

Biologics, Clinical Context, and the Asthmas



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It has been more than 15 years since the US Food and Drug Administration approved omalizumab for the therapy of moderate-to-severe perennial allergic asthma. The concept of removing one of the key triggers of asthma, IgE, excited the scientific and medical community. Indeed, with 80% of children and 50% of adults having a significant allergic trigger to their asthma, it was envisioned that this approach could lead to long-standing remission or perhaps even a cure for many patients. Moreover, serum IgE levels had been shown to be increased in smokers, implicating a potential role for IgE in the pathogenesis of smoking-related lung diseases such as chronic obstructive pulmonary disease (COPD). Thus, an anti-IgE mAb was envisioned to be a significant therapeutic breakthrough for patients with obstructive airway diseases regardless of the type. With this enthusiasm, there was also concern. After all, wasn't IgE important for host defense? IgE was thought to be a key component of the defense mechanisms involved in parasitic infections, and isolated IgE deficiency, although rare, was associated with respiratory tract infections and autoimmune diseases. IgE was also implicated in cancer surveillance. Fortunately, the use of omalizumab has not been associated with clinically meaningful increases in severe parasitic infections, respiratory infections, or malignancy. The Epidemiologic Study of Xolair (omalizumab): Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS) assessed the long-term safety of omalizumab in a clinical practice setting as part of a phase IV US Food and Drug Administration postmarketing commitment.¹ Data from EXCELS suggest that omalizumab therapy is not associated with an increased risk of malignancy. Thus, omalizumab has taught us that IgE might be important, but not essential, for host defense mechanisms

involved in parasitic infections and cancer. Interestingly, the use of omalizumab has recently been associated with a decreased incidence of viral-induced respiratory infections leading to asthma exacerbations via restored IFN responses.²⁻⁴ However, with the assurances of the relative safety of blocking IgE came the realization that this approach is not curative. Even with long-term successful therapy with omalizumab, discontinuation often results in recurrence of disease.⁵

During the same time period that omalizumab was being studied, the understanding that key cytokines were important in the pathogenesis of asthma led to innovative therapeutic approaches, including inhalational soluble IL-4 receptor and intravenous anti-IL-5 mAbs. Initial studies with inhalational soluble IL-4 receptor were very promising,⁶ but subsequent studies were negative. Because IL-4 was thought to be a critical cytokine for IgE production, mucus secretion, and T_H2 cell development, the failure of soluble IL-4 receptor was postulated to be due to an issue in drug delivery. However, intravenous anti-IL-4 mAb was also ineffective, and further attempts at blocking IL-4 alone were abandoned.

In a proof-of-concept study, the anti-IL-5 mAb mepolizumab was found to rapidly and profoundly decrease both blood and sputum eosinophil levels, but did not inhibit allergen-induced late-phase asthmatic responses nor airway hyper-responsiveness assessed by histamine inhalation.⁷ In the first large-scale therapeutic trial of mepolizumab, blood and sputum eosinophils were again found to be decreased, but clinical end points were not improved.⁸ These failures brought into question the roles of IL-5 and eosinophils in the pathogenesis of asthma. It wasn't until several years later, when the results of 2 small studies were published in the *New England Journal of Medicine* showing the positive therapeutic benefits of mepolizumab in patients with elevated eosinophils, that the paradigm of treating eosinophilic patients with IL-5-blocking strategies was established.^{9,10} Subsequently, the 3 IL-5-blocking strategies in clinical trials, mepolizumab, reslizumab, and benralizumab, focused their clinical development strategies in patients with elevated blood or sputum eosinophils. The results of these studies reviewed in this issue of the journal^{11,12} led to the approval of all 3 agents for patients with severe asthma and the eosinophilic phenotype.

The failure of anti-IL-4 strategies was thought to be in part related to the redundancy of the immune system. Specifically, many of the effects of IL-4 could be induced by IL-13, and IL-13 had additional effects such as promotion of airway hyperresponsiveness that led investigators to postulate that blocking this cytokine might be a better strategy. In addition, periostin and dipeptidyl peptidase-4, which are induced by IL-13 and can be measured in serum, provided a rationale for their potential utility as biomarkers to guide anti-IL-13-directed therapy. In the first large-scale asthma clinical trial examining the efficacy of an anti-IL-13 mAb, lebrikizumab, improvements in pulmonary function values were greater in patients

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with higher blood levels of periostin.¹³ The results of this study were very encouraging because this represented a significant step toward precision use (ie, individuals with elevated periostin or dipeptidyl peptidase-4) of biologics in patients with asthma. However, phase 3 trials of lebrikizumab and a different anti-IL-13 mAb, tralokinumab, failed to meet prespecified end points, hindering further development for asthma.

The concept of antagonizing the effects of IL-4 or IL-13 for the therapy of asthma was revitalized when strategies were developed to block the common alpha chain of the IL-4 receptor important in signaling for both cytokines. Dupilumab, the mAb that binds to the IL-4 receptor alpha chain, is the latest of the 5 Food and Drug Administration–approved mAbs for the therapy of asthma. As reviewed in this issue of the journal,¹¹ dupilumab has been shown to have a much better therapeutic profile than either of the anti-IL-4 or anti-IL-13 strategies alone.

The above narrative of the initial sputtering development of targeted T2-focused biologic therapy for asthma, which has now evolved into exploration of a plethora of both potential T2- and non-T2-focused therapies (as outlined by Corren¹⁴ in this issue), may be taken as a story of the trials and tribulations of drug development. However, to take that reductionist approach is to ignore the unprecedented information these biologically targeted interventions are providing in terms of understanding the underlying pathobiology of the asthmas and stimulus-response heterogeneity in these diseases. Yes—the asthmas and these diseases. What the currently available biologics, those being tested, and those coming down the road are allowing us to do is to begin to separate the phenocopies of asthma—phenocopies that all end up with the variable airway obstruction we know as asthma. This process began 20 years ago with the first targeted therapies in asthma—the leukotriene modifiers. Their particular effectiveness in aspirin-exacerbated respiratory disease led us to understand that, to a greater extent than other forms of asthma, aspirin-exacerbated respiratory disease was driven by leukotriene overproduction.^{15,16} Furthermore, it became clear that all stimuli to bronchoconstriction were not equally dependent on these mediators, with greater effects in allergen-induced bronchoconstriction than in exercise- or cold air–induced bronchoconstriction. The different treatment effects of these biologics, as discussed in several articles in this issue,^{11,12,14} allow us to extend this paradigm. The introduction of anti-IgE, with a predominant effect on exacerbations with little effect on airway caliber, laid the groundwork for the concept that these 2 clinical manifestations of asthma (airway obstruction and exacerbations) might be cotravelers but not pathobiologically completely overlapping. Anti-IL-5 therapy, with its very focused effects on eosinophils, has allowed us to understand that eosinophils have an outsized effect on exacerbations, but, in retrospect, not surprisingly, only in patients in whom eosinophils are present (or have been present but suppressed by oral corticosteroids). The introduction of dupilumab, with its dual anti-IL-4 and anti-IL-13 effects and its observed effects on exacerbations and airway function (see Table I in Pavord and Hanania¹² in this issue), even as peripheral eosinophils rise, is not totally unexpected in view of its potential for pleomorphic effects (as illustrated in Figure 1 of Krings et al¹¹) on smooth muscle through IL13, IgE production through IL4, and unclear mechanisms of inhibition of eosinophil effector function.

Although these biologics are providing insight into asthma pathobiology, how is the clinician to decide which patients with severe asthma to treat with which biologics, if any? Pavord and

Hanania¹² address some of these issues in their Controversies in Allergy discussion in this issue. The higher a patient's blood eosinophils, the more likely they are to respond to anti-IL-4/13, anti-IL-5, and possibly an anti-IgE. If eosinophils are not elevated and fractional exhaled nitric oxide is high, there is still a reasonable chance that exacerbations will respond to anti-IL-4/13 as reviewed by Krings et al.¹¹ If a patient meets criteria for anti-IgE therapy and does not have elevated blood eosinophils, they are clearly a candidate for anti-IgE therapy. If both T2 biomarkers (IgE and eosinophils are elevated), there is more room for discussion. However, one might argue, as does Hanania, for anti-IL-4/13 therapy because it seems to be effective in patients with elevated eosinophils and will lower IgE. One must also remember, as illustrated by the Difficult Case presented by Caminati et al¹⁷ in this issue, that it is possible that in certain cases, targeting both T2 pathways (IgE and eosinophils) may be necessary. Whether dupilumab alone can be effective in such cases, or dual anti-IgE and antieosinophil therapy would be required, remains to be determined.

As we consider biomarkers to guide our therapy, the review by Yousuf et al¹⁸ in this issue regarding effects of antieosinophilic drugs in eosinophilic COPD injects an important cautionary note. Biomarkers need to be considered in the clinical context. Eosinophils in asthma represent a subphenotype strongly influenced by eosinophils. In COPD, where multiple other mechanisms are operative, eosinophils may contribute less to the clinical presentation of the disease, and thus targeting them may not be as fruitful unless they are at levels much higher than those seen in asthma. Biomarkers can guide therapy, but clinical context is key.

We have come a long way in identifying potential immunologic targets important in the pathogenesis of asthma and COPD. The failures have been extremely important in our understanding of the biology of obstructive airway diseases. However, as reviewed in this issue, we still lack specific biomarkers for reliably predicting the effectiveness of a particular biologic. In addition, we do not have good therapies for T2- low patients, those with a neutrophil-predominate inflammation, and have failed to identify accurate point-of-care biomarkers for this phenotype. Finally, none of these agents have been shown to induce true immunomodulation. Nonetheless, the approved therapies and those under development provide new therapeutic advancements for our patients with obstructive airway diseases and allow us to better understand how to begin to classify patients with variable airway obstruction in therapeutically important ways.

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