Emerging Therapies in the Evolving Biologic Platform for Psoriasis Treatment

BY JERRY BAGEL, MD

In the last decade, biologic therapy has emerged as a critical treatment modality for moderate to severe psoriasis. During that time, long-term studies for have confirmed the safety profiles for TNF inhibitors such as etanercept (Enbrel, Amgen) and adalimumab (Humira, AbbVie). More recently, discoveries involving various interleukin (IL) pathways have led to the development of several new agents, notably the IL-12/23 inhibitor ustekinumab (Stelara, Janssen). This has led to a flurry of new activity in the biologic pipeline for psoriasis treatment. Ahead, I will examine the latest advances in the growing treatment armamentarium and offer a glimpse of what the psoriasis treatment arena may look like in coming years.

SMALL IMMUNOSUPPRESSANT MOLECULES

Already FDA-approved for psoriatic arthritis, the oral agent apremilast (Otezla, Celgene) is an inhibitor of phosphodiesterase. This results in an increase in intracellular cyclic adenosine monophosphate (cAMP), which is known to decrease the amount of pro-inflammatory molecules that are produced. By increasing cAMP, apremilast decreases TNF IL-17 in dendritic cells, neutrophils, T-cells, macrophages. In one study, 33 percent of patients receiving apremilast 30mg BID achieved PASI 75 after 16 weeks of treatment, while 54 percent of patients achieved PASI 50.1 Over 28 weeks, patients receiving apremilast saw a 60 percent improvement in PASI, which was maintained through 52 weeks. Thus, although short-term efficacy data for apremilast is moderate, long-term data is potentially significant.

In addition, apremilast is remarkably safe. The most notable side effects are early disturbing flatulence and loose stools, which can be minimized by decreasing early dosage. Moreover, abnormal labs in clinical trials were so negligible compared to placebo that no lab monitoring is necessary in the treatment of psoriatic arthritis, not even PPDs.2

Therapies in the Pipeline. The next two oral small molecules—baricitinib and tofacitinib—act via Janus Kinase (JAK) inhibition. JAK, when activated, results in phosphorylation of STAT (Signal Transducer and Activator of Transcription). This results in the protein synthesis of pro-inflammatory molecules such as IL-22, IL-23, IL-12, and IL-6. These two
molecules block JAK from phosphorylating STAT, hence decreasing the production of these two interleukins.

In one study, 50 percent of patients treated with the investigational agent baricitinib 10mg BID achieved PASI 75 by week 12 and maintained these results through 24 weeks. Moreover, 35 percent of patients achieved PASI 90.¹

Tofacitinib has also shown promise in early trials. In one study, 63 percent of patients achieved PASI 75 at 12 weeks, compared to 58 percent of patients receiving etanercept.⁴ However, several serious infections were reported, and since STAT is involved in hematopoiesis, patients will probably need their white blood cell counts and hemoglobins monitored.

IL-23

With the 2009 approval of the anti-IL12/23 agent ustekinumab, a new pathway in treating psoriasis treatment was opened. In the last five years, researchers and physicians have learned much about the role of interleukin pathways in the systemic inflammation of psoriasis. Specifically, we have learned that IL-23 induces the proliferation of Th-17 cells, the upshot of which is the release of IL-17 and IL-22, which both are more specifically involved in the hyperproliferation of the epidermis than other interleukins or chemokines. The discovery of Th17 cells that were different from Th1 or Th2 cells led to the shift in thought away from Th1-induced TNF as the driving force in psoriasis. Th17 cells produce IL-17 and IL-22, which are both involved in the stimulation of keratinocyte proliferation, an excess of which results in the abnormal epidermis seen in psoriasis.⁵

There is an increased expression of IL-23 as noted by an excess of p19 subunit in the lesional skin of psoriatic plaques but not that of the p35 subunit.⁶ One part of the initial trigger is keratinocyte-mediated expression of IL-1B, IL-6, and TNF alpha, resulting in activation of antigen-presenting cells that in turn produce IL-23 and proliferation of Th-17 cells via the activation of the innate immune system through dendritic cell activation.

As we have learned more about IL-23, we have also refined our knowledge of TNF and its role in psoriatic disease. TNF is more broadly active at multiple points in the inflammatory cascade. Macrophages, mast cells, keratinocytes, and lymphocytes produce TNF, which is involved in the recruitment of T-cells from lymph nodes and helps halt their proliferation. TNF IL-17A and INF gamma also stimulate keratinocytes to produce antimicrobial peptides and chemokines. Moreover, genetic analyses have linked IL-23 and IL-17 to psoriasis susceptibility.⁷

Therapies in the Pipeline. Two monoclonal antibodies to IL-23 are currently in development. The first is guselkumab (Janssen), which in Phase II trials has shown to be comparable to ustekinumab in head to head studies. Recent data presented at the American Academy of Dermatology meeting in Denver, CO, found that 85 percent of patients receiving guselkumab 100mg every eight weeks achieved a PGA score of 0 or 1 by 16 weeks, with 78 percent of patients also achieving PASI 75. Moreover, at the 40-week mark, nearly 90 percent of patients in the 100mg group achieved PASI 75.⁸ However, early safety markers did show some major adverse cardiac events.

The other IL-23 agent under investigation is tildrakizumab, also known as MK-322 (Merck), which is currently in Phase III trials, the results of which are expected in 2015. In preliminary findings, 75 percent of patients receiving tildrakizumab achieved PASI 75 at 12 weeks.⁹

IL-17 AND IL-22

More recently, researchers have learned of the importance of the IL-17 cytokine family, which has six subtypes—IL-17A through IL-17F.¹⁰ There are numerous IL-17 receptors expressed in the skin, lungs, kidneys, liver, and spleen. IL-17 is involved in acute inflammation and has been shown to be important in the host defense against extracellular pathogens, i.e. Staph and Candida, whereas Th1 (TNF and IFN) are involved in host defense against intra-cellular pathogens, i.e. tuberculosis (TB) and salmonella. IL-17 released from Th17 cells or innate immune cells acts on keratinocytes to cause hyperproliferation and the release of antimicrobial peptides attract neutrophils, which produce more IL-17.¹¹

IL-22 produced from Th17 cells also contributes to keratinocyte hyperproliferation and expression of antimicrobial peptides acting synergistically with IL-17A. Therefore we have developed the notion that IL-17 is one of the key drivers in the pathogenesis in psoriasis.

Therapies in the Pipeline. Three new agents are in development to interfere with IL-17.
Ixekizumab (Eli Lilly) is another agent that has shown promise. In one trial, 62 percent patients receiving ixekizumab 75mg achieved PASI 90 within 20 weeks, as compared to 70 percent of patients receiving 150mg. However, these results appear to plateau at week 52, with PASI 75/90/100 rates of 85, 75, and 50 percent, respectively. In addition, ixekizumab has a strong safety profile.15,16

Secukinumab (Novartis) is also showing strong potential. In a Phase III head to head trial with etanercept, patients receiving secukinumab 300mg achieved a PASI 75 score of 86 percent, as compared to 72 percent in the secukinumab 150mg group, and 64 percent of etanercept-treated patients.17 After secukinumab was discontinued, PASI 75 scores were 72 percent for the 300mg group, 62 percent in the 150mg group, and 41 percent for the etanercept group. Moreover, PASI 75/90/100 scores were maintained for 141 days and 90 days, respectively.17 The researchers also noted efficacy with psoriatic arthritis from HAQ score improvement.

Regarding adverse events, there was a signal that secukinumab might exacerbate Crohn’s disease and ulcerative colitis. In addition, there seems to be a decrease in absolute neutrophil count (ANC), which seems to have been very encouraging for several small and large molecules in development, more data is needed to confirm safety.

Brodalumab (Amgen) is a monoclonal antibody against the IL-17 RA receptor and 5/6 IL-17 receptors. In one study, PASI 75, 90, 100 responses at week 12 were 83, 75, and 63, respectively (210mg QO week). Another study found that patient reported symptoms were decreased significantly after 12 weeks of treatment.15 Maintenance of response was essentially maintained through 48 weeks. Brodalumab has shown benefit in treating psoriatic arthritis, with one study showing patients achieving ACR 20 of 64 at 24 weeks, and an ACR 50 of 43, which may be even better than previous TNF data.14 In terms of adverse events, two cases of asymptomatic neutropenia were observed that came back to normal after discontinuation of the drug. Early data indicating that brodalumab clears almost two-thirds of all patients with severe psoriasis within 12 weeks is a previously unseen and potential breakthrough in efficacy.


Dr. Bagel has served as consultant, researcher, or speaker for Amgen, AbbVie, Janssen, Eli-Lilly, Novartis, Celgene, and Pfizer.

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