IL-23 inhibitors for moderate-to-severe psoriasis

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Abstract

Since the identification of high levels of interleukin 23 (IL-23) in psoriasis lesional skin, as well as finding that IL-23 was the most important source of the p40 subunit shared by IL-12 and IL-23, significant effort has been made in identifying potential new drugs that specifically block the unique IL-23 p19 subunit. At this time, 2 inhibitors of IL-23 p19 have been approved by the United States Food and Drug Administration, guselkumab and tildrakizumab. Two other agents, risankizumab and mirikizumab, have completed phase 3 and phase 2 of development, respectively. Pivotal trials in the development of these agents and clinical use of the approved agents are discussed. Thus far, this class of medications seems to provide a high level of efficacy, along with infrequent dosing and very favorable safety results.

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Most recent models of psoriasis pathophysiology have centered on the critical role of the interleukin 23 (IL-23)/Th helper cell type 17 (Th17) immunological axis as the central pathway in inducing lesions of this disease. Studies of anti-tumor necrosis factor agents have suggested that this pathway is central to the efficacy of agents that have success in the treatment of psoriasis. Moreover, since the identification of high levels of IL-23 in lesional skin as well as finding that IL-23, not IL-12, was the most important source of the p40 subunit shared by IL-12 and IL-23, significant effort has been made in identifying potential new drugs that can block IL-23 specifically. In theory, high-level inhibition of this immunological pathway could lead to highly effective medications for psoriasis.

The IL-23/Th17 axis has been implicated as the major pathway driving inflammation and contributing to the pathophysiology of psoriasis. IL-23, produced by antigen-presenting cells, stimulates survival and proliferation of Th17 and Th22 cells. These cells, in turn, are a primary source of pro-inflammatory cytokines IL-17 and Th22, which mediate the tissue inflammation and keratinocyte hyperproliferation of psoriasis. Binding of IL-23 to its receptor induces activation of Janus kinase 2, tyrosine kinase 2, and signal transducer and activator of transcription (STAT) signaling. Polymorphisms of both IL-23 and its receptor have been identified as genetic loci associated with an increased susceptibility to psoriasis. IL-23 is composed of p19 and p40 subunits, which bind to the IL-23 receptor. The p40 subunit of the receptor is shared between IL-12 and IL-23, whereas p19 is unique. Research has suggested that preservation of IL-12 may be beneficial due to its role in immune surveillance, so agents that specifically target IL-23 p19 were developed, with promising initial results.

At this time, 2 inhibitors of IL-23 p19 have been approved by the United States Food and Drug Administration (FDA), guselkumab and tildrakizumab. Two other agents, risankizumab and mirikizumab, have completed phase 3 and phase 2 of development, respectively. Each of these medications demonstrates important clinical characteristics that make this class of biologics unique and centrally important in the treatment of patients with psoriasis.

Guselkumab

Guselkumab (CNTO1959; Janssen Research & Development, Raritan, New Jersey), approved in July 2017, was the first medication available in the United States that binds to the p19 subunit of IL-23 specifically. Guselkumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that is delivered as a 100-mg subcutaneous injection dosed at week 0, 4, and then every 8 weeks.

Clinical development

The first 2 trials in the development of guselkumab were the first demonstration in a large comparator trial that blockade of IL-23 p19 was sufficient for having a great impact on the disease. This promising trial established the dose and dosing schedule that was followed in the pivotal phase 3 program, which included 3 major clinical trials. Two of these trials, VOYAGE 1 and VOYAGE 2, were comparison trials with adalimumab. NAVIGATE, the third trial, investigated whether transition from blockade of both IL-12 and IL-23 with ustekinumab to guselkumab inhibiting IL-23 alone could be an effective strategy for establishing high-level responses in psoriasis.

Efficacy

The efficacy of guselkumab was established in 3 phase 3 trials. The first 2 trials, VOYAGE 1 and VOYAGE 2, were randomized, placebo-controlled trials that compared guselkumab to adalimumab and placebo. The primary endpoints of these studies were an investigator global assessment of 0 or 1 (IGA 0/1) (clear or minimal disease) and 90% improvement in the psoriasis area and severity index (PASI) at 16 weeks of therapy. Guselkumab was given as a 100-mg subcutaneous injection at week 0, 4, and every 8 weeks thereafter, while adalimumab was used in its FDA-prescribed dosing regimen. The 2 trials differed after 16 weeks in that the active comparator arm with adalimumab continued for a full 48 weeks in

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VOYAGE 1, while subjects underwent a randomized withdrawal study approach in VOYAGE 2.

In the first 16 weeks of study, both trials demonstrated significantly greater efficacy of guselkumab compared with both placebo and adalimumab. In VOYAGE 1, Guselkumab was superior to placebo on the coprimary endpoints, with significantly higher proportions of guselkumab patients achieving IGA 0/1 (85.1% versus 6.9%) and PASI 90 (73.3% versus 2.9%) at week 16. PASI 75 and PASI 100 were also higher for guselkumab at week 16 compared with placebo. Guselkumab was also superior to adalimumab, with significantly higher proportions of patients achieving IGA 0/1 (85.1% versus 65.9%), PASI 90 (73.3% versus 49.7%), and PASI 75 (91.2% versus 73.1%) at week 16. PASI 100 response for guselkumab compared with adalimumab at weeks 24 and 48 was also significantly higher.5

These short-term results were mirrored very closely by the results from VOYAGE 2. At week 16, significantly higher proportions of guselkumab patients achieved IGA 0/1 (84.1% versus 8.5%) and PASI 90 (70.0% versus 2.4%), with the higher percentage of improvement in PASI score noted as early as week 2. As in VOYAGE 1, PASI 75 and PASI 100 were also higher for guselkumab at week 16 compared with placebo.6 Subgroup analysis of these 2 trials demonstrated that these findings were consistent regardless of age, sex, ethnicity, weight, or prior biologic usage.7

The 2 VOYAGE studies varied in their design after 24 weeks. In VOYAGE 1, subjects continued on the treatment to which they were initially randomized, with the placebo control period ending at week 16. This design was meant to evaluate longer-term responses with guselkumab compared with adalimumab. At week 24 and week 48, guselkumab continued to outperform adalimumab with PASI 90 and IGA 0/1 scores continuing to be statistically greater than adalimumab (80.22% versus 50.3% and 84.2% versus 61.7% at week 24; 76.3% versus 47.9% and 80.5% versus 55.4% at week 48). Interestingly, complete clearance of disease, measured by PASI 100, continued to improve throughout the trial in the guselkumab group, going from 37.4% to 47.4% between weeks 16 and 48.

In VOYAGE 2, at week 24, subjects on adalimumab were crossed over to guselkumab therapy, while those who were initiated on guselkumab underwent a randomized withdrawal in which half of subjects continued on guselkumab while the other half were given placebo until they had recurrence of their disease. Two interesting observations emerge from this study design. First, about two-thirds of subjects treated with adalimumab who did not achieve the primary endpoint of the study—PASI 90—and then were treated with guselkumab were able to have a PASI 90 response 20 weeks after the transition. These data suggest that suboptimal responders to adalimumab may have a very significant rate of response to guselkumab. Also, the median time to loss of PASI 90 response—a very high level of response—in patients who were randomized to placebo was over 19 weeks from the time of their last injection. Therefore, patients with high-level responses to guselkumab tend to maintain their skin improvement for extended periods after stopping the medication.

The NAVIGATE trial was a uniquely designed trial meant to answer the question of whether transition to guselkumab could help improve subjects who had suboptimal responses to ustekinumab. This question is of scientific interest because both ustekinumab and guselkumab inhibit the activity of IL-23 but ustekinumab additionally impacts IL-12. This difference could account for differences in efficacy of the medications.

### Table. Summary of key data to date for the IL-23 inhibitors (mirikizumab does not yet have enough published data to include)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Guselkumab</th>
<th>Tildrakizumab</th>
<th>Risankizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully human IgG1 monoclonal antibody that binds to IL-23 p19</td>
<td>High-affinity, humanized IgG1κ antibody targeting IL-23 p19</td>
<td>High-affinity, fully humanized IgG1 monoclonal antibody targeting IL-23 p19</td>
<td></td>
</tr>
<tr>
<td>Phase of development</td>
<td>Approved by FDA for US in July 2017</td>
<td>Approved by FDA for US in March 2018</td>
<td>Phase 3 complete, awaiting publication</td>
</tr>
<tr>
<td>Dosing (dose, schedule)</td>
<td>100 mg at week 0, 1, then q8 weeks</td>
<td>100 mg given at week 0, 4, then q12 weeks</td>
<td>90-180 mg given at week 0, 4, then q12 weeks (phase 2 data)</td>
</tr>
<tr>
<td>PASI 75/90/100 (%) at primary endpoint</td>
<td>91/73/37 at week 16 (results from VOYAGE 1)</td>
<td>64/35/14 at week 12 (results from 100-mg dose of reSURFACE)</td>
<td>93/77/45 at week 12 (results from phase 2 data)</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS:** FDA, Food and Drug Administration; IgG1, immunoglobulin G1; IL-23, interleukin 23; PASI, psoriasis area and severity index; q8, every 8.
NAVIGATE was a phase 3 randomized, double-blind multicenter study evaluating the efficacy and safety of guselkumab in patients with moderate to severe plaque psoriasis who had an inadequate response to ustekinumab. This trial consisted of a 16-week open-label period, a 28-week randomized active-treatment period, and a 16-week follow-up period. Patients received open-label ustekinumab (45 or 90 mg based on weight) at weeks 0 and 4. At week 16, those patients with an inadequate response to ustekinumab (n = 268) as defined by IGA ≥2 were randomized to either continue ustekinumab (every 12 weeks through week 40; n = 133) or to receive guselkumab 100 mg (weeks 16, 20, and every 8 weeks thereafter through week 44; n = 135). The rest of the patients continued open-label ustekinumab. The dosing regimen used was based on what is approved worldwide, and dose escalation was not permitted.

The primary endpoint was the number of visits at which patients achieved IGA 0/1 and ≥2-grade improvement during weeks 28 to 40 (relative to week 16) for patients randomized due to inadequate response to ustekinumab (ie, those with IGA ≥2). Major secondary endpoints included visits at which patients achieved IGA 0 or PASI 90 during weeks 28 to 40 and a Dermatology Life Quality Index score of 0 or 1 (DLQI 0/1).

At week 16 (open-label run-in), 68.5% of patients achieved IGA 0/1, 73.7% achieved PASI 75, and 49.0% achieved PASI 90. Among randomized patients (week 16 vs weeks 28-40), the guselkumab group had a significantly higher mean number of visits at which patients achieved the primary outcome compared with the ustekinumab group (1.5 versus 0.7). Compared with ustekinumab, greater proportions of patients receiving guselkumab also achieved IGA 0/1 and a ≥2-grade improvement at week 28 (31.1% versus 14.3%) and week 52 (36.3 versus 17.3%), as well as PASI 90 (51.1% vs. 24.1%). PASI 100 (20.0% versus 7.5%) and DLQI 0/1 scores were also higher (38.8% versus 19.0%) although not statistically significant. By evaluating the number of visits at which patients had a high degree of response to either agent, the study assessed consistency of response, accounting for differing peak and trough concentrations of the 2 biologics.8

There have been a number of secondary outcomes of importance that have been studied in the VOYAGE trials. Evaluation of nail psoriasis, for example, showed improvements in both trials. Interestingly, however, these results did not differ significantly from those seen with the adalimumab control arms. Additionally, a number of patient-reported outcomes of importance have also been studied. Improvement in DLQI was consistently better in guselkumab-treated subjects than those treated with adalimumab and placebo. Additionally, analysis of symptoms of psoriasis through the Psoriasis Symptoms and Signs Diary demonstrated greater improvement in the guselkumab-treated groups.5 Formal analysis of anxiety and depression also demonstrated significant improvement in subjects treated with guselkumab.9

Safety
Nasopharyngitis, headache, and upper respiratory tract infection were the most commonly reported events in both trials. The rates of infection, infection requiring treatment, and serious infection were similar among groups in the placebo and active comparator periods of VOYAGE 1 and 2. Malignancy and major adverse cardiovascular events did not appear to be significantly different between groups. There were slightly higher numbers of nonmelanoma skin cancer in guselkumab groups than adalimumab groups (4 versus 1), but further data were not provided. Both trials reported injection site reactions more commonly in adalimumab patients. Antibody titers were detected in 5.3% of patients in VOYAGE 1 and 6.6% of patients through week 48 of VOYAGE 2.5,6

The safety data for the NAVIGATE study were overall consistent with the VOYAGE trials. The rates of adverse events (AEs) and serious adverse events between all agents (guselkumab, ustekinumab, adalimumab, and placebo) were reported to be comparable. The most frequently reported AE in this study was infection. However, in the randomized controlled period of the trial, the incidence of AEs was slightly higher in the group receiving guselkumab, with mild injection site reactions as well as musculoskeletal and connective tissue disorders (back pain and psoriatic arthropathy) reported compared with ustekinumab.8

Tildrakizumab
Tildrakizumab (MK-3222; Sun Pharmaceutical Industries, Mumbai, India) is a high-affinity, humanized IgG1κ antibody targeting IL-23 p19 that is now approved for the treatment of moderate to severe psoriasis by the FDA. Though tildrakizumab was studied in both 100- and 200-mg doses, only the 100-mg dose—given week 0, 4, and every 12 weeks thereafter—was approved by the FDA.

Clinical development
A phase 2 dose-ranging study of tildrakizumab that demonstrated promising results was performed.11 This trial suggested that the infrequent dosing intervals and the higher doses tested would be optimal for therapy with this medication. Based on this information, a phase 3 program including 2 pivotal phase 3 clinical trials, reSURFACE 1 and reSURFACE 2, were conducted to evaluate tildrakizumab compared with placebo and etanercept in the treatment of chronic plaque psoriasis.

Efficacy
The efficacy of tildrakizumab was evaluated in reSURFACE 1 and 2.12 These studies compared doses of 100 mg and 200 mg given week 0, 4, and every 12 weeks thereafter to placebo. In reSURFACE 2, an active comparator of etanercept was also used for psoriasis, given at the FDA-approved dose of 50 mg twice weekly and transitioning to 50 mg once weekly. The primary endpoint in these studies was 75% improvement in PASI (PASI 75) and physician’s global assessment of 0 or 1 (PGA 0/1). In these studies, subjects had some dose alteration based on response at week 28. To date, data to week 28 have been published.

In reSURFACE 1, tildrakizumab outperformed placebo at all primary endpoints. At week 12, 62% of patients in the tildrakizumab 200-mg group and 64% of patients in the 100-mg group achieved PASI 75, which was significantly greater than the 6% of placebo patients. Compared with 7% of the placebo group, 59% and 58% (of tildrakizumab 200 and 100 mg, respectively) achieved PGA 0/1. PASI 90 at week 12 was achieved by 35% of patients in both tildrakizumab groups at week 12 compared with 3% of placebo
patients, and 14% of patients in both groups achieved PASI 100 compared with placebo. Of the 200- and 100-mg patients, 44% and 42%, respectively, achieved DLQI 0/1 compared with 5% of placebo patients.

In reSURFACE 2, PGA responses were significantly higher than placebo in all groups. Patients receiving 200-mg tildrakizumab had a higher PGA response than those receiving etanercept at week 12 ($P = .0031$), but the 100-mg group did not differ significantly at this time point. PASI 90 and 100 results were again significantly higher for tildrakizumab compared with placebo at week 12. PASI 90 was achieved by 37% (200-mg tildrakizumab) and 39% (100-mg tildrakizumab) of tildrakizumab patients compared with 21% of etanercept patients, which was a significant difference in both groups ($P < .0001$). PASI 100 was achieved by 12% of patients in each tildrakizumab group at week 12 compared with 5% of etanercept patients ($P <.05$). DLQI 0/1 for tildrakizumab 200 mg was 47% at week 12 compared with 36% for etanercept ($P = .0029$), whereas the difference was not statistically significant for the 100-mg group compared with etanercept. However, at week 28, tildrakizumab 200 mg outperformed etanercept at all endpoints with statistical significance. The 100-mg dose also outperformed etanercept on all endpoints except PASI 100 ($P = .0002$) and DLQI 0/1 ($P = .0003$).

**Safety**

In both reSURFACE 1 and 2, the safety profile of tildrakizumab was very encouraging. Nasopharyngitis was the most common adverse event seen in both studies, followed by injection site erythema and upper respiratory tract infection. Major adverse cardiovascular events, malignancies, and severe infections were similar in incidence across treatment groups.12

**Anti-IL-23 in the clinic**

In the discussion above, it is clear that treatments that specifically block the p19 subunit of IL-23 provide a number of characteristics that are critical for patients with psoriasis. As a whole, these medications provide a high level of efficacy, infrequent dosing, and very favorable safety results. When these elements are considered together, there are multiple clinical scenarios that make anti-IL-23 therapy a major part of the treatment arsenal for psoriasis.

Both approved agents in the anti-IL-23 class, guselkumab and tildrakizumab, show excellent efficacy in the treatment of plaque psoriasis. While it is impossible to compare results across trials that include different patients, investigative sites, and slightly different outcome measures, it seems clear that guselkumab has an advantage over tildrakizumab in overall efficacy. Alternatively, tildrakizumab is dosed less frequently at every 12 weeks versus every 8 weeks. In either case, the clinical characteristics of these medications will be viewed very favorably by patients and clinicians alike. One does not need to be very imaginative to believe that the adherence to the infrequent dosing schedule along with high-level responses will result in superior drug survival for these medications.

There are a number of clinical scenarios for which the data suggest a special role for anti-IL-23 therapies. In the guselkumab phase 3 trial program, subjects had suboptimal response to the more traditional biologics adalimumab and ustekinumab and were then transitioned to guselkumab. These subjects achieved high levels of response, greater than a PASI 90, in most cases. Therefore, in patients who fail to reach a level of response that is sufficient for their needs, transitioning to guselkumab should be considered.

A second unique aspect of these medications is their seemingly extended effects on psoriasis even after the medication is stopped. Whether this effect is simply related to the pharmacokinetics of the medications discussed or a more complex pharmacodynamic effect is unclear. However, this distinction is not particularly relevant as the clinical consequences could be very important. Though the traditional treatment approach with biologic therapies has been to maintain a constant dosing schedule, prolonged, high-level responses after discontinuation with these medicines, particularly in the guselkumab and the phase 2 risankizumab studies, suggest that other schedules could be studied. Obviously, if patients are required to stop due to payer issues or other health concerns, having this long response time is a significant advantage. Depending upon response to retreatment and repeated starts and stops, these data suggest the potential for more extended dosing periods or as-needed treatment for patients in the future. It is critical to remember that alternative dosing plans would need to be studied prior to implementation, but the unique treatment effects of anti-IL-23 medications makes speculation on this matter interesting.

The safety profile of the anti-IL-23 biologic immunotherapies also provides unique opportunities for patients. Many clinicians, rather than considering the ideal patient for a specific medication, will often first consider what medications cannot be used for a given patient. Unlike for all other biologics, the safety profile of the anti-IL-23 class does not isolate any specific groups in whom these medications should not be used. These therapies afford the clinician the opportunity to use them in patients with multiple co-
existential and comorbid diseases without specific concerns about worsening of their other conditions.

Anti-IL-23 therapies may have considerable promise for another, likely undertreated, group of psoriasis patients. Many patients who have less body surface area involvement than those who were studied in the pivotal clinical trials of biologics have disease that has a very significant impact on their quality of life. Additionally, gene expression data suggest that the inflammatory process of more limited disease is just as immunologically active as more extensive disease, suggesting that it would be appropriate to use highly efficacious medications for these patients. With a very clean safety record and convenient dosing, along with extremely high levels of efficacy, it is sensible to believe that anti-IL-23 therapy could be the treatment for more limited forms of psoriasis.

Finally, it is critical to understand the potential weakness in the data to date for this class of medications. Because these treatments are new, long-term safety has not been fully evaluated. Additionally, safety in higher-risk patients, who are excluded from clinical trials of psoriasis, is not known. Like all medications, time and evaluation in long-term registry trials in which a greater variety of patients are included will give us the ultimate safety profile of these medications. Additionally, efficacy in the treatment of psoriatic arthritis, the most common comorbid disease with psoriasis, has not been sufficiently evaluated for any anti-IL-23 medication.

Conclusion
The anti-IL-23 biologic immunotherapies present an exciting new class of medications for the treatment of psoriasis. Thus far, data from trials of the IL-23 agents suggest that they are a safe and effective option for the management of chronic plaque psoriasis and that they may be comparable or superior to biologics currently available. The high-level efficacy and clean safety record in clinical trials, along with the longer period between doses with these agents, may help chronic psoriatic patients adhere to treatment. Further long-term studies are necessary to assess the safety of the various IL-23 agents over a longer period of time. However, the clinical characteristics of these treatments should provide long-term success with these agents. Finally, these characteristics invite speculation on new, potentially exciting ideas on novel ways to use them for the benefit of all patients with psoriasis.

References