mg group, 79% (P<.001) in the 50-mg group, 86% (P<.001) in the 100-mg group, 83% (P<.001) in the 200-mg group, and 58% (P<.001) in the adalimumab group achieved physician global assessment (PGA) scores of 0 (clear) or 1 (minimal psoriasis) compared to 7% of the placebo group. Achievement of PASI 75 similarly favored the guselkumab (44% [P<.001]; 76% [no P value given]; 81% [P<.001]; 79% [P<.001]; and 81% [P<.001], respectively) and adalimumab treatment arms (70% [P<.001]) compared to 5% in the placebo group. In longer-term comparisons to week 40, participants in the 50-, 100-, and 200-mg guselkumab groups showed significantly greater remission of psoriatic lesions, measured by a PGA score of 0 or 1, than participants in the adalimumab group (71% [P=.05]; 77% [P=.005]; 81% [P=.01]; and 49%, respectively).[4]

Preliminary results from VOYAGE 1 (N=837), the first of several phase 3 trials, further demonstrate the superiority of guselkumab 100 mg at weeks 0 and 4 and then every 8 weeks over adalimumab (standard dosing) and placebo; at week 16, 73.3% (P<.001 for both comparisons) versus 49.7% and 2.9% of participants, respectively, achieved PASI 90, with sustained superiority of skin clearance in guselkumab-treated participants compared to adalimumab and placebo through week 48.[3]

Long-term safety data showed no dose dependence or trend from 0 to 16 weeks and 16 to 52 weeks of treatment regarding rates of AEs, SAEs, or serious infections.[4] Between weeks 16 and 52, 48.9% of all guselkumab-treated participants exhibited AEs compared to 60.5% of adalimumab-treated participants and 51.3% of placebo participants. Overall infection rates also were lowest in the guselkumab group at 29.8% compared to 36.8% and 35.9%, respectively. Three participants treated with guselkumab had major cardiovascular events, including a fatal myocardial infarction. No cases of tuberculosis or serious opportunistic infections were reported.[4]

Tildrakizumab—Tildrakizumab (formerly known as MK-3222)(Sun Pharmaceutical Industries Ltd) is a human monoclonal antibody also targeting the p19 subunit of IL-23. In a phase 2 study of 355 participants with chronic plaque psoriasis, participants received 5-, 25-, 100-, or 200-mg subcutaneous tildrakizumab or placebo at weeks 0 and 4 and then every 12 weeks for a total of 52 weeks.[6] At week 16, PASI 75 results were 33.3%, 64.4%, 66.3%, 74.4%, and 4.4%, respectively (P<.001 for each comparison). Improvement began within the first month of treatment, with median times to PASI 75 of 57 days at 200-mg dosing and 84 days at 100-mg dosing. Of those participants achieving PASI 75 by drug discontinuation at week 52, 96% of the 100-mg group and 93% of the 200-mg group maintained PASI 75 through week 72, suggesting low relapse rates after treatment cessation.[6]

In October 2016, the efficacy results of 2 pivotal phase 3 trials (reSURFACE 1 and reSURFACE 2) involving more than 1800 participants combined revealed PASI 90 achievement in an average of 54% of participants on tildrakizumab 100 mg and 59% of participants on tildrakizumab 200 mg at week 28.[5] Achievement of PASI 100 occurred in 24% and 30% of participants at week 28, respectively. The second of these trials included an etanercept comparison group and demonstrated head-to-head superiority of 100 and 200 mg subcutaneous tildrakizumab at week 12 by end point measures.[5]

Treatment-related AEs occurred at rates of 25% in tildrakizumab-treated participants and 22% in placebo-treated participants, most frequently nasopharyngitis and headache.[6] At least 1 AE occurred in 64% of tildrakizumab-treated participants without dose dependence compared to 69% of placebo-treated participants. Severe AEs thought to be drug treatment related were bacterial arthritis, lymphedema, melanoma, stroke, and epiglottitis.[6]

IL-17 Inhibitors

Ixekizumab—Ixekizumab (Eli Lilly and Company), a monoclonal inhibitor of IL-17A, is the most recently approved psoriasis biologic on the market and has been cleared for use in adults with moderate to severe plaque psoriasis. Recommended dosing is 160 mg (given in two 80-mg subcutaneous injections via an autoinjector or prefilled syringe) at week 0,

followed by an 80-mg injection at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every 4 weeks thereafter. The FDA approved ixekizumab in March 2016 following favorable results of several phase 3 trials: UNCOVER-1, UNCOVER-2, and UNCOVER-3.[7,8]

In UNCOVER-1, 1296 participants were randomized to 1 of 2 ixekizumab treatment arms—160 mg starting dose at week 0, 80 mg every 2 or 4 weeks thereafter—or placebo.[7] At week 12, 89.1%, 82.6%, and 3.9% achieved PASI 75, respectively ($P<.001$ for both). Importantly, high numbers of participants also achieved PASI 90 (70.9% in the 2-week group and 64.6% in the 4-week group vs 0.5% in the placebo group [$P<.001$]) and PASI 100 (35.3% and 33.6% vs 0%, respectively [$P<.001$]), suggesting high rates of disease clearance.[7]

UNCOVER-2 (N=1224) and UNCOVER-3 (N=1346) investigated the same 2 dosing regimens of ixekizumab compared to etanercept 50 mg biweekly and placebo.[8] At week 12, the percentage of participants achieving PASI 90 in UNCOVER-2 was 70.7%, 59.7%, 18.7%, and 0.6%, respectively, and 68.1%, 65.3%, 25.7%, and 3.1%, respectively, in UNCOVER-3 ($P<.0001$ for all comparisons to placebo and etanercept). At week 12, PASI 100 results also showed striking superiority, with 40.5%, 30.8%, 5.3%, and 0.6% of participants, respectively, in UNCOVER-2, and 37.7%, 35%, 7.3%, and 0%, respectively, in UNCOVER-3, achieving complete clearance of disease ($P<.0001$ for all comparisons to placebo and etanercept). Responses to ixekizumab were observed as early as weeks 1 and 2, while no participants in the etanercept and placebo treatment groups achieved comparative efficiency.[8]

In an extension of UNCOVER-3, efficacy increased from week 12 to week 60 according to PASI 90 (68%–73% in the 2-week group; 65%–72% in the 4-week group) and PASI 100 measures (38%–55% in the 2-week group; 35%–52% in the 4-week group).[7]

The most common AEs associated with ixekizumab treatment from weeks 0 to 12 occurred at higher rates in the 2-week and 4-week ixekizumab groups compared to placebo, including nasopharyngitis (9.5% and 9% vs 8.7%, respectively), upper respiratory tract infection (4.4% and 3.9% vs 3.5%, respectively), injection-site reaction (10% and 7.7% vs 1%, respectively), arthralgia (4.4% and 4.3% vs 2.9%, respectively), and headache (2.5% and 1.9% vs 2.1%, respectively). Infections, including candidal, oral, vulvovaginal, and cutaneous, occurred in 27% of the 2-week dosing group and 27.4% of the 4-week dosing group compared to 22.9% of the placebo group during weeks 0 to 12, with candidal infections in particular occurring more frequently in the active treatment groups and exhibiting dose dependence. Other AEs of special interest that occurred among all ixekizumab-treated participants (n=3736) from weeks 0 to 60 were cardiovascular and cerebrovascular events (22 [0.6%]), inflammatory bowel disease (11 [0.3%]), non–skin cancer malignancy (14 [0.4%]), and nonmelanoma skin cancer (20 [0.5%]). Neutropenia occurred at higher rates in ixekizumab-treated participants (9.3% in the 2-week group and 8.6% in the 4-week group) compared to placebo (3.3%) and occurred in 11.5% of all ixekizumab participants over 60 weeks.[7]

Brodalumab—Brodalumab (Valeant Pharmaceuticals International, Inc) is a human monoclonal antibody targeting the IL-17A receptor currently under review for FDA approval after undergoing phase 3 trials. The first of these trials, AMAGINE-1, showed efficacy of subcutaneous brodalumab (140 or 210 mg administered every 2 weeks with an extra dose at week 1) compared to placebo in 661 participants.[9] At week 12, 60%, 83%, and 3%, respectively, achieved PASI 75; 43%, 70%, and 1%, respectively, achieved PASI 90; and 23%, 42%, and 1%, respectively, achieved PASI 100 ($P<.001$ for all respective comparisons to placebo). These effects were retained through 52 weeks of treatment. The median time to complete disease clearance in participants reaching PASI 100 was 12 weeks. Conversely, participants who were re-randomized to placebo after week 12 of brodalumab treatment relapsed within weeks to months.[9]

AMAGINE-2 and AMAGINE-3 further demonstrated the efficacy of brodalumab (140 or 210 mg every 2 weeks with extra dose at week 1) compared to ustekinumab (45 or 90 mg weight-based standard dosing) and placebo in 1831 participants, respectively.[10] In AMAGINE-2, 49% of participants in the 140-mg group ($P<.001$ vs placebo), 70% in the 210-mg group ($P<.001$ vs placebo), 47% in the ustekinumab group, and 3% in the placebo group achieved PASI 90 at week 12. Similarly, in AMAGINE-3, 52% of participants in the 140-mg group ($P<.001$), 69% in the 210-mg group ($P<.001$), 48% in the ustekinumab group, and 2% in the placebo group achieved PASI 90. Impressively, complete clearance (PASI 100) at week 12 occurred in 26% of the 140-mg group ($P<.001$ vs placebo), 44% of the 210-mg group ($P<.001$ vs placebo), and 22% of the ustekinumab group compared to 2% of the placebo group in AMAGINE-2, with similar rates in AMAGINE-3. Brodalumab was significantly superior to ustekinumab at the 210-mg dose by PASI 90 measures ($P<.001$) in both studies and at the 140-mg dose by PASI 100 measures ($P=.007$) in AMAGINE-3 only.[10]

Common AEs were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia, all occurring at grossly similar rates (49%–60%) across all experimental groups in AMAGINE-1, AMAGINE-2, and AMAGINE-3 during the first 12-week treatment period.[9,10] Brodalumab treatment groups had high rates of specific interest AEs compared to ustekinumab and placebo groups, including neutropenia (0.8%, 1.1%, 0.3%, and 0%, respectively) and candidal infections (0.8%, 1.3%, 0.3%, and 0.3%, respectively). Induction phase (weeks 0–12) depression rates were concerning, with 6 cases each in AMAGINE-2 (4 [0.7%] in the 140-mg group, 2 [0.3%] in the 210-mg group) and AMAGINE-3 (4 [0.6%] in the 140-mg group, 2 [0.3%] in the 210-mg group). Cases of neutropenia were mild, were not associated with major infection, and were transient or reversible. Depression rates after 52 weeks of treatment were 1.7% (23/1567) of brodalumab participants in AMAGINE-2 and 1.8% (21/1613) in AMAGINE-3. Three participants, all on constant 210-mg dosing through week 52, attempted suicide with 1 completion[10]; however, because no other IL-17 inhibitors were associated with depression or suicide in other trials, it has been suggested that these cases were incidental and not treatment related.[12] An FDA advisory panel recommended approval of brodalumab in July 2016 despite ongoing concerns of depression and suicide.[13]

Conclusion

The robust investigation into IL-23 and IL-17 inhibitors to treat plaque psoriasis has yielded promising results, including the unprecedented rates of PASI 100 achievement with these new biologics. Risankizumab, ixekizumab, and brodalumab have demonstrated superior efficacy in trials compared to ustekinumab. Tildrakizumab has shown low disease relapse after drug cessation. Ixekizumab and brodalumab have shown high rates of total disease clearance. Thus far, safety findings for these pipeline biologics have been consistent with those of ustekinumab. With ixekizumab approved in 2016 and brodalumab under review, new options in biologic therapy will offer patients and clinicians greater choices in treating severe and recalcitrant psoriasis.

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