EDITORIAL

Immunological intervention with anti-immunoglobulin-E antibody to prevent asthma exacerbations

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The challenge to develop new therapeutic strategies to treat asthma is difficult, since drugs such as inhaled steroids and long-acting β_2 -agonists are very successful and advocated by most national and international guidelines to be the long-term therapies of choice in most of the chronic situations [1]. The better understanding of the mechanisms of asthma as an inflammatory disease has led to the development of several new immunological approaches, which have been mostly disappointing after introduction in the clinic. The major reasons for this are linked to the complexity and the redundancy of the inflammatory processes in asthma, which are able to counterpoise the inhibition of a single cellular or molecular pathway [2].

Therefore, the global situation for asthma should be increasingly satisfactory based on the currently available treatments, but there are several remaining problems. First, the prevalence and the costs of the disease are still increasing. Secondly, most of the patients deny their asthma symptoms and severity and are mostly under-treated and uncontrolled [3]. If mild and moderate asthma can be controlled by the current strategies, poor compliance of the patients still contributes to the excess morbidity and costs. And finally, there is a group of patients that remains uncontrolled despite good compliance, because the severity of their disease often requires an addition of oral doses of corticosteroids to avoid exacerbations. Those patients have a poor quality of life and require several hospitalizations each year [4].

In this issue, SOLER *et al.* [5] report a large multicentre study showing the safety and efficacy of subcutaneous treatment with anti-immunoglobulin-E (IgE) (monoclonal antibody rhuMAB-E25/omalizumab) of patients with moderate asthma. They demonstrate improved asthma control by anti-IgE therapy, as shown by a significant decrease in the number of asthma exacerbations. These data confirm and extend the previous findings by MILGROM *et al.* [6] in relation to better asthma control, an inhaled steroid-sparing effect and the efficacy of this immunological strategy in elderly patients.

The role of IgE in the pathogenesis of allergic asthma is derived from different lines of evidence. Several epidemiological studies report close associations

between IgE levels and the presence of asthma [7]. Anti-IgE auto-antibodies have been described and block the binding of IgE to their high-affinity receptor [8]. Animal studies have confirmed the potential prevention of the occurrence of antigen-induced bronchoconstriction and bronchial eosinophil infiltration in sensitized mice treated by anti-IgE monoclonal antibody [9]. The anti-IgE potentially affects allergic diseases by binding the circulating IgE already present, to form inert complexes avoiding the cross linking on mast cells and other inflammatory cells and/or preventing the synthesis of new IgE, thereby avoiding the progression of airway inflammation.

The potential role of IgE in asthma in humans was demonstrated in humans by FAHY *et al.* [10] who showed the attenuation of both early- and late-phase responses to airway allergen challenge in allergic asthmatic patients by pretreatment with an anti-IgE monoclonal antibody. The reduction of sputum eosinophilia was additional evidence of a real anti-inflammatory effect. Anti-IgE antibody was also effective in the treatment of seasonal allergic rhinitis [11].

In this issue of the *European Respiratory Journal*, SOLER *et al.* [5] report their study in which 274 patients with moderate persistent allergic asthma (treated with 500–1,200 μ g daily beclomethasone) received subcutaneous IgE antibody or placebo therapy for 7 months. The number of asthma exacerbations requiring a short course of treatment by oral corticosteroids was reduced in the rhuMAB-E25 antibody group. Eighty-three per cent of patients on placebo had at least one exacerbation as compared to 35% in the anti-IgE treated group. This difference remained the same despite the inhaled steroid (ICS) reduction strategy used. This ICS reduction was moderate but significantly greater in the anti-IgE group as compared to the placebo group. Despite this step down in ICS dose, there was a significant reduction of symptoms, rescue medication use and a small increase in airway function (morning peak expiratory flow (PEF) and forced expiratory volume in one second (FEV₁)) in the anti-IgE group. The treatment with IgE antibody injected subcutaneously was well tolerated by all the patients, confirming previous safety data obtained using other routes of administration. Interestingly, there were no immunologically driven side-effects, such as the formation of anti-omalizumab antibodies or the occurrence of autoimmune diseases affecting the kidney or the skin.

How can these results be interpreted? The heterogeneous clinical expression of asthma in humans suggests a process more complex than the one that is recreated using animal models. The exact role of IgE in the pathogenesis of asthma is still uncertain. Thus, the mechanisms of action of IgE antibody require further investigation. Allergic asthma affects the vast majority of the asthmatic patients with relatively mild forms of the disease, but the exact relationship between allergic sensitization and the occurrence of asthma symptoms is not always easy to demonstrate in the real world. Interestingly, patients with no demonstrable allergy seem to suffer from the same kind of inflammation in the airways as those with allergy, affecting their nose as well as their lower airways [12]. They tend to have a more severe disease and, therefore, they may be a further target for the anti-IgE strategy considering that some of them have elevated IgE levels. A systemic treatment may improve all kinds of symptoms including upper airway diseases, increasing adherence to treatment.

The study of SOLÈR *et al.* [5] is of great clinical importance as it shows a decrease in number and severity of asthma exacerbation, which are of real concern in this chronic disease. Furthermore, the tolerance of anti-IgE and the use of a subcutaneous treatment regimen may increase compliance in moderate asthma patients. The indirect evidence of an anti-inflammatory effect, as reflected by the decrease of the inhaled corticosteroid doses, might represent a good therapeutic alternative to be tested in the severe form of asthma where new therapies are required.

Clearly more clinical and mechanistic data is needed to establish a place for this encouraging new treatment approach in the management of chronic asthma.

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