

IL-33 antagonism does not improve chronic atopic dermatitis: What can we learn?



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The article “Phase 2 randomized clinical trial of astegolimab in patients with moderate to severe atopic dermatitis” by Maurer et al¹ in the current issue of the *Journal of Allergy and Clinical Immunology* reports the results of a clinical trial of astegolimab in atopic dermatitis (AD). Astegolimab is a human mAb that inhibits IL-33 signaling by binding to the IL-33 receptor ST2.² IL-33 signaling is implicated in the pathogenesis of atopic disease, with IL-33 thought to decrease filaggrin expression, increase itch, and activate type 2 innate lymphoid cells.³ Astegolimab was previously successful in reducing exacerbations of asthma, a related atopic disease.² Thus, the astegolimab trial in AD conducted by Maurer et al¹ was well supported at inception.

Despite its promising starting point, the randomized, placebo-controlled, phase 2 study did not report a positive result. The primary end point of 16-week Eczema Area and Severity Index did not differ statistically or clinically between the treatment and placebo arms.¹ Indeed, the authors stated, “There was no observable trend for better or worsened outcomes in any efficacy parameter with astegolimab treatment.” This result is analogous to those of the trials of etokimab, an antibody that targets the IL-33 cytokine itself, with a phase 2a trial showing a treatment effect but a subsequent phase 2b trial not doing so.^{4,5} Maurer et al¹ undertook appropriate analyses to understand whether technical issues may have underpinned the results. The trial did not enroll as expected (65 individuals were randomized versus the 90 planned); despite this, Maurer et al¹ stated, “the reduced sample size still provided approximately 80% power to detect a difference of 34% in the percent change from baseline in Eczema Area and Severity Index score at week 16.” A pharmacokinetic analysis was also performed; throughout the trial, it showed trough astegolimab levels similar to those in a successful astegolimab trial in asthma.²

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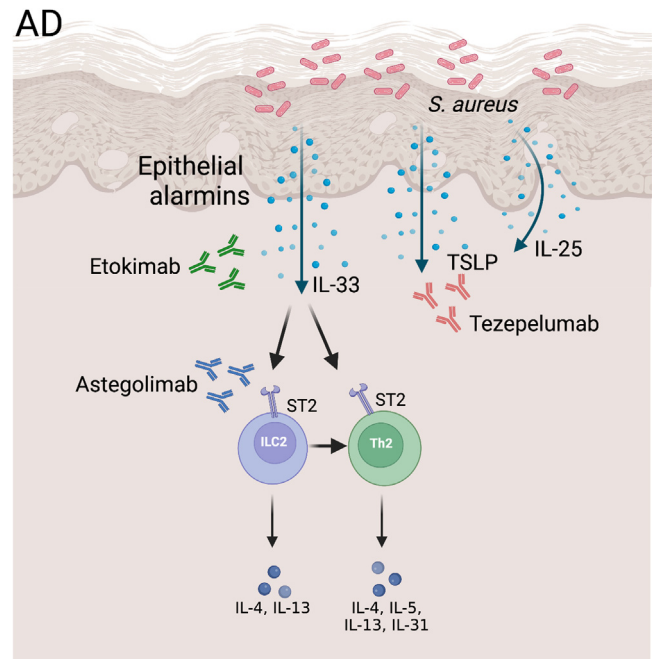


FIG 1. IL-33 is an epithelial alarmin along with IL-25 and TSLP. Alarmins are released as part of inflammatory responses, including to *Staphylococcus aureus*, a common pathogen in atopic skin. IL-33 has a role in activating type 2 responses in both type 2 innate lymphoid cells and Th2 cells. Several biologics targeting these pathways have been evaluated in clinical trials in AD; they include the anti-IL-33 agent etokimab, the anti-TSLP agent tezepelumab, and in the study by Maurer et al,¹ the anti-IL-33 receptor (ST2) inhibitor astegolimab, with all of them showing limited to no clinical efficacy.

Lastly, a biomarker analysis of blood eosinophils, IL-5, and CCL13, which are thought to be connected to IL-33 signaling in AD, could not explain the negative result. Blood eosinophil and serum IL-5 levels showed nonsignificant decreases in both the placebo and astegolimab groups at week 16, with no difference between groups. Serum CCL13 level showed a trend toward decrease from baseline in the placebo group, but it was not statistically different from the unchanged CCL13 value for the astegolimab group. In sum, one might conclude that the present trial did not improve AD for biologic reasons.

Why might IL-33 antagonism fail to improve AD? The situation may be akin to that of thymic stromal lymphopoietin (TSLP). TSLP antagonism with the mAb tezepelumab successfully reduces asthma exacerbations⁶; however, TSLP antagonism has been unsuccessful in AD.⁵ Both IL-33 and TSLP, along with IL-25, are alarmins, which are compounds released by epithelial cells during cell injury from toxins, infections, and allergens. Alarmins are often considered “upstream” of other cytokines, such as IL-4 and IL-13 (Fig 1).⁷ This terminology may be apt; perhaps the role of IL-33 in chronic AD maintenance is less prominent than previously considered. IL-33 could be critical for

initiation of skin-based inflammation but have a more limited or superfluous role in ongoing skin inflammatory responses. Indeed, if the role of IL-33 and other alarmins in human AD lies in initiation (rather than maintenance) of disease, the result of the present trial might be expected.

Another consideration along these lines is the population studied; the present study enrolled adults with chronic AD. Immune responses change over time. Chronic AD develops increasing features of T_H1 and T_H17 inflammation with a growing local mixed T-cell infiltrate, and some authors posit that autoimmune skin processes eventually occur.⁸ Furthermore, long-standing epithelial barrier disruption in AD is thought to derange the microbiome and resultant skin immune responses to commensal organisms.⁹ A population with chronic AD may thus possess a great diversity of inflammatory signaling responses at any given time, making the role of any one cytokine, such as IL-33, too limited to dictate the broader immune milieu.

The underlying cause of this trial's result will be difficult to define without additional mechanistic work. This work demonstrates that because IL-33 does not improve chronic AD, its role in AD is more complex and less understood than previously appreciated. Although clinical trials that do not meet an end point may not support adoption of a new medicine, they can have significant value. Given the substantial cost, effort, and sacrifice

involved, such trials ought to be published to prompt reconsideration of existing biologic paradigms and further mechanistic work in light of the clinical data provided. In this way, "negative" trials can still be used to their fullest extent. This can occur only if such trials are published, as has been done here.

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