Pipeline Watch: A Paradigm Shift in Atopic Dermatitis

BY TED PIGEON, MANAGING EDITOR

Pipeline Watch is a feature appearing periodically in Practical Dermatology® that explores the potential of therapeutic agents currently under investigation. In each edition, investigators offer insights about the development and investigation of agents on the clinical trial circuit. In this entry, Emma Guttman-Yassky, MD, PhD Associate Professor of Dermatology and Immunology at Icahn Medical School at the Mount Sinai Medical Center in New York City, reflects on the monoclonal antibody dupilumab and its role in the rapidly changing therapeutic landscape for atopic dermatitis.

Despite atopic dermatitis (AD) being the most common inflammatory skin disease, the pathogenesis of the condition has long been difficult to identify and address. That’s why successful intervention is rarely a guarantee, despite a bevy of prescription and non-prescription approaches available. Recently, however, scientists have made important discoveries regarding the systemic components of AD. According to Dr. Guttman-Yassky, the renewed focus on immunological aspects stems from new discoveries regarding the major pathogenic pathways of the disease. These findings have ushered in a new development phase. “We are seeing a revolution in how atopic dermatitis is treated, with many immune-based and targeted agents currently under investigation,” Dr. Guttman-Yassky notes.

TARGETING IMMUNE PATHWAYS

The first of the new wave of immunosuppressive agents is dupilumab (Regeneron/Sanofi), an antibody targeting interleukin 4 receptor alfa that modulates signaling of both the IL-4 and IL-13 cytokines, thus targeting the whole Th2 pathway, developed specifically for the treatment of AD. Dupilumab is now in phase 3 trials. Dr. Guttman-Yassky served as a lead investigator on the mechanistic clinical trial where her lab collaborates on the mechanistic studies for dupilumab, and and she also serves as an investigator in the phase 3 dupilumab trial. One particular recent study (see sidebar) found rapid improvement of the molecular structure of AD with targeted anti-IL-4 receptor therapy. “What the study shows is that shutting off T helper 2 immune pathways leads to rapid improvement in epidermal responses,” says Dr. Guttman-Yassky. This, she says, opens the door to development of other immune targeted therapeutics targeting Th2 and other immune pathways, and indeed several biologics and small molecules are in development. While the phase 3 trials for dupilumab are finalizing, other agents also specifically developed for AD to address sTh2 (anti IL-13) or different pathways (such as PDE4 or TH22), are in phase 2 trials.

The emphasis on addressing immune abnormalities is a new chapter in the debate regarding the best ways to treat this disease. “A few years ago we were still having an active debate: Is atopic dermatitis primarily a disease of barrier dysfunction or is it primarily an immune disease?” Dr. Guttman-Yassky explains. “For many years, manufacturers did not know what they were targeting—we saw many agents that targeted different aspects of the barrier, such as lipids, ceramides, etc. But now that we can show with a narrow immune targeted treatment that we can actually reverse barrier responses, finally settling the debate, and classify atopic dermatitis as primarily an immune disease,” she
DUPILUMAB: IN FOCUS

The first report showing rapid improvement of the atopic dermatitis molecular signature with targeted anti-IL-4 receptor therapy was published in the December 2014 edition of the Journal of Allergy of Clinical Immunology. In it, researchers sought to evaluate dupilumab modulation of the AD molecular signature. They performed transcriptomic analyses of pre-treatment and post-treatment skin biopsy specimens from patients with moderate-to-severe AD treated weekly with 150mg or 300mg of dupilumab or placebo. Results showed that dupilumab improved the AD signature both dosages.

Specifically, the expression of genes upregulated in AD lesions decreased in patients treated with dupilumab by 26 percent and 65 percent for treatment with 150mg and 300mg, respectively, whereas genes downregulated in AD lesions increased by 21 percent and 32 percent, respectively. These molecular changes paralleled improvements in clinical scores, they observed further. They also saw significant decreases in mRNA expression of genes related to hyperplasia, T cells, and dendritic cells (CD1b and CD1c), and potent inhibition of TH2-associated chemokines (CCL17, CCL18, CCL22, and CCL26) without significant modulation of TH1-associated genes (IFNG). According to the researchers, these data suggest that IL-4 and IL-13 drive a complex, TH2-centered inflammatory axis in patients with AD.


observes. "We are currently experiencing a pathogenic shift in disease." However, while severe patients need an immune driven treatment, barrier-targeting treatments are still important as an adjunct or for more mild disease.

The swift rise in the development of targeted biologic therapies for AD follows a similar path forged more than a decade ago in psoriasis. During that period, continued research and deeper inquiry into the systemic nature of psoriasis yielded the development of more refined agents and more efficacious outcomes. After many years’ worth of research and use of biologic agents in the psoriasis arena, the starting point for the development of dupilumab was much more advanced. This surely plays a role in why data has been so promising, according to Dr. Guttmann-Yassky.

Regarding the adoption of biologic therapy in atopic dermatitis, Dr. Guttmann-Yassky expects to see a similar pattern. While the prescription rates for biologics for psoriasis were low for many years but are rising steadily, Dr. Guttmann-Yassky believes that urgency to treat AD coupled with familiarity with the modality will usher swifter adoption of new agents. “When patients are itching like crazy and the available agents cannot control the condition, physicians will more readily turn to biologic agents, particularly with more familiarity and awareness.”

THE NEED FOR IMMUNE-BASED THERAPIES

Though it has taken several decades, the shift toward systemic solutions for atopic dermatitis is greatly needed, according to Dr. Guttmann-Yassky. “Four to seven percent of the American population has atopic dermatitis,” she notes. “One-third of these cases belong to the moderate to severe category.” Noting the high volume of patients needing care, she also points out that enrollment for dupilumab trials is very fast. “In our clinic there are many patients waiting for clinical trials.” The immune based treatments are game-changers, and are able to reverse the disease clinically and in skin tissues, showing results that are comparable if not better that immune suppressants like cyclosporine, that have multiple side effects. “For moderate to severe patients who require systemic agents like cyclosporine, a biologic would likely be a safer alternative,” she explains.

Additionally, Dr. Guttmann-Yassky believes that the swell of research into the underlying systemic components of skin conditions like psoriasis and now also atopic dermatitis is leading to better understandings of these diseases work. Moreover, it implicitly highlights the importance of aggressive intervention to possibly prevent systemic manifestations of these diseases. “We’re already seeing with biologic agents for psoriasis that early intervention prevents some systemic manifestations in addition to the clinical benefit,” she says. “Why put patients on cyclosporine if you can control the disease with a safer, possibly more effective agent?”

As the volume of data continue to reveal the underlying immune factors of AD, the case continues to build for the systemic nature of the disease, notes Dr. Guttmann-Yassky. She observes further that many more studies are currently being performed that will likely reveal more about the mechanism of the disease. Other things being investigated include the potential benefits of currently approved biologics for atopic dermatitis, as well as targeting other cytokines.

Summing up the current moment in atopic dermatitis research, Dr. Guttmann-Yassky calls it both a ‘steep learning phase’ and a ‘hopeful time’ for those stricken with atopic dermatitis. “The next two to three years will be extremely important as far as how we understand and can treat this disease in a much better and specific fashion,” she notes. “The future is brighter, and I urge all patients to be patient an help by participating in these important studies that will change the therapeutic schema of AD. All of us—researchers, clinicians and, most importantly, patients—need to jointly make this translational revolution happen for atopic dermatitis.”