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WE HAVE TO LEARN TO DO WITHOUT KNOWING ENOUGH: ANTI-EOSINOPHILIC TREATMENTS FOR SEVERE ASTHMA

Alberto Papi[1], Bianca Beghé[2], and Leonardo M. Fabbri[1,3]

[1]Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [2]Department of Medical and Surgical Sciences, Section of Respiratory Diseases, University of Modena and Reggio Emilia, Modena, Italy; [3]Sahlgrenska University Hospital, Gothenburg, Sweden

Corresponding author:

Leonardo M. Fabbri, MD, FERS

Professor of Internal and Respiratory Medicine, University of Modena & Reggio Emilia (-2016)

Eminent Scholar of Internal and Respiratory Medicine, University of Ferrara, 2017-

Visiting Professor of Internal and Respiratory Medicine, University of Gothenburg COPD Center, Sahlgrenska Hospital, Gothenburg, 2017-

Address: Viale Giuseppe Verdi 56/15 - 41121 MODENA

Email: leonardo.fabbri20@gmail.com

Interleukin-5 (IL-5) is the main eosinophilic cytokine that promotes the differentiation, survival, and activation of eosinophils, which are the key inflammatory cells in severe eosinophilic asthma (1, 2). Thus, it is no surprise that anti-IL-5 pathways have been explored for several years for their ability to reduce eosinophilic inflammation and thus to improve the treatment of this disease (3, 4).

Two anti-IL-5 monoclonal antibodies are now registered (mepolizumab and reslizumab), and one anti-IL-5 Rα antibody (benralizumab) (5) is on its way to registration. Other anti-eosinophilic agents acting through different mechanisms are also being explored, e.g., the anti-IL-13 monoclonal antibody lebrikizumab (6), the anti-IL-4 receptor-α antibody dupilumab (7), the CRTh2 antagonists fevipiprant (8) and tezepelumab, a human monoclonal antibody specific for the epithelial cell-derived cytokine thymic stromal lymphopoietin (9).

Mepolizumab is a humanized monoclonal antibody that targets the IL-5 ligand and inhibits IL-5 receptor signaling in eosinophils. Mepolizumab reduces exacerbation and asthma symptoms, improves lung function, and reduces oral corticosteroid use in oral steroid-dependent patients with severe asthma (10). Reslizumab is a humanized anti-IL-5 monoclonal antibody that also targets the IL-5 ligand (11), reduces asthma exacerbations, and increases lung function (FEV_1) in severe eosinophilic asthmatics (≥400 cells/μL) (12).

Whereas mepolizumab is administered subcutaneously (SC) at a fixed dose (100 mg SC every 4 weeks, Q4W), reslizumab is administered as a weight-adjusted intravenous dose of 3 mg/kg Q4W. No direct comparison of efficacy and safety between these two treatments has been reported before. Mukherjee et al. (13) compare mepolizumab and reslizumab in 10 prednisone-dependent asthmatics (sputum eosinophils >3% and blood eosinophils >300 cells/μL), who had previously received mepolizumab (100 mg SC Q4W) for at least 1 year. Patients received two infusions of placebo (Q4W) followed by four infusions of 3.0 mg/kg reslizumab Q4W in a single-blind, placebo-controlled sequential trial. Primary outcomes were reductions of blood and sputum eosinophils; additional outcomes included clinical and functional parameters and some exploratory biomarkers.

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Mukherjee et al. (13) found that weight-adjusted intravenous reslizumab was superior to fixed-dose SC mepolizumab in attenuating airway eosinophilia in these prednisone-dependent asthmatics, and that this effect was associated with better asthma control.

This was a small study—more a proof-of-concept, hypothesis-generating study—that nonetheless provides clinically relevant information. It was conducted in oral steroid-dependent patients with severe eosinophilic asthma, the most difficult population to manage. Results clearly showed that a fixed-dose treatment is inferior to a weight-adjusted dose, although there is no information on the difference in potency between mepolizumab and reslizumab or the different effects of various forms of administration. The study has the strength of coming from a group that has unique experience in sputum eosinophil analysis and in the management of steroid-dependent patients with severe eosinophilic asthma. Although conducted in only 20 steroid-dependent asthmatics—9 treated with mepolizumab and 11 treated with placebo (14)—their previous pivotal study has helped to reverse the idea that mepolizumab is useless in asthma (15) unless a very select group at risk of exacerbations is treated and unless exacerbations are chosen as the primary outcome of the study.

The present study also has the merit of investigating the potential mechanism and the complexity of local immunologic processes leading to an effective blockade of IL-5 activities and eosinophilic inflammation at the tissue level. Indeed, airway eosinophilopoiesis, immune complex formation, and autoimmune mechanisms were explored as possible pathways of IL-5 treatment when local IL-5 dosage is inadequate. Thus, the authors provide information on the reasons that make severe asthma non- or less responsive to high-dose corticosteroids and shed new light on the importance of the immunologic events that occur when the monoclonal antibody reaches and confronts its specific target. Likewise, the authors highlight the need for studies that address the pharmacokinetics/pharmacodynamics of airway bioavailability of monoclonal antibodies in patients with severe asthma. Previously, data have been obtained only in patients with mild asthma; thus, we

have missed potentially important considerations for the appropriate clinical use of these drugs in terms of both effectiveness and safety (3, 4).

The study has several limitations, which are acknowledged by the authors. In particular, for ethical reasons, the comparison of the effects between the two treatments is not balanced. The changes between post-mepolizumab and pre-mepolizumab were assessed and compared with the differences between changes from baseline of post-reslizumab versus post-placebo. This is not always statistically irrelevant: For equivalency, pre- and post-mepolizumab should have been compared with pre- and post-reslizumab. If so, from a statistical viewpoint, reslizumab would appear less effective for FEV_1 (Figure 3A), and the difference between treatments would not be so clear-cut for some of the effects on eosinophilic inflammation (Figure 4). Indeed, there is often a deterioration during the placebo treatment that is sometimes close to statistical significance (Figure 3A). This makes the uneven design of the study questionable, and its conclusions require a follow-up from properly designed and powered studies. Finally, although not statistically significant ($p= 0.06, 0.07$), the differences between the two study arms in blood/sputum eosinophils at baseline are quite consistent. (The percentage of sputum and blood eosinophils in the mepolizumab arms on average half that in the reslizumab arm, a substantially different starting point for the primary objective assessed in the study.)

The clinical conclusion of the study is that we have to learn to use these new expensive monoclonal antibodies without knowing their pharmacokinetics and pharmacodynamics, or their biological concentration and effect on the target cells in the target organs. The criteria for use (and/or reimbursement) will be based only on clinical elements (severity, use of resources, pharmacologic treatment, circulating eosinophils, response to other pharmacologic treatments). In other words, as often happens in medicine, we will have to learn to do without knowing enough.

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