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Unexpected Clinical Lessons Learned From IL-4 and IL-13 Blockade

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ABSTRACT

In 2017, dupilumab became the first FDA approved systemic therapy for atopic dermatitis. Since its approval, extensive clinical experience and continued research have revealed a number of unexpected effects that are highly clinically relevant. We will review these clinical effects and the supporting evidence.

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INTRODUCTION

1. IL-4 and IL-13 Blockade is Not Immunosuppressive

Treating widespread, moderate-to-severe atopic dermatitis (AD) has classically been done with immunosuppressive medications, such as methotrexate, cyclosporine, or azathioprine. Dupilumab changed this paradigm, avoiding immunosuppression by specifically targeting Th2 inflammation via blockade of IL-4 and IL-13 signaling.[1] The lack of immunosuppression has been demonstrated clinically via numerous reports of administration to individuals with HIV and cancer without progression of their disease.[1-8] In addition, there are multiple reports of initial worsening of molluscum contagiosum followed by clearance, a sequence of events that is consistent with immunologic recognition of the virus.[9-12] Finally, there has been no evidence in clinical trials suggesting an increased risk for malignancy, cancer, or infection.[1,8]

2. IL-4 and IL-13 Blockade Normalizes the Cutaneous Microbiome

Individuals with AD have a disruption of the normal microbiome, manifesting as a reduction in microorganism diversity and high rates of colonization with *Staphylococcus aureus*. In addition, multiple studies have shown that AD patients are more likely to have serious cutaneous, multi-organ, and systemic infections when compared with those without AD.[13-16] Recent work has shown that activation of the IL-4 and IL-13 receptors on keratinocytes leads to decreased anti-microbial peptide production and that blockade of these receptors with dupilumab leads to an increase in anti-microbial peptide production and a subsequent normalization of the microbiome.[17-19] This normalization of the microbiome is believed to be the underlying cause of the roughly 40% reduction in the risk of skin infections seen across multiple dupilumab trials.[14,18-20]

3. IL-4 And IL-13 Blockade Has a Direct Effect on the Neurological Aspects of Itch

Patients with AD are known to have chronic itch and neural itch sensitization. Type 2 cytokines, specifically IL-4 and IL-13, have been shown to directly activate sensory neurons and are responsible for inducing itch in patients.[21] Itch sensitization manifests as a reduction in the threshold necessary to depolarize the itch neurons. Clinically, this results in alloknesis, defined as an itch response from stimuli that wouldn't normally activate itch neurons, as well as hyperknesis, defined as an increase in the intensity of the itch sensation triggered by stimuli that are typically itch inducing. By directly inhibiting IL-4 and IL-13 receptors, dupilumab blunts the neural itch response in patients with atopic dermatitis. One study showed that dupilumab resulted in a significant improvement in the baseline itch in patients with AD, while the control group which was treated with topical cortical steroids alone experienced increased histaminergic and mechanical hyperknesis.[22] Another report on dupilumab for the treatment of pruritus of unknown origin also demonstrates that the anti-pruritic effects of dupilumab are not simply a sequelae of the reduction in inflammation.[23]

4. IL-4 and IL-13 Blockade Directly Improves the Skin Barrier

Activation of the IL-4 and IL-13 receptors on keratinocytes causes a decrease in filaggrin production and a change in the activity of ceramide elongating enzymes, leading to shorter ceramides that create a less effective barrier against transepidermal water loss.[24,25] Additionally, it has also been shown that Type 2 inflammation, which is seen in AD, causes lipid abnormalities that further disrupt the integrity of the epidermal skin barrier.[26,27] By normalizing the IL-4 and IL-13 signaling pathways, dupilumab leads to an increase in filaggrin production and a normalization

of ceramide elongation, directly promoting skin barrier function. Studies have shown that prolonged remission of AD after the cessation of dupilumab is possible.[28,29] After proper restoration of the skin's epidermal barrier and normalization of the microbiome found on the skin surface, patients treated with dupilumab have visible skin clearance at week 16 with sustained results after one year.[1] For individuals who decide to stop the medication completely, their AD comes back more slowly compared with traditional systemic medications.[28] We hypothesize that the relatively prolonged remissions reported after dupilumab discontinuation are due to the time it takes for the filaggrin and ceramides to be metabolized away and for the microbiome to return to being Staph dominant after anti-microbial peptide production declines.

5. The IL-4 Overproduction Associated With Atopic Dermatitis is Protective Against Psoriasis, Inflammatory Arthritis and Seborrheic Dermatitis

There have been numerous cases of new onset psoriasis, inflammatory arthritis, or seborrheic dermatitis (Ps, IA, SD) in patients treated with dupilumab.[30-32] All of these effects are hypothesized to be triggered by the elimination of IL-4 induced inhibition of the Th1 and Th17 pathways. Thus, in individuals who are predisposed to a Th1 or Th17 skin or joint disease, the IL-4 over-expression induced by AD was protective against expression of that predisposition.

DISCLOSURES

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