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New Biologics for Treatment of Moderate to Severe Psoriasis

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Plaque psoriasis (PsO) is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[1,2] Men and women are affected equally, with the onset peaking before 40 years of age. PsO affects about 2% of the United States population.[2] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[3] People with psoriasis are at increased risk of psoriatic arthritis, inflammatory bowel disease, cardiovascular disease, diabetes, and depression.[1] The prevalence of depression in patients with psoriasis may be as high as 60%.[4]

The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, history of streptococcal infections, obesity, stress, smoking, and excessive alcohol consumption. Certain medications such as beta-blockers, lithium, chloroquine, and nonsteroidal anti-inflammatory drugs can trigger or exacerbate PsO.[5] Typically, PsO is classified as mild, moderate, or severe. Mild disease involves less than 5% of the body surface area (BSA) with lesions that do not occur on the face, hands or feet. Moderate PsO affects >5% but <10% BSA and severe PsO affects greater than 10% of the patient's body surface area.

Per National Institute for Health and Care Excellence (NICE) guidance, topical medications including corticosteroids, vitamin D analogs, and coal tar are first line agents for treatment of mild PsO.[6] Phototherapy is an option for moderate to severe PsO that has not responded to topical therapy. Systemic non-biologic treatments are recommended for moderate to severe PsO and include cyclosporine, acitretin and methotrexate. Biologics or targeted immunomodulators are also options for moderate to severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include tumor necrosis factor (TNF) inhibitors, (adalimumab, etanercept, infliximab), an interleukin (IL)-12/23 inhibitor (ustekinumab) and IL-17 inhibitors (brodalumab, ixekizumab, secukinumab). A small molecule, apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, is also approved for treatment of moderate to severe PsO. PDE4 is a key enzyme in the degradation of cyclic adenosine monophosphate (cAMP), which plays an important role in controlling pro-inflammatory and anti-inflammatory mediators.[7] Apremilast offers another alternative to patients who do not choose to be on immunosuppressive biologic therapy.

Assessment of Therapy

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the Psoriasis Area and Severity Index (PASI), the Static Physician's Global Assessment Scale (sPGA), or the Psoriasis Symptom Inventory (PSI). The PASI is used most often in clinical trials and is considered the most validated scale.[8] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. A 75% improvement in the PASI score (PASI-75) is widely used to establish the effectiveness of therapies in clinical trials of patients with severe psoriasis. PASI-100 indicates full disease clearance. There is no consensus on the most reliable scale in clinical practice.

New Biologic Agents

TNF inhibitors were the first biologic agents to demonstrate efficacy in treating psoriasis. Recent drug developments have focused on the IL cytokines which have been identified as key pathways involved in the pathogenesis of psoriasis. The IL inhibitors provide an alternative treatment for patients that cannot tolerate or lose response to TNF inhibitors. Ustekinumab was the first IL-12/23 inhibitor approved in 2009, followed by secukinumab, an IL-17 inhibitor in 2015. Ixekizumab and brodalumab are the newest IL-17 inhibitors approved by the Food and Drug Administration (FDA) to treat moderate to severe psoriasis.

In 2016, the FDA approved ixekizumab to treat moderate to severe PsO based on 3 randomized, placebo controlled trials conducted in patients who could not tolerate or did not improve with non-biologic systemic therapy.[9] These phase 3 trials also assessed the superiority of ixekizumab 80 mg subcutaneously every 2 or every 4 weeks over etanercept 50 mg subcutaneously twice weekly. The primary efficacy endpoints for all 3 trials were the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (minimal) with a ≥2-point improvement at Week 12 and a PASI-75 at week 12. Ixekizumab was superior to placebo or etanercept in terms of the proportion of patients achieving a ≥75% reduction from baseline in the PSAI and in those achieving a sPGA score of 0 or 1, after 12 weeks of induction treatment.[9] The pooled results of these trials (UNDERCOVER 2 and 3) are presented in **Table 1**. Adverse events reported during ixekizumab trials included infection (26-38%), injection site reaction (17%), neutropenia (12%), candida infections (3%), and inflammatory bowel disease (1%). Neutropenia was transient and did not result in discontinuation of ixekizumab. The phase 3 trials for ixekizumab were conducted for a total of 60 weeks, and therefore, long-term safety and efficacy data is lacking.

Brodalumab received FDA approval to treat moderate to severe PsO in 2017 on the basis of 3 randomized, multicenter, double-blind, placebo-controlled phase 3 trials.[10] Two trials also included patients randomized to ustekinumab as the active comparator.[10] Primary endpoints for these trials included the proportion of patients with a 75% improvement in PASI and proportion of patients with a sPGA score of 0 or 1. In all phase 3 trials, use of brodalumab 210 mg every 2 weeks demonstrated consistent symptom improvement compared to placebo after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. The results of the AMAGINE 3 trial are summarized in **Table 1**. At a lower dose of 140 mg every 2 weeks, brodalumab did not demonstrate consistent improvement compared to ustekinumab in both trials. Adverse reactions reported during the trials included infections (25%), joint pain (5%), injection site reaction (2%) fatigue (3%), and neutropenia (1%). Suicidal ideation and behavior occurred in patients treated with brodalumab. The relative risk of suicide with brodalumab was approximately 3 times higher than other biologic agents (58 vs. 14 suicides/100,000 patient-years).

However, because analyses were conducted retrospectively, the exact incidence of neuropsychiatric events is unclear.[11] For this reason, brodalumab package insert contains a black boxed warning and the drug is only available under a Risk Evaluation and Mitigation Strategy (REMS) program.

Systematic Review

The Institute for Clinical and Economic Review (ICER) published a systematic evaluation of the biologics for the treatment of moderate to severe PsO in late 2016.[12] A total of 80 references met inclusion criteria including 36 randomized controlled trials (RCTs) and 11 observational studies. Seven studies were head-to-head comparative evaluations of biologic agents for plaque psoriasis in patients with moderate to severe PsO that tried and failed topical and oral systemic therapies. In direct comparative trials, response rates from ustekinumab, secukinumab, and ixekizumab were superior to etanercept, as measured by the PASI 75.[12] Additionally, secukinumab and brodalumab were superior to ustekinumab.[12] The proportion of patients responding to different biologics from the comparative trials are summarized in **Table 1.**

Table 1. Comparative Trials: Proportion of Patient Response Rates at 10-16 Weeks[12]

Treatment	PASI 75	PASI 90	sPGA Score < 2
ACCEPT[13]			
Etanercept 50 mg twice weekly	57%	NR	49%
Ustekinumab 45 mg	68% E vs U45: NNT 9	NR	65% E vs. U45: NNT 7
Ustekinumab 90 mg	74% E vs. U90: NNT 6	NR	71% E vs. U90: NNT 5
FIXTURE[14]			
Etanercept 50 mg twice weekly	44%	NR	NR
Secukinumab 150 mg	67% E vs. S150: NNT 5	NR	NR
Secukinumab 300 mg	77% E vs. S300: NNT 3	NR	NR
UNDERCOVER 2 & 3[15] (data reported as pooled from both studies)			
Etanercept 50 mg twice weekly	42-53%	NR	39%
Ixekizumab 80 mg every 2 weeks	87%	NR	82% E vs. I q2: NNT 3
Ixekizumab 80 mg every 4 weeks	90%	NR	74% E vs. I q4: NNT 3
AMAGINE 3[11]			
Ustekinumab 45 mg or 90 mg*	69%	NR	NR
Brodalumab 210 mg	85% U vs. B: NNT 7	NR	NR
CLEAR[16]			
Ustekinumab 45 mg or 90 mg	NR	58%	NR
Secukinumab 300 mg	NR	79% U vs. S: NNT 5	NR
Abbreviations: NNT = number needed to treat; NR = not reported			

Emerging Therapies

Several IL-23 inhibitors currently under investigation for safety and efficacy include tildrakizumab, risankizumab and guselkumab. Tofacitinib, an oral janus kinase inhibitor, is FDA approved to treat rheumatoid arthritis, and is being studied for efficacy in moderate to severe plaque psoriasis.

Conclusion

In summary, biologic agents offer targeted therapy to patients with moderate to severe psoriasis. NICE guidelines recommend initiating systemic biological therapy for severe PsO defined as a total PASI greater than 10 that has not responded to standard systemic therapy or if the patient is intolerant of, or has a contraindication to these treatments.[6] Adalimumab and etanercept have been on the US market the longest and are generally the least expensive options in this class of drugs. Etanercept is the only biologic approved for use in children aged 4 years and older. Trials assessing the efficacy and safety of other biologics in children are ongoing. Ustekinumab, secukinumab, ixekizumab, and apremilast all have proven efficacy in managing moderate to severe psoriasis and all are reasonable options for patients. Given the black box warning associated with the use of brodalumab, it should be considered for patients that have not responded to other IL inhibitors. Future research directions would include determining which biologic is appropriate for an individual patient, making the treatment individualized as the disease.

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