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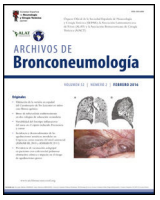

Editorial

Emerging Therapies in Severe Eosinophilic Asthma

Nuevas terapias para el asma eosinofílica grave

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Asthma is a complex, heterogeneous disease characterized by chronic airway inflammation, episodic respiratory symptoms, and associated with variable expiratory airflow limitation. The prevalence of asthma is increasing, and is estimated to affect 358 million people worldwide in the recent Global Burden of Disease report.[1] 5%–10% are said to have severe asthma, defined as asthma that requires treatment with high dose inhaled corticosteroids and a second controller for the previous year, and/or systemic corticosteroids for ≥50% of the previous year to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[2] This subset of patients has poorer lung function, quality of life, and recurrent exacerbations; is at increased risk of significant morbidity and mortality, and exerts a substantial burden on healthcare resources.

Understanding the heterogeneity of the airway inflammation in severe asthma is of particular importance to predict future risk of exacerbations and response to therapy. The presence of eosinophilic airway inflammation is associated with poorer asthma control and increased risk of exacerbations,[3] and is a good predictor of a favorable response to corticosteroids.[4] Beyond corticosteroids, monoclonal antibodies targeting Type 2 (T2) immunity and consequent eosinophilic inflammation in severe asthma has been developed.

The first monoclonal antibody for asthma was omalizumab, a humanized monoclonal antibody against IgE used since 2003 in adults, adolescents and children over 6 years of age with moderate to severe persistent allergic asthma inadequately controlled with standard therapy. It improved asthma symptoms and health-related quality of life. It also reduced exacerbations and daily inhaled corticosteroid dose.[5] Response to omalizumab was better in asthmatics with increased biomarkers of T2 immunity and eosinophilic inflammation including serum periostin, blood eosinophil count and fraction of exhaled nitric oxide.[6]

Anti-interleukin-5 (IL-5) monoclonal antibodies are the second class of biological therapy for severe eosinophilic asthma. IL-5 cytokine plays an important role in the maturation and activation of eosinophils. Mepolizumab is a humanized monoclonal antibody that binds to IL-5, preventing it from binding to IL-5 receptors. The first large phase IIb/III trial (DREAM study) showed that mepolizumab at a range of doses significantly reduced severe exacerbation rate in subjects with recurrent exacerbations and evidence of eosinophilic inflammation.[7] The results were also replicated in another phase III trial using a lower intravenous Mepolizumab dose of 75 mg and a subcutaneous dose of 100 mg.[8] Mepolizumab has also been shown to have steroid-sparing effects by significantly reducing daily systemic corticosteroid use compared to placebo, while maintaining its exacerbation reduction effect.[9] The efficacy of mepolizumab appeared to be more pronounced in subjects with higher baseline blood eosinophil levels and more frequent exacerbations, with no benefit in exacerbation reduction in those with a blood eosinophil count <150 cells/μL. On the strength of these positive trial results, it has since been licensed for use in severe eosinophilic asthma. Reslizumab, another monoclonal antibody targeting IL-5, was also recently licensed for use in severe eosinophilic (≥400 blood eosinophils/μL) asthma following phase III trials demonstrating significant improvement in forced expiratory volume in 1 second (FEV1), asthma control scores, asthma-related quality of life and frequency of asthma exacerbations.[10,11] However, when used across a broad range of blood eosinophil counts, reslizumab had no effect on lung function and asthma control.[12] Benralizumab differs from mepolizumab and reslizumab as it acts on the alpha chain of the IL-5 receptor causing eosinophil apoptosis. Two recent phase III trials in subjects with inadequately controlled asthma, frequent exacerbations and elevated blood eosinophil count showed significant reduction of annual asthma exacerbation rate compared to placebo.[13,14] It also significantly improved FEV1, Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores in those receiving the treatment every 8 weeks.

Inhibiting other T2-cytokines such as IL-13 neutralization (Lebrikizumab and Tralokinumab) or the alpha chain of the IL-4 receptor which attenuates both IL-4 and IL-13 signaling (Dupilumab) are attractive targets. None of these strategies have demonstrated an effect on reducing eosinophilic inflammation, but benefits for these approaches are greater in those with upregulated T2-immunity and eosinophilic inflammation. Recent

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phase III studies for Lebrikizumab failed to demonstrate consistent benefit for reduction in asthma exacerbations[15] and phase III studies for Tralokinumab are ongoing (NCT02194699 and NCT02161757). Findings from a phase IIb study of Dupilumab were more encouraging, showing reductions in exacerbation frequency and improvements in symptoms in all comers with greatest response in those with eosinophilic inflammation.[16]

In addition to biological therapy, small molecule inhibitors have shown promising results in severe asthma. Prostaglandin D_2 (PGD_2) is a prostanoid mainly produced by mast cells, which binds and activates G protein-coupled receptors: D prostanoid 1, thromboxane A_2 receptor and D prostanoid 2 (DP_2). DP_2 is also known as chemoattractant receptor-homologous molecule on T helper Type 2 cells ($CRTh_2$), selectively expressed on Th2 cells, eosinophils, basophils, Type 2 innate lymphoid cells (ILC2s), epithelial cells and airway smooth muscle. In a recent single-center randomized placebo-controlled study of patients with moderate-to-severe asthma and sputum eosinophilia ($\geq$2%), fevipiprant (a potent and highly selective DP_2 antagonist) showed significant reduction in eosinophilic inflammation in both sputum and bronchial submucosa compared with placebo.[17] There was significant effect on AQLQ score, post bronchodilator FEV1 and functional residual capacity in all patients, and the ACQ-7 score in a pre-defined subgroup of patients who had uncontrolled asthma. The effect on asthma exacerbations is now being evaluated in phase III clinical trials.

Thus, the armamentarium for the treatment of severe eosinophilic asthma is expanding. Future research is needed to give further insight into which patients are most likely to have the greatest response to which treatment, and to better define both response and failure to respond to these new therapies. This might require head-to-head pragmatic real life trials of licensed therapies. Notwithstanding this limitation, the prospect of new and effective treatments is now within our grasp.

Conflict of Interest

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