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Clinical Translation of Basic Science in Asthma

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Basic science has enriched our understanding of the pathophysiology of severe asthma. Clinical translation of these discoveries has resulted in biologic therapies that target key components of asthma-related disease pathways. For example, identification and validation of biomarkers such as elevated blood eosinophil counts made it possible to implement tailored biologic treatments targeting the function of cytokines such as interleukin-5, interleukin-4, and interleukin-13.¹ The success of these strategies has prompted investigations of other molecules that are active in the pathogenesis of severe asthma. The results of two pertinent trials are reported in this issue of the *Journal*.

In a randomized, controlled, phase 2a trial, Brightling and colleagues² assessed the monoclonal antibody risankizumab in the inhibition of the cytokine interleukin-23, which is implicated in the proliferation of CD4+ type 17 helper T (Th) lymphocyte cells, neutrophil recruitment, Th2 cytokine production, and delayed resolution of inflammation.⁴ The authors hypothesized that blocking the activity of interleukin-23 would reduce the risk of severe asthma exacerbations. However, asthma-related outcomes were worse in the risankizumab group than in the placebo group. Downstream biologic responses to risankizumab were detectable (altered interleukin-23 gene-related expression was observed), which implies attenuation of apposite pathways, nonetheless without discernible clinical benefit.

Wechsler and colleagues³ evaluated the monoclonal antibody itepekimab against the alarmin interleukin-33. Itepekimab was also combined with dupilumab (an inhibitor of interleukin-4 receptor [R] α) to block both upstream (interleukin-33) and downstream (interleukin-4 and inter-

leukin-13) pathways. The primary end point was an event indicating loss of asthma control.³ Both the itepekimab and dupilumab monotherapies led to a lower incidence of events indicating loss of asthma control and to improved lung function. However, the combination of itepekimab and dupilumab was not superior to either treatment alone. Clinical translation of manifestly sound scientific rationale did not result in the anticipated success — why not?

The key question is whether the trial design allowed for the detection of therapeutic benefit. Both trial designs were similar to those of previous successful trials that targeted individual cytokines in severe asthma.¹ Furthermore, patient numbers and therapeutic doses appeared to be adequate. In the trial of risankizumab, the dose was selected on the basis of demonstrated efficacy in psoriasis and Crohn's disease.^{5,6} Itepekimab therapy showed a benefit with respect to improved outcomes that was broadly similar to that of dupilumab therapy, and it is likely that a lack of additive benefit for the combination of biologic agents cannot be attributed to underdosing of itepekimab.

Our understanding of basic science provides several clues as to why these therapies did not work as predicted (Fig. 1). Targeting the interleukin-23 and Th17 axis with risankizumab can reduce development of pathogenic Th17 cells; however, interleukin-23 is not critical for the development of Th17 cells and, in contrast to pathways operated by interleukin-5 and interleukin-4R α , interleukin-23 has only a limited auxiliary role in amplifying type 2 responses.^{4,7} It is possible that the trial conducted by Brightling and colleagues failed because signaling through alternative disease pathways nullified

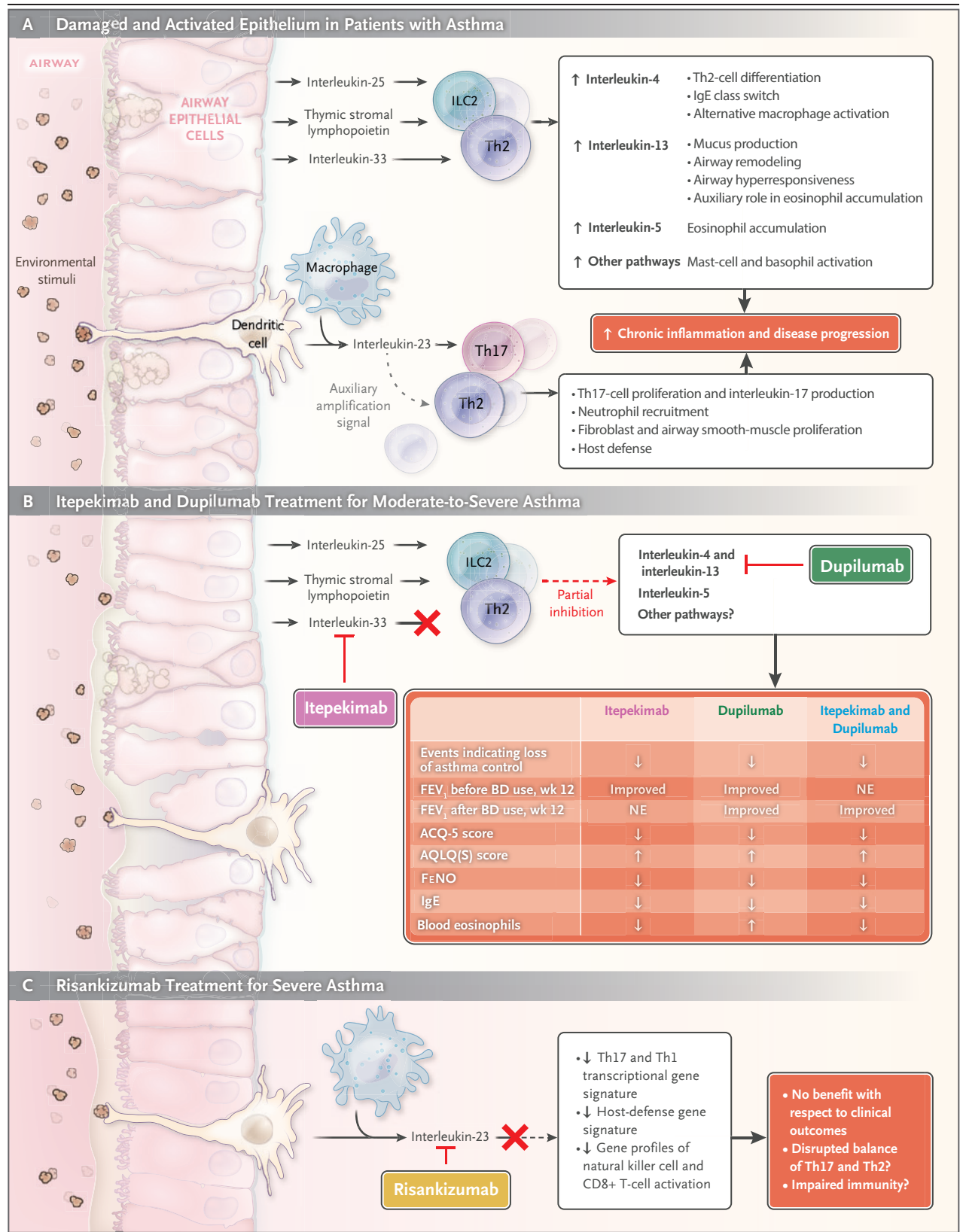


Figure 1 (previous page). Effector Pathways for Type 2 Responses and Consequences of Blocking Interleukin-33 and Interleukin-23 in Patients with Asthma.

Patients with asthma have activated airway epithelial cells that release the alarmin cytokines interleukin-33, interleukin-25, and thymic stromal lymphopoietin in response to external stimuli (Panel A). These cytokines promote type 2 airway inflammation by activating group 2 innate lymphoid cells (ILC2) and type 2 helper T (Th) cells with the release of proinflammatory factors. A key cytokine that is produced is interleukin-5, which mediates eosinophil accumulation independently of pathways regulated by interleukin-4 and interleukin-13. The interleukin-4, interleukin-13, and interleukin-4 receptor [R] α axis is active in a range of inflammatory and structural cells that drive pathognomonic features of disease. Interleukin-23 is released by macrophages and dendritic cells and induces expansion of Th17 cells, with secondary amplification of Th2 activities. Inhibition of interleukin-33 signaling by itepekimab results in suppression but not abolition of ILC2 and Th2 cytokine release, reducing eosinophil levels (Panel B). Dupilumab blocks downstream effector mechanisms mediated through interleukin-4R α , such as chemokine pathways that promote eosinophil movement from the blood to the lung. Combining itepekimab and dupilumab may therefore not yield additive benefit because interleukin-25 and thymic stromal lymphopoietin can bypass interleukin-33 to promote eosinophil accumulation (and possibly other pathways), leading to persistent type 2 airway inflammation. This notion is consistent with variable clinical responses observed after treatment combining these biologic agents. A decrease in the score on the five-item Asthma Control Questionnaire (ACQ-5) indicates improved asthma control. An increase in the score on the Asthma Quality of Life Questionnaire with Standardized Activities (AQLQ[S]) indicates improved asthma-related quality of life. Despite down-regulation of interleukin-23 target genes, no benefit was observed in patients with asthma after risankizumab treatment, a finding that highlights redundancy in cytokine systems that promote Th17 and type 2 inflammation (Panel C). However, reducing interleukin-23 activities may also impair host-defense responses or disrupt the balance of Th17 and type 2, conceivably resulting in suboptimal clinical outcomes in these patients. Solid arrows indicate active pathways, and dashed arrows indicate partial inhibition. BD denotes bronchodilator, FeNO fraction of exhaled nitric oxide, FEV₁ forced expiratory volume in 1 second, and NE not evaluated.

the inhibition of interleukin-23. Nonetheless, we need to consider (as do the authors) that the interleukin-23 and Th17 axis may not have been operational during risankizumab treatment or that stratification of patients according to interleukin-23 serum levels or the presence of non-pathogenic (a low frequency of interleukin-23R) or pathogenic (a high frequency of interleukin-23R) Th17 cells would have been more successful. Finally, inhibition of interleukin-23 with risankizumab yielded poorer outcomes than placebo, which is a signal of harm that is at odds with similar studies of biologic therapies targeting individual cytokines in asthma.⁸ The reasons for the poorer outcomes are unclear, but because interleukin-23 is vital for effective mucosal immunity,⁹ risankizumab may have conferred a predisposition in patients to more severe or more frequent virus-induced exacerbations. Overall, these findings support a cautious approach in future research investigating biologic therapies in asthma.

The epithelial-derived alarmin interleukin-33 is an attractive target because of its ability to promote the proliferation and activation of innate lymphoid type 2 cells (ILC2s) and Th2 cells.¹⁰ These cells secrete cytokines such as interleukin-4, interleukin-5, and interleukin-13 to induce pathognomonic features of asthma, including the spatiotemporal accumulation of eosinophils in the lung. Indeed, biologic agents that target the interleukin-5 and interleukin-5R

axis and the interleukin-4, interleukin-13, and interleukin-4R α axis are highly effective, although patients still have disease exacerbations after treatment,¹ indicating that alternative pathways operate within or outside of this paradigm. In this context, other epithelial alarmins such as interleukin-25 and thymic stromal lymphopoietin, operating independently of interleukin-33, promote type 2 inflammation. Combination therapy with itepekimab and dupilumab may have failed because these pathways bypass interleukin-33. Although interleukin-33 blockade can reduce production of interleukin-5 and interleukin-13, it is also possible that preexisting ILC2 and Th2 cells have residual capacity to release mediators. Finally, the trial design may have precluded detection of benefit for the combination, since interleukin-33 is an alarmin that could have been more effective as a therapeutic target in a longer-term exacerbation-type trial, in which epithelial infection and other relevant stimuli instigate exacerbated disease. Combination therapy may be capable of lowering exacerbations rather than preventing loss of control in chronic disease.

Clinical translation of basic science in asthma remains a challenge to be pursued. To quote Salman Rushdie, "It is normally supposed that something always gets lost in translation; I cling, obstinately, to the notion that something can also be gained." It is imperative to harness scientific insights from translational studies

that frustrate our hopeful expectations — so that something can also be gained.

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

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