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Long-Term Skin Clearance With Brodalumab in Patients With Psoriasis and Inadequate Response to Prior Biologics

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ABSTRACT

Background: Despite the emergence of multiple biologic drug options for psoriasis, unmet treatment needs remain. Biologic therapies can vary in their effectiveness and adverse events, and many patients experience a loss of treatment effect over time. After lack of response, treatment may be switched to a biologic with a different mechanism of action. Brodalumab, a human interleukin-17 (IL-17) receptor A antagonist, is approved for the treatment of adult patients with moderate-to-severe psoriasis with inadequate response or loss of response to prior systemic therapies. Because brodalumab targets the IL-17 receptor instead of the ligand itself, it not only targets a broader set of IL-17 isoforms but also may be effective in patients who received prior IL-17 inhibitors or failed to respond to anti–IL-17 treatment. This is supported by long-term evidence from clinical trials and real-world studies of patients receiving brodalumab who were previously treated with IL-17 inhibitors. Additionally, brodalumab produces reliable treatment effects after use of biologics with other mechanisms of action, such as tumor necrosis factor α and IL-12/IL-23 inhibitors, as well as after the use of multiple biologic therapies. For patients with psoriasis with inadequate response to one or more biologic therapies, brodalumab is an option that has the ability to lead to long-term skin clearance.

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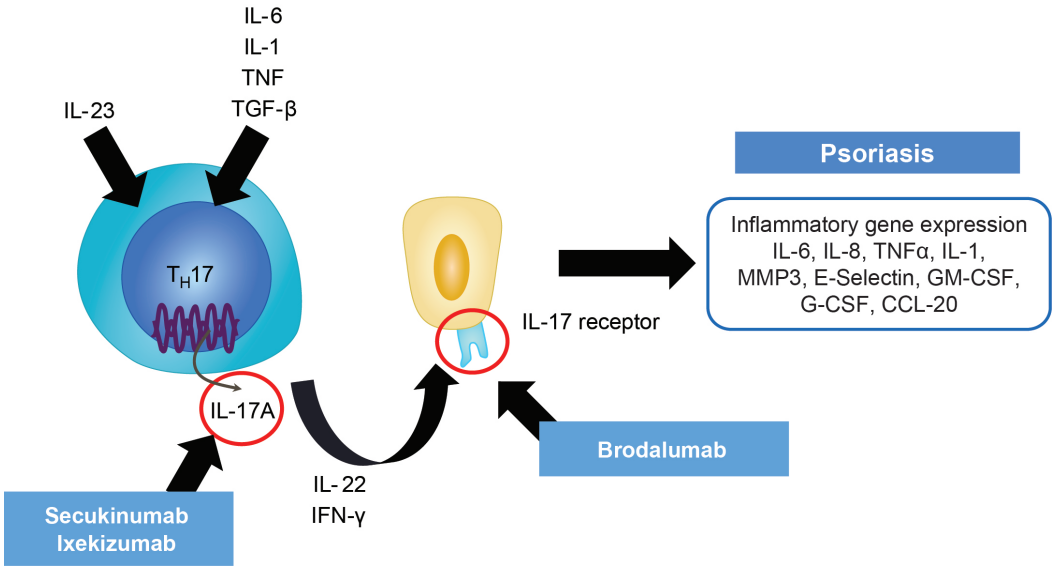
INTRODUCTION

Psoriasis is a chronic inflammatory condition that affects 2% to 3% of the world's population and can be challenging to treat.[1,2] For patients with more extensive disease, difficult-to-treat areas (such as the scalp and palmoplantar surfaces), or greater reductions in quality of life, determining an optimal therapeutic regimen is a multifactorial and often challenging process. Biologics have altered the landscape of psoriasis treatment by providing effective and safe options for patients with moderate-to-severe psoriasis without the need for corticosteroids or other conventional immunosuppressive medications, which may cause liver, kidney, or bone marrow toxicity.

Although biologic therapies have significantly advanced psoriasis treatments, many unmet needs remain. Long-term treatment is required in up to 90% of cases because of the relapsing-remitting nature of the disease.[3,4] Although biologics effectively target the inflammatory pathways driving psoriasis, some patients experience reduction or loss of therapeutic response over time.[5] Such situations require a switch in biologic therapy, ideally to a drug with a different mechanism of action.[5,6] However, given the number of biologics available for the treatment of psoriasis, the choice of therapy after treatment failure requires careful consideration from clinicians.[7]

The pathogenesis of psoriasis involves the (interleukin)-23–mediated differentiation of T cells into the helper T-cell subtype T_H17, which then leads to production of IL-17.[8] Interleukin-17 encompasses a total of 6 proteins (IL-17A to IL-17F) that drive inflammation in several cell types, including keratinocytes.[8] This cycle of inflammation produces the painful, pruritic plaques seen in psoriasis, which commonly appear on the extensor surfaces of the limbs but also occur in areas such as the scalp, intertriginous areas, and palmoplantar surfaces.[9]

FIGURE 1. Mechanisms of brodalumab and IL-17A inhibitors.[14-16] CCL, chemokine ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; TGF, transforming growth factor; T_H17, helper T-cell subtype 17; TNFα, tumor necrosis factor α.



Current biologic options for psoriasis include tumor necrosis factor α (TNFα) inhibitors (adalimumab, infliximab, etanercept, certolizumab pegol), IL-17 inhibitors (secukinumab, ixekizumab), IL-12/IL-23 inhibitors (ustekinumab), and IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab).[10,11] As patients do not respond uniformly to psoriasis treatment, there has been a drive to develop biologics with novel mechanisms of action that address the needs of patients with inadequate response to first- or second-line biologic therapy.[12] Brodalumab, which was approved in 2017 by the US Food and Drug Administration (FDA) for the treatment of adult patients with moderate-to-severe psoriasis who have failed to respond or have lost response to other systemic therapies, blocks the IL-17 receptor (Figure 1).[5,13-16]

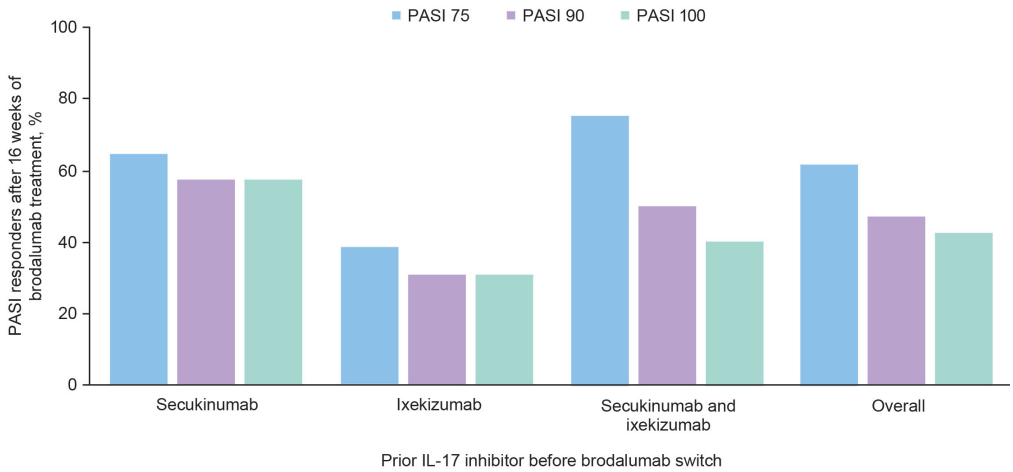
In AMAGINE-1, 42% of patients treated with brodalumab achieved psoriasis area and severity index 100% improvement from baseline (PASI 100) by week 12. Moreover, the PASI 100 response rate was 74% at week 52, which was maintained through week 120.[17] Similarly, in AMAGINE-2, patients treated with continuous brodalumab achieved a PASI 100 rate of 65% at week 52, which remained stable through week 120 at 61%.[18] Meta-analyses also support this evidence, indicating that brodalumab has greater long-term PASI response rates compared with ustekinumab and adalimumab.[10]

The long-term efficacy and rapid onset of treatment effect seen in brodalumab clinical trials (AMAGINE-1/-2/-3) is likely to be in part attributable to its unique mechanism.[2,19] By targeting the IL-17 receptor, brodalumab influences the activity of multiple IL-17 isoforms (IL-17A, IL-17A/F, IL-17C, IL-17E, and IL-17F),[16] which may contribute to its efficacy. In contrast, other IL-17–directed drugs target only a subset of isoforms; secukinumab and ixekizumab are IL-17A inhibitors, whereas the currently investigational drug bimekizumab only targets IL-17A and IL-17F.[8,20]

The immunogenicity profile of brodalumab also supports its potential efficacy as a long-term treatment option. In a long-term analysis of 4246 patients treated with brodalumab in phase 2 and 3 trials, only 2% developed brodalumab-specific antibodies, and in more than half of these patients (1%), these antibodies were transient.[3] In contrast, analyses of adalimumab have shown that antidrug antibodies may occur in 17% to 45% of patients treated for 24 weeks.[21] Among 1079 evaluable patients who received risankizumab for psoriasis treatment, incidences of antidrug antibodies and neutralizing antibodies were 24% and 14%, respectively, over 52 treatment weeks.[22] Moreover, 7% of patients treated with guselkumab for 48 weeks and 7% of patients treated with tildrakizumab for up to 64 weeks developed antidrug antibodies.[3] Because antidrug antibodies are one of the mechanisms that contribute to loss of biologic effect over time, the results of brodalumab compare favorably to other biologic drugs and may in part account for its durable efficacy.[21]

Brodalumab was approved by the US FDA after evidence for its use as a long-term, effective therapy for patients with prior biologic failure. Most of these data come from the aforementioned pivotal phase 3 AMAGINE trials, which compared brodalumab with placebo (AMAGINE-1) and ustekinumab (AMAGINE-2/-3). In these trials, prior biologic exposure and prior biologic failure were assessed at baseline.[2,19] During the 12-week induction period of AMAGINE-2/-3, 1236 patients received brodalumab 210

FIGURE 2. Proportion of patients with previous inadequate response to secukinumab, ixekizumab, or both who achieved PASI 75, PASI 90, and PASI 100 with brodalumab at week 16. Prior IL-17 inhibitors: secukinumab (n=14); ixekizumab (n=13); secukinumab and ixekizumab (n=20); overall (n=47).[24] PASI 75, 90, and 100, psoriasis area and severity index 75%, 90%, and 100% improvement.



mg every 2 weeks. Of those patients, 27% (n=334) had exposure to at least one prior biologic, with most having been treated with TNFα inhibitors (89% [n=296]).[5] Furthermore, in AMAGINE-2/-3, a subset of the ustekinumab-treated patients who had inadequate treatment response switched to brodalumab so that the efficacy of brodalumab as a rescue therapy could be assessed.[23]

Because up to 60% of patients report prior biologic exposure in other clinical trials of biologics for psoriasis, understanding how prior exposure correlates with treatment effect is highly relevant.[4] Patients with prior biologic exposure are likely to have more severe psoriasis that requires a longer treatment duration, and it is therefore important that they switch to a biologic agent with long-term effectiveness.[4] Herein, we highlight the evidence for the long-term improvement of psoriasis after brodalumab treatment in patients with inadequate response to prior biologics. These data may help inform clinical decisions when a change in therapy is required to achieve long-term skin clearance.

Brodalumab Improves Plaque Psoriasis Lesions After Failure of IL-17 Inhibitors

Brodalumab is a viable treatment option for patients who fail to respond to other IL-17 inhibitors.[5] In a retrospective study of patients switching to brodalumab after secukinumab or ixekizumab failure, 50% (3/7) and 67% (2/3) achieved PASI 75, respectively, after 12 weeks of treatment.[24,25] Similarly, in an open-label study measuring outcomes for 39 patients switching to brodalumab after being treated with secukinumab or ixekizumab for ≥3 months without achieving PASI 75 or with a 50% loss of original improvement, 76%, 50%, and 32% achieved PASI 75, PASI 90, and PASI 100, respectively, after 16 weeks of brodalumab treatment.[24,26] In another cohort of 23 patients with prior IL-17A–inhibitor failure, 48% achieved PASI 75 after 12 weeks of brodalumab treatment.[24] In 16 patients with psoriasis who were treated with brodalumab after failing secukinumab treatment, 75% achieved PASI 100 at week 16.[27]

One study of 20 patients with IL-17A–inhibitor treatment failure found that brodalumab improved outcomes at 3 months with no significant difference between patients with primary treatment failure and secondary treatment failure (PASI 75, PASI ≤2, or both achieved in 67% [2/3] and 71% [12/17] of patients with primary or secondary treatment failure, respectively). Overall, PASI 90 and PASI 100 were achieved in 40% and 15% of patients, respectively. Additionally, half of patients achieved dermatology life quality index of 0 or 1 after 3 months of brodalumab treatment.[28] Although these study populations are relatively small, they indicate that a substantial proportion of individuals can achieve improvement in psoriasis with brodalumab after IL-17–inhibitor treatment. By binding to the IL-17 receptor, brodalumab not only acts upon a distinct part of the pathogenic pathway in psoriasis, but it may have broader effects compared with biologics that only inhibit limited IL-17 isoforms.[8]

The switch from IL-17 inhibitors to brodalumab after inadequate treatment response is supported by real-world evidence. For example, in a retrospective study of 47 patients with plaque psoriasis who initiated brodalumab after secukinumab or ixekizumab treatment (or both), most (94%) switched treatments specifically because of nonresponse. Of those, 30% discontinued secukinumab, 28% discontinued ixekizumab, and 43% discontinued previous treatment with both drugs. At week 16, 62%, 47%, and 43% of patients achieved PASI 75, PASI 90, and PASI 100, respectively (Figure 2).[24] Response to brodalumab, measured by PASI 90, was seen across subgroups stratified by a number of previous biologics. For those with one prior biologic treatment, the rate of PASI 90 success with

brodalumab was 43% (3/7), whereas 39% (5/13) of those with 2 prior biologic treatments and 58% (7/12) of those with 3 prior biologic treatments achieved PASI 90 with brodalumab. Moreover, two-thirds of those treated with 6 previous biologics (67% [2/3]) achieved PASI 90 with brodalumab.[24] Patients switching from secukinumab to brodalumab were more likely to achieve PASI 100 (57% [8/14]) compared with those switching from ixekizumab (31% [4/13]). Secondary nonresponders (ie, those with loss of IL-17A–antagonist treatment response after achieving PASI 75 at weeks 12 to 16) also had a greater rate of PASI 100 compared with primary nonresponders (ie, those who did not achieve PASI 75 at weeks 12 to 16), with differences observed when stratified by prior biologic treatment. Whereas 62% (13/21) and 44% (10/23) of secondary nonresponders to secukinumab and ixekizumab, respectively, achieved PASI 100 with brodalumab, 25% (3/12) and 13% (1/8) of primary nonresponders achieved PASI 100 with brodalumab. This study provides real-world evidence that a meaningful proportion of patients may experience substantial or even complete clearance of psoriatic lesions when switching to brodalumab after failure with other IL-17 biologics.

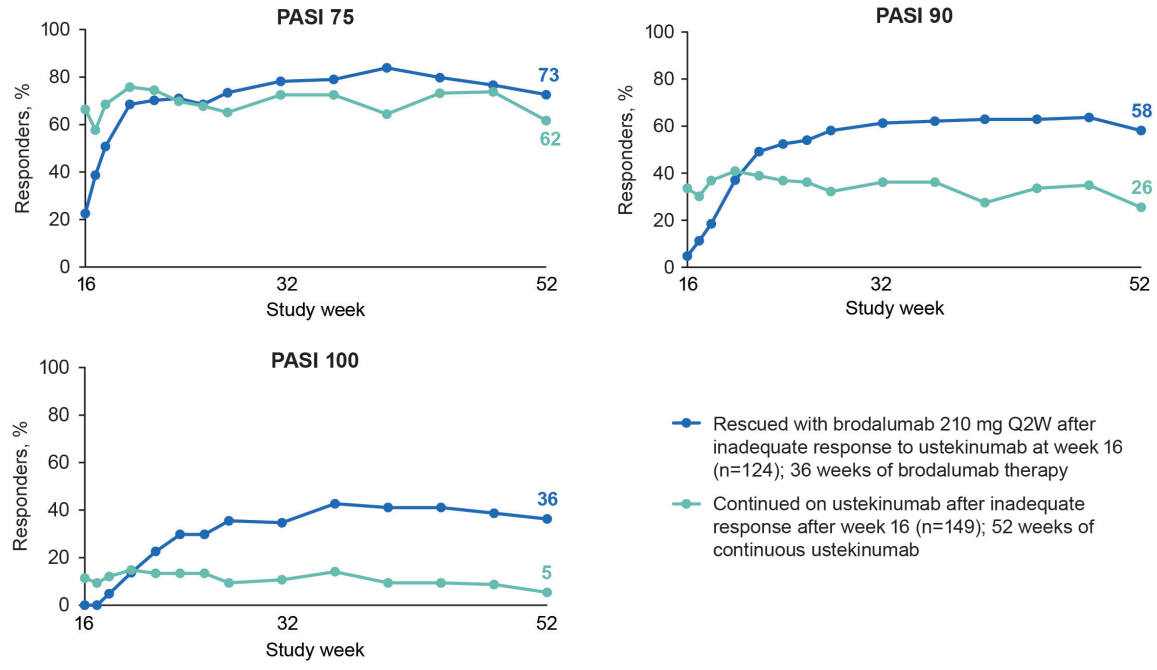
Brodalumab Has Long-term Effectiveness After Failure of TNFα Inhibitors

The TNFα inhibitor adalimumab is a commonly prescribed biologic for the treatment of several autoimmune disorders, including plaque psoriasis.[29] Treatment history of adalimumab was analyzed in post hoc analyses of phase 3 brodalumab trials. Among 3712 patients in the AMAGINE-2/-3 trials, 386 (10%) received prior adalimumab; of these, 199 (52%) did not respond to adalimumab treatment. At 120 weeks of continuous brodalumab treatment, 88%, 73%, and 52% of adalimumab nonresponders achieved PASI 75, PASI 90, and PASI 100, respectively. Notably, treatment success was similar in patients whose disease responded to prior adalimumab treatment (74%, 67%, and 44% for PASI 75, PASI 90, and PASI 100, respectively).[2,30,31] Furthermore, in adalimumab nonresponders, brodalumab was associated with greater skin clearance compared with ustekinumab at week 52; whereas 41% of adalimumab nonresponders treated with brodalumab achieved PASI 100, complete skin clearance was seen in only 8% of adalimumab nonresponders treated with ustekinumab.[32]

Brodalumab Produces Treatment Response in Patients Previously Treated With IL-12/IL-23 Inhibitors

Ustekinumab modulates inflammation by binding to a subunit common to IL-12 and IL-23 and is approved for the treatment of moderate-to-severe psoriasis in patients who are candidates for systemic therapy.[33,34] In the AMAGINE-2/-3 trials, ustekinumab was utilized as a head-to-head comparator of brodalumab. Initially, patients were randomized to brodalumab (1 of 2 regimens), ustekinumab, or placebo for a 12-week induction period. At week 12, patients receiving brodalumab were rerandomized to 1 of 4 brodalumab regimens, those receiving placebo switched to brodalumab, and those receiving ustekinumab remained on ustekinumab through week 52. However, patients receiving ustekinumab were "rescued" with brodalumab at week 16 if they had inadequate treatment response (defined as a static

FIGURE 3. Efficacy of brodalumab in patients with psoriasis who had inadequate response to ustekinumab in a subgroup analysis of AMAGINE-2/-3.[23] PASI 75, 90, and 100, psoriasis area and severity index 75%, 90%, and 100% improvement.



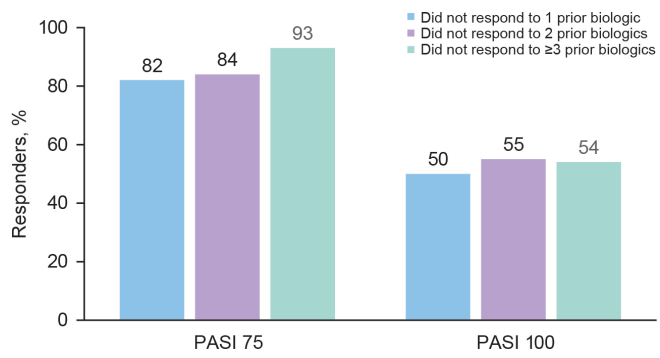
physician's global assessment [sPGA] of ≥3 or persistent sPGA of 2 over a ≥4-week period). Patients who received ustekinumab and had inadequate treatment response after week 16 continued on ustekinumab. During the open-label extension (from weeks 52 to 120), patients in the ustekinumab group switched to brodalumab 210 mg every 2 weeks.[2]

A similar proportion of patients in the AMAGINE-2 and AMAGINE-3 trials originally receiving ustekinumab were rescued with brodalumab therapy at week 16 (AMAGINE-2, 18% [55/300]; AMAGINE-3, 22% [69/313]). In a pooled analysis of the AMAGINE-2/-3 trials, brodalumab rescue of patients in the ustekinumab group was effective in those both with and without prior biologic treatment. Between weeks 12 and 52, the proportion of patients achieving PASI 75, PASI 90, and PASI 100 was greater among patients rescued with brodalumab compared with those who received only ustekinumab. Of the ustekinumab-treated patients rescued with brodalumab (n=124), 36% achieved complete skin clearance at 52 weeks, vs only 5% who continued with ustekinumab (Figure 3). Among patients in the ustekinumab group rescued with brodalumab, 26% with prior biologic exposure achieved PASI 100 by week 52, compared with 42% who were biologic naive. However, among inadequate treatment responders after week 16 who continued ustekinumab without brodalumab rescue, only 2% of the biologic experienced and 7% of the biologic naive achieved PASI 100.[23]

Brodalumab Induces Long-term Treatment Response, Even After Failure of Multiple Biologics

Because of the chronic nature of psoriasis and the potential loss of biologic treatment effect over time, patients may be prescribed various drugs throughout the course of their disease.[6] Therefore, it is important for clinicians to consider drug efficacy after the lack or loss of response to multiple biologics. The potential of brodalumab as a therapy for patients with single or multiple biologic failures was considered in a post hoc analysis of the AMAGINE-2/-3 trials, which stratified patients who received brodalumab by number of prior biologic failures (n=408): 1 biologic (n=160), 2 biologics (n=112), or ≥3 biologics (n=136). After 120 weeks of treatment with brodalumab, PASI 75 rates were 82%, 84%, and 93%, and PASI 100 rates were 50%, 55%, and 54% in the subgroups who received 1, 2, or ≥3 prior biologics, respectively (Figure 4). These results demonstrate that efficacy rates were similar in patients who received a single previous biologic relative to those with more extensive experience. This suggests that brodalumab is an appropriate treatment option for patients seeking relief from psoriasis after a single or multiple inadequate trials of biologics and highlights that brodalumab treatment can be effective throughout a period of more than 2 years.[31]

FIGURE 4. Proportion of patients who received brodalumab stratified by prior biologic use who achieved PASI 75 and PASI 100 with brodalumab at week 120.[31] PASI 75 and 100, psoriasis area and severity index 75% and 100% improvement.



DISCUSSION

Psoriasis is a chronic disease that can vary substantially among affected individuals in terms of severity, areas involved, and response to treatments. Consequently, patients may need to undergo multiple drug trials to find the treatment regimen that best addresses their needs. While primary failure of biologic drugs is a substantial challenge, so too is the loss of treatment response over time. This complicates the achievement of long-term control of psoriasis, which is an important outcome for many patients. For instance, in a survey eliciting treatment goals in 500 patients with psoriasis, 94% reported that long-term maintenance of clear skin (ie, 2–3 years) was highly important.[35]

When a patient experiences treatment failure with a biologic therapy, some clinicians advocate switching to a drug with a different mechanism. With each biologic failure, treatment options narrow. In a complex treatment landscape where patients may undergo treatment with multiple biologics, clinicians must consider the interactions between different drug mechanisms to recommend the optimal therapy.[31] In this regard, brodalumab, which has a unique mechanism that inhibits the receptor of the central cytokine implicated in psoriasis pathogenesis, is promising; brodalumab not only has a broader effect on downstream inflammatory pathways, but it also overcomes the loss of response to IL-17 inhibitors. This concept is supported by several studies showing that substantial proportions of patients achieve PASI goals after switching from secukinumab or ixekizumab to brodalumab.[24] Evidence also supports the efficacy of brodalumab after failure of other common biologics such as ustekinumab and adalimumab, as well as after the use of multiple biologics.[31]

Patients with prior biologic failure or loss of response are a subset of individuals with psoriasis who most likely have a more severe disease with a greater impact on quality of life. It is important to determine therapeutic approaches that will help these patients long-term, as psoriasis can have multifaceted physical effects and psychosocial consequences. Additionally, switching between multiple biologics is associated with clinical

consequences (eg, development of antidrug antibodies), which may limit the efficacy of subsequent biologic therapies.[36] Many factors should be considered when selecting the optimal therapy for a patient with psoriasis.[37,38] Clinical studies show that brodalumab is a suitable option for patients seeking both rapid and long-term relief from psoriasis symptoms. In a pooled analysis of the AMAGINE-2/-3 trials, the time to onset of brodalumab treatment effect was shorter compared with ustekinumab (median time to PASI 75, 4.2 vs 9.4 weeks, respectively). Indirect comparisons of brodalumab with other IL-17 inhibitors, including secukinumab and ixekizumab, also indicate a more rapid onset of treatment effect.[39] As demonstrated here, brodalumab also induces meaningful treatment responses in patients previously treated with one or more of these other biologics with inadequate improvement, with an immunogenicity profile that may maintain continued efficacy in these patients. Given this evidence, brodalumab is a viable treatment for patients who have failed or lost efficacy to a single prior biologic, while also offering long-term skin clearance for patients with a history of multiple biologic drug failures.

DISCLOSURES

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