Think You Know IL-17 Pathway? Think Again

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When today's dermatology residents were born, the concept of psoriasis as a systemic disease was relatively new. Early in the 1980s, topical therapy was the mainstay for medical management of this "skin condition." Systemic therapies were beginning to be used for severe psoriasis, although it was unclear how they provided benefit. Three decades later, dermatologists have a much better—though perhaps still incomplete—understanding of the pathogenesis of psoriasis and its related comorbidities. Novel therapies have emerged to target the immunologic drivers at the heart of the disease.

The emergence of anti-TNF agents in the early 2000s instigated a paradigm shift in the approach to psoriasis treatment and gave rise to the era of biologic therapies. While such agents are widely used and represent an important treatment option for many psoriasis patients, they have yielded to newer therapies that target IL-17 and IL-23 with clinically more significant clearance of disease.

The current array of FDA approved biologic therapies to treat psoriasis now provides dermatologists the opportunity to target immunologic drivers of the disease at various different points. As eloquently reviewed in the pages ahead, the skin manifestations of psoriasis develop secondary to a complex interplay between the innate and adaptive immune systems. Dendritic cells secrete IL-12 and IL-23 cytokines, which stimulate naive T cells to differentiate into TH1 cells and TH17 cells, respectively.[1,2] TH17 cells secrete a number of inflammatory cytokines including IL-17, regarded as a key cytokine in psoriasis pathogenesis. The "IL-23/IL-17 axis" describes the complex network of interactions between IL-23, IL-17, TH17 cells, and other IL-17-releasing cells, which triggers a cascade of inflammatory molecules that ultimately lead to what we clinically see on the skin.[1,3] These same inflammatory pathways are implicated in the range of systemic comorbidities now linked to psoriasis and psoriatic arthritis.[2]

Therapies that target IL-23 and IL-17 have similar but not identical mechanisms for addressing the pathogenesis of psoriasis, as they target distinct immunologic mediators. It should also be noted that agents of the same class may bind and affect different ligands. It is not clear whether one target is more important than another, although it is worth noting that IL-17 production is both a consequence of IL-23 activation and also a driver of IL-23 production. The clinical significance of this is not yet clear, but it warrants consideration. However, we also know that IL-17 is NOT only released by TH-17 cells, which are regulated by IL-23. Therefore, IL-23 inhibition means only partial blocking of IL-17. As treatment options evolve, we further understand that among all the IL-17-targeting drugs, brodalumab is the only biologic agent that inhibits downstream effects of all five IL-17 subtypes (IL-17A, IL-17AF, IL-17F, IL-17C, and IL-17E) by blocking the IL-17RA receptor.[4]

As the relative new-comers, the IL-23 and IL-17 inhibitors are the focus of optimism for psoriasis. They appear to offer consistent and high levels of therapeutic benefit, at rates that may surpass those seen with anti-TNF agents. Prescribers are curious to identify differences in the effects of these newer agents and to determine whether clues may emerge regarding how to best tailor treatment selection for each individual patient. While prescribers will no doubt gain confidence with the use of these agents over time, dermatology providers can be confident that there is no need for undue hesitation. IL-23 and IL-17 inhibitors are safe and effective options for management of psoriasis—a serious, systemic disease.

DISCLOSURE

Dr Kircik has been either an investigator, consultant, advisory board member, or speaker for Amgen, Celgene, Ely Lilly, Novartis, OrthoDermatologics, Pfizer, SunPharma, and UCB.

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