

Ditching the Itch with Anti–Type 2 Cytokine Therapies for Atopic Dermatitis

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Atopic dermatitis is a chronic inflammatory disease characterized by intense pruritus and dry, inflamed skin. An impaired skin barrier and a dysregulated immune response to a variety of triggers are key factors in the complex pathophysiological mechanism of this disease. The predominant early immunologic response in atopic dermatitis includes type 2 helper T (Th2) cells, innate lymphoid cells, and keratinocytes that produce the type 2 cytokines, such as thymic stromal lymphopoietin (TSLP, a major promoter of atopy) and interleukins 4, 13, and 31.¹ Interleukins 4 and 13 and TSLP inhibit the differentiation of keratinocytes and thereby reduce the production of skin-barrier proteins and epidermal lipids.¹ Studies have shown that the presence of receptors for TSLP and interleukin-31 on neurons provide a possible explanation for how the type 2 responses activate sensory neurons and trigger pruritus.^{2,3}

For some patients with atopic dermatitis, the pruritus, time-intensive skin-care routines, and associated sleep disturbance make the disease intolerable. This reality has been highlighted in the popular HBO crime drama miniseries “The Night Of,” in which the main character has atopic dermatitis and scratches his feet with a chopstick. The treatment of atopic dermatitis has focused on hydration of the skin barrier with emollients, trigger avoidance, behavioral approaches to reduce itching, antibacterial measures, and topical antiinflammatory agents.⁴ The systemic medications that are used for severe atopic dermatitis are immunosuppressants, such as cyclosporine, that have a number of undesirable side effects. The understanding of the systemic type 2 responses in atopic dermatitis has led to the evaluation of new drugs to block type 2 cytokines.⁵

In this issue of the *Journal*, Ruzicka et al.⁶ report the results of a phase 2 trial of subcutaneous nemolizumab, a humanized antibody against interleukin-31 receptor A, in adults with moderate-to-severe atopic dermatitis that was inadequately controlled by topical therapies. Rather than relying on a typical investigator-based skin score

as the primary end point, the investigators chose the percentage improvement from baseline in the pruritus score on a patient-reported visual-analogue scale at 12 weeks. In the treatment group, there was a significant, dose-dependent reduction from baseline in the pruritus score. Nemolizumab appeared to work quickly, with a reduction of nearly 30% in the score within the first week, as compared with only a slight placebo effect. There were no statistical comparisons for secondary outcomes, although possible improvements in sleep scores (sleep onset, total sleep time, and sleep efficiency) and the Eczema Area and Severity Index are suggested. Although these preliminary results appear to be promising, additional larger studies are needed to confirm efficacy and safety.

In another recent article in the *Journal*, Simpson et al.⁷ reported the results of two placebo-controlled, phase 3 trials of subcutaneous dupilumab, a human monoclonal antibody against interleukin-4 receptor alpha that inhibits signaling of the crucial type 2 cytokines, interleukins 4 and 13. More than 1300 adults were enrolled in the two trials, and multiple outcomes were assessed. What is most notable about these trials is that significant improvement was seen in the primary outcome as well as in all secondary efficacy and patient-reported outcomes, including pruritus, sleep disturbance, quality of life, and symptoms of anxiety or depression. In these trials, and in the previously reported phase 2b trial,⁸ the numbers of adverse events were similar in the dupilumab groups and the placebo groups except for the incidence of conjunctivitis, which developed in 5 to 11% of the patients who received dupilumab, as compared with 1 to 2% of those who received placebo. It is critical to understand the cause, clinical course, and treatment of the conjunctivitis and to identify risk factors for this condition. Longer treatment in a larger number of patients is needed to assess for uncommon adverse events.

Even with these excellent results, some of the patients in the treatment groups did not have

improvement in their symptoms. Perhaps another immunologic mechanism may be prominent in their disease. In acute atopic dermatitis, Th2 cells predominate, but the activation of Th17 and Th22 cells and cytokines was also seen.¹ For certain ethnic groups and ages, these immunologic responses may be important in disease persistence.^{9,10} Currently, we approach atopic dermatitis as one disease, even though the condition has many clinical phenotypes. The development of biomarkers for different phenotypes of atopic dermatitis will be important in determining the most effective treatments.

The results of these studies provide hope for adults with moderate-to-severe atopic dermatitis. Data from larger long-term studies and pediatric trials are needed to fully understand how these new agents will fit into the management of atopic dermatitis. It will be important to evaluate how quickly patients have disease flares after stopping the agents and whether the addition of topical agents may provide more effective or longer remission. For the best patient care, these new therapies should be included as part of a comprehensive approach that includes education on skin care and trigger avoidance, psychological support to enhance adherence and reduce itching, and treatment of the already established mental health and sleep disorders.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe1616072

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