Biologics for Psoriasis: A Status Update

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Biologic therapies—once novel and exciting in the field of dermatology—are now well-established for some, scary to others, but still as exciting as ever. The field had grown substantially from the early 2000s to include now a dozen innovator systemic agents (counting apremilast, which is not technically a biologic) and a host of biosimilars approved for psoriasis or psoriatic arthritis, as well as the JAK inhibitors for atopic dermatitis. And more agents are on the horizon.

To help keep you up to date on the field, here is a closer look at the efficacy data for the drugs approved for plaque psoriasis in the last five years, as well as some emerging research on each agent. It should be noted that while these newer agents demonstrate impressive efficacy, they, like the generation of biologics that preceded them, will require some time to establish a long-term safety profile.

TILDRAKIZUMAB

Ilumya (tildrakizumab-asmn100mg/mL, Sun Pharmaceuticals) is an injectable IL-23 inhibitor approved by the FDA for the treatment of moderate to severe plaque psoriasis in adults. Ilumya injections are administered by a healthcare provider every 12 weeks, following starter doses at Week 0 and Week 4.

A pooled analysis of Phase 3 trial data in which tildrakizumab 100mg or tildrakizumab 200mg was compared to placebo, found significantly greater proportions of Psoriasis Area and Severity Index (PASI) 75 responders at week 12 for tildrakizumab 100mg (62.3 percent) and tildrakizumab 200mg (64.8 percent), compared to placebo (5.6 percent; P < 0.0001). Similarly, the proportion of responders for PASI 90, PASI 100, and Physician’s Global Assessment (PGA) of “clear” or “minimal” were all significantly higher for active treatment vs. placebo. Responses increased from weeks 12 to 28. Data indicate that week 8 PASI 50 response predicted long-term PASI 90 response.¹

The Phase 2 and Phase 3 trials also compared treatment with tildrakizumab to treatment with etanercept. Pooled analysis of data show that 59 percent of patients who received tildrakizumab 200mg achieved a PGA response of “clear” or “minimal,” compared with 48 percent for etanercept (P = 0.0031).²

Research Note: There is a risk with any biologic therapy for development of neutralizing or anti-drug antibodies (ADA). Researchers investigated the rate of ADA development with tildrakizumab treatment for 52-64 weeks, and it was low. Approximately three percent of subjects developed TE-POS NAb POS ADA and showed lower serum concentrations and corresponding reduced efficacy. No relationship between ADA and safety was observed.³

BRODALUMAB

Siliq (brodalumab, Ortho Dermatologics) binds to IL-17RA; by binding the receptor, it acts differently from other agents that block IL-17. It is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. The agent is contraindicated in patients with Crohn’s disease. Brodalumab has a Boxed Warning and a Risk Evaluation and Mitigation Strategy (REMS) due to observed suicidal ideation and behavior in clinical trials. A safety assessment of brodalumab based on publically available adverse event data from Phase 2 and 3 clinical trials determined that the most common adverse events associated with treatment were nasopharyngitis, upper respiratory tract infection, and candidiasis. Current evidence, therefore, suggests that brodalumab has a similar safety profile to other IL-17 antagonists used to treat moderate to severe plaque psoriasis.⁴ Results from the Phase 3, randomized, controlled clinical trial AMAGINE-1 suggest that treatment with brodalumab reduced anxiety and depression in patients with moderate to severe plaque psoriasis. In the study, patients receiving brodalumab had decreases in depression and hospital anxiety and depression scale.
Data suggest that brodalumab may have the most rapid onset of action of available antipsoriatic therapies.\textsuperscript{5} Pooled analysis of data from six clinical trials involving more than 4,100 patients favored brodalumab over placebo in terms of the Psoriasis Area and Severity Index (PASI) 75 and PASI 100. Analysis of secondary outcomes showed that brodalumab was superior to placebo in terms of static physician’s global assessment and psoriasis symptoms inventory scores. Meta-regression analysis indicated that there is a significant linear association between brodalumab dose and the effect size on PASI and psoriasis symptoms inventory scores.

Few studies have assessed the efficacy of biologic treatments in specific racial groups. A recent 52-week study has shown that brodalumab 210mg is well tolerated and efficacious across diverse racial and ethnic subgroups in patients with psoriasis, including black, Asian, white, and Hispanic/Latino patients. Across all racial and ethnic subgroups, patients receiving brodalumab had higher rates of 75 percent, 90 percent, and 100 percent improvement in PASI from baseline and sPGA score ≤ 1, than did patients who received ustekinumab.\textsuperscript{7}

\textit{Research Note:} Data analysis suggests that brodalumab was associated with the lowest cost per PASI 75, 90 and 100 among the biologics evaluated. Total annual costs to a health plan per patient with adalimumab, brodalumab, ixekizumab, secukinumab and ustekinumab were estimated at $51,246, $38,538, $65,484, $57,510 and $57,013.\textsuperscript{8}

**CERTOLIZUMAB**

Cimzia (certolizumab pegol, UCB) is the first Fc-free, PEGylated anti-TNF treatment option for psoriasis. The absence of the Fc component helps to minimize potential Fc-mediated cytotoxicity from complement or other antibody dependent mechanisms. It is also hypothesized that the absence of the Fc region may be influential in the prevention of active transfer of certolizumab pegol across the placenta during pregnancy.\textsuperscript{9}

Three Phase 3 clinical trials in psoriasis enrolled more than 1,000 patients; nearly one-third of these had prior biologic exposure. A statistically significant proportion of patients receiving active treatment achieved PASI 75 or PASI 90 by week 16 in two trials and by week 12 in the third. Active treatment was also associated with a statistically significantly greater proportion of subjects achieving at least a two-point improvement on a five-point PGA scale to a final score representing clear or almost clear skin at week 16, versus placebo.

The labeling for certolizumab for psoriasis offers flexibility based on weight. The recommended dose of certolizumab for adults with moderate to severe plaque psoriasis is 400mg (given as two subcutaneous injections of 200mg each) every other week. For some patients (with body weight ≤ 90 kg), certolizumab 400mg (given as two subcutaneous injections of 200mg each) initially and at weeks 2 and 4, followed by 200mg every other week can be considered.\textsuperscript{10,11} In clinical trials, the incidence of adverse events was generally similar between subjects receiving certolizumab 400mg and those receiving placebo and somewhat lower in subjects receiving 200mg, versus placebo.\textsuperscript{9}

\textit{Research Note:} The FDA approved a label update that includes pharmacokinetic data showing negligible to low transfer of certolizumab through placenta and minimal transfer to breast milk from mother to infant. Although there is evidence that therapeutic monoclonal antibodies do not increase clinical risk of congenital anomalies during conception or early pregnancy, there has been concern historically about placental transfer of drug during the third trimester. Research shows that the amount of certolizumab that transfused through the placenta was less than one percent of the other biologics and less than the control in one study.\textsuperscript{12}

**IXEKIZUMAB**

Ixekizumab (Taltz, Eli Lilly and Company), is an IL-17a inhibitor for treatment of moderate to severe plaque psoriasis. In Phase 3 trials, subjects were randomized 2:2:2:1 to 80mg ixekizumab every two or four weeks, 50mg etanercept twice...
weekly, or placebo. At week 12, patients switched to ixekizumab every four weeks during a long-term extension (LTE) period. Analysis of 12 week data show that, among patients treated with ixekizumab two-week dosing, 81.8 percent had an sPGA score of 0 or 1 and 89.1 percent had a PASI 75 response. In the four-week dosing group, the respective rates were 76.4 percent and 82.6 percent, compared to 3.2 percent and 3.9 percent, respectively, in the placebo groups.

In the UNCOVER-1 and UNCOVER-2 trials, among the patients who were randomly reassigned at week 12 to receive 80mg of ixekizumab every four weeks, 80mg of ixekizumab every 12 weeks, or placebo, 73.8 percent, 39.0 percent, and 7.0 percent of the patients, respectively, maintained an sPGA score of 0 or 1. Adverse events reported during ixekizumab use included neutropenia, candidal infections, and inflammatory bowel disease.

Analysis of data out to 108 weeks, (n = 385), among patients receiving ixekizumab every two weeks for weeks 0-12 and every four weeks during LTE, the 108-week as-observed, MI, and mMI response rates were 93.4 percent, 88.3 percent, and 83.6 percent, respectively, for patients achieving ≥75 percent improvement from baseline in PASI, and the 108-week as-observed, MI, and mMI response rates were 82.6 percent, 78.3 percent, and 74.1 percent, respectively, for patients with a static PGA score of 0 or 1. During LTE, 1,077 (84.5 percent) patients reported ≥1 treatment-emergent adverse event, and 85 percent were mild or moderate in severity. Discontinuation because of adverse events occurred in 6.4 percent of patients.

Research Note: The FDA has approved a label update for Taltz injection 80mg/mL to include data in psoriasis involving the genital area. Taltz is the first treatment FDA approved for moderate to severe plaque psoriasis that includes such data in its label. In a randomized, double-blind, placebo-controlled study in moderate to severe psoriasis involving the genital area, 149 patients with plaque psoriasis affecting the genital area were treated with Taltz or placebo. The majority of patients treated with Taltz achieved clear or almost clear genital skin at week 12.

GUSELKUMAB

Guselkumab (Tremfya, Janssen) is a subcutaneously administered monoclonal antibody that targets the p19 cytokine subunit in IL-23 and IL-39. It is administered as a 100mg subcutaneous injection once every 8 weeks, after starter doses at weeks 0 and 4. In clinical trials, it was effective in treating psoriasis in patients who were unresponsive to adalimumab or ustekinumab.

In Phase 3 trials of guselkumab, at week 16, the proportion of patients attaining at least PASI 90 was 73.3 percent in VOYAGE 1 and 70.0 percent in VOYAGE 2. Guselkumab remained efficacious through 48 weeks of treatment. Guselkumab maintained a satisfactory safety profile with the most frequently reported adverse events being nasopharyngitis, headache, and upper respiratory tract infection.

Recently reported results from the open-label extension of the Phase 3 VOYAGE 1 study showed that at week 100, 82.4 percent of patients initially randomized to guselkumab treatment achieved an IGA score of 0/1 (cleared or minimal disease) and 82.1 percent achieved a PASI 90 score, while 53.8 percent of patients achieved an IGA score of 0 and 49 percent achieved PASI 100.

Research Note: The FDA recently approved Tremfya One-Press, a single-dose, patient-controlled injector for adults with moderate to severe plaque psoriasis. In the Phase 3, multicenter, randomized ORION study of One-Press, the mean score for “Satisfaction with Self Injection” was 9.18 (with 10 indicating “Very Satisfied”) and the mean score for “Ease of Use” was 9.24 (with 10 indicating “Very Easy”). In the study, 81 percent and 76 percent of patients, respectively, achieved an IGA score of 0 or 1 or a PASI 90 response at week 16; scores for placebo were both zero.

SECUKINUMAB

Secukinumab (Cosentyx, Novartis) is an IL-17 inhibitor dosed at 300mg by subcutaneous injection at Weeks 0, 1, 2, 3, and 4 followed by 300mg every four weeks.

Among 738 patients in one study, 81.6 percent of those receiving secukinumab 300mg, 71.6 percent of subjects receiving secukinumab 150mg, and 4.5 percent of controls achieved PASI 75 at week 12. In a second study involving 1,306 subjects, 77.1 percent of subjects receiving secukinumab 300mg, 67 percent of subjects receiving secukinumab 150mg, 44 percent of subjects receiving etanercept, and 4.9 percent of controls achieved PASI 75 at week 12. The proportion of patients with a response of 0 or 1 on the modified investigator’s global assessment at week 12 was higher with each secukinumab dose than with placebo or etanercept. The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept.

Research Note: The FDA approved a label update for Novartis’ Cosentyx to include data in moderate to severe scalp psoriasis. The label update was based on 12-week primary endpoint results from the US study of moderate to severe scalp psoriasis patients where Cosentyx (300mg) demonstrated superior efficacy compared to placebo.

APREMILAST

Apremilas (Otezla, Celgene) is not a biologic. It is a small molecule that inhibits phosphodiesterase 4 (PDE-4) in
Psoriasis is a chronic inflammatory disorder of the skin. It is characterized by red, itchy patches covered with silvery scales. The disease affects approximately 3% of the US population with a prevalence higher in women than in men. The condition is highly individualized, taking into account factors such as age, sex, race, and genetic predisposition. Psoriasis can affect any area of the body, including the scalp, nails, and joints. It is often associated with other chronic conditions such as type 2 diabetes and cardiovascular disease.

In two Phase 3 controlled trials, at 16 weeks, 33 percent and 29 percent of subjects, respectively, treated with apremilast achieved PASI 75, compared to five and six percent, respectively, of those in the placebo group. Fifty-nine percent and 45 percent of patients, respectively, achieved PASI 50, compared to 17 percent and 19 percent, respectively, in the placebo group. Among subjects that continued treatment for 52 weeks, 61 percent achieved PASI 75.

Regarding safety, the most common adverse events were:

- Pruritus
- Fatigue
- Pain
- Headache
- Musculoskeletal pain

Psoriasis treatment is highly individualized, taking into account a variety of factors including but not limited to the degree of impact of the disease, the patient’s willingness or desire to use certain therapies, and the patient’s overall health and potential comorbidities. For women—especially those of childbearing age—there may be additional considerations, including the impact of psoriasis and its treatment on a potential pregnancy.

The potential impact of psoriasis on an individual’s quality of life cannot be overstated. Among men and women with psoriasis and psoriatic arthritis, 88 percent of patients say the conditions affected overall wellbeing, and 82 percent said they interfered with enjoyment of life.18

Twelve percent of surveyed patients were unemployed, and 92 percent cited psoriasis and/or psoriatic arthritis as the sole reasons for not working.19

There is evidence that women may bear the impact of psoriasis differently than men do. An analysis of data from German and Swiss psoriasis registries shows that women rated 20 (out of 25) items reflecting patient needs as significantly more important than men did. The greatest differences related to depression, sleep quality, and everyday productivity.

Another analysis shows that severity of psoriasis (assessed in this case as a function of BSA) was less influential on depression among patients with psoriasis than factors related to gender and body image perceptions.20 Researchers concluded that the main contributors to depression were female gender, beliefs about appearance and its relationship to one’s self-worth, greater psychological distress, and lower levels of emotional social support. In the US specifically, data confirm that women with psoriasis—and particularly those with concomitant PsA—are at increased risk for depression compared to women without psoriasis.21

The potential impact of psoriasis on a patient’s quality of life and functioning indicates a need to offer efficient treatment. For the female patient of childbearing potential, the selection of an effective treatment must be weighed against potential impact on any planned or unintentional pregnancy.

Interestingly, pregnancy may have a positive effect on psoriasis. More than half of patients who were not treated for psoriasis reported that the disease improved during pregnancy, while 21 percent reported no change; 23 percent reported worsening. However, in the postpartum period, 65 percent of patients reported worsening of psoriasis, 26 percent had no change, and nine percent reported improvement of psoriasis.22 A review of multiple studies and case reports concludes that overall, there is no clear evidence of increased adverse outcomes in pregnant women with psoriasis.23

Among women undergoing biologic therapy for psoriasis, those who continued on therapy during pregnancy had low levels of disease activity and few flares during pregnancy, while those who discontinued treatment with biologics before pregnancy had higher rates of flares during pregnancy and the postpartum period.24

Taken together, the data suggest that women with psoriasis who are candidates for biologic therapy should remain on therapy through pregnancy and the post-partum period. In terms of therapeutic selection among the biologic agents, dermatologists have limited data to inform treatment selection.

There is some suggestion in the data that TNF inhibitors may be associated with increased risk of congenital malformations and preterm birth and may alter the immune system of infants towards hypersensitivity and reduced response to infections.25 Nonetheless, adalimumab in the US and Europe and etanercept in Europe have updated labeling suggesting they may be used during pregnancy, although there is evidence that they cross the placenta. Certolizumab has not been shown to cross the placenta. It has labeling to suggest minimal to no fetal exposure when used during pregnancy and to show little to no transfer to human breast milk of nursing mothers.
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diarrhea, nausea, and vomiting: only one patient had to discontinue from the clinical trials due to these adverse events.

Use of a titration pack during the first week of treatment seems to diminish the incidence of these adverse events.

There was a 1.3 percent incidence of depression compared to 0.6 percent of patients receiving placebo, so there is a recommendation to evaluate and monitor individuals with a history of depression.