EDITORIAL

ASTHMA: WILL THE THERAPEUTIC STRATEGY CHANGE?

New possibilities for the treatment of asthmatic patients are currently coming to light: for many years the care of asthmatic patients has been based on resolving dyspnea crises and the basic treatment – with few variations over the years – has consisted of preventing crises through chromones or ketotifen, reducing inflammation (first through oral corticosteroids and nowadays preferentially through inhaled corticosteroids), and maintaining bronchial permeability (first through extended-release xanthines and currently through long-acting beta-agonists). These therapeutic strategies were designed to combat the pathogenic basis of the disease – inflammation. On the other hand, etiologic treatment of allergic asthma is based on immunotherapy, which is designed to reduce sensitivity to the allergens provoking the process. Adopting environmental control measures to reduce allergens in the home also contributes to this aim.

The efficacy of current treatments is undoubted, as they have improved asthmatic patients' long-term prognosis and quality of life. However, prolonged corticosteroid treatment is not without problems, including lack of compliance with the prescribed regimens. Therefore, instead of combatting inflammation, the ideal solution would be to prevent the process from becoming chronic, with the consequent airway remodeling.

Ever-increasing knowledge of the pathogenesis of asthmatic reactions, that is, the cytochemical elements that participate in inflammation, is giving rise to a new strategy for tackling the disease that aims to prevent progress of the various phases of the chain of elements that play a role in the allergic reaction.

The first drugs to be designed on the basis of this knowledge were anti-leukotrienes, the aim being to block the action of the various leukotrienes, whether at the start of the metabolic chain of arachidonic acid, through a 4-lipoxigenase (5-LO) inhibitor such as zileuton, or in a subsequent phase (against cysteinyl-leukotrienes) with drugs such as montelukast or zafirlukast.

The cells most characteristic of allergic inflammation are eosinophils and consequently these are a clear target of future therapies against asthma and other allergic diseases. Interleukin (IL)-5, mainly derived from Th2 lymphocytes, is the key interleukin for eosinophil maturation in bone marrow, eosinophil activation (hypodense eosinophils) and transport (chemotaxis) to the site of the inflammatory reaction. Blocking IL-5 production or activity would prevent this reaction. Anti-IL-5 antibodies (mAB-IL-5) are already availa-

ble and are being tested in clinical trials, although to date the results have been unsatisfactory, despite arrest of bone marrow eosinophil maturation and reduction of eosinophil progenitors in the bronchial mucosa, since antibody administration does not seem to decisively influence asthma control[1-3].

Other ways of controlling eosinophil maturation and increase in the bronchial mucosa (anti-CCR-3 eosinophil receptor, nonactin, OM-01 transcription gene inhibitor) are undergoing investigation. Among these, the most encouraging could be inhaled galectin-3 (Gal-3) if the results of a study by Spanish researchers are confirmed[4]. Gal-3 is a protein that attaches to IgE and regulates IL-5 gene expression in different cell types through the CD32 receptor (FcγRII). This study was performed in Brown-Norwey rats, a strain that has immunological and clinical characteristics equivalent to those of asthmatics: eosinophilic inflammation, elevated serum IgE, bronchial hyperreactivity, and Th2 cytokines. Endotracheal instillation of plasmid DNA encoding gal-3 in rats previously sensitized with ovalbumin improved cellular inflammatory infiltration, reduced eosinophil and T cell count in bronchoalveolar lavage fluid, and strongly inhibited pulmonary IL-5 mRNA. The effect was maintained for at least thirty days after instillation. Because Gal-3 is easy to administer, inexpensive and seems to produce no adverse effects, the authors are optimistic about its possible application in humans, although this remains a long way off.

In addition to IL-5, other cytokines play a role in asthmatic reactions and consequently the possibility of inhibiting these reactions through specific antibodies is being investigated[5]. Inhibition of the most notable of these substances, IL-4, which activates IgE-producing B lymphocytes, is the object of special study. As with other anti-cytokines undergoing investigation (IL-13, IL-9, IL-1, IL-10, IL-12, IFN-γ, TNF-α) the desired results have still not been obtained[6,7].

The onset of allergic disease in predisposed individuals is due to the production allergen-specific IgE antibodies. The atopic predisposition is characterized by the predominance of the activation of lymphocytes towards the Th2 class, from which the various above-mentioned lymphokines are derived, some of which (IL-4, IL-13) activate IgE-producing B lymphocytes[8]. IgE binds to mastocytes through the high-affinity receptor (FcϵRI) and renewed contact with the allergen produces first the release of mediators of the asthmatic reaction present in the cell granules (histamine, tryptase) and subsequently leukotrienes. All these elements are to a certain extent involved in provoking airway obstruction.

Conventional subcutaneous immunotherapy modulates the Th1/Th2 lymphocyte balance, thus diminishing IgE production, reducing sensitization to the allergens used and preventing new sensitizations[9,10]. There are several possible strategies for improving efficacy and avoiding adverse reactions. The application of recombinant DNA technology to the characterization of allergens has allowed cloning of proteins from several aller-

gens (epitopes). This possible variant of immunotherapy has been undergoing investigation for several years and recombinant allergens will probably soon be available as an alternative to the currently-available allergenic extracts, thus providing the advantage of being able to use specific antigens. This would improve efficacy and reduce the risk of adverse reactions[11,12].

More recently, another possible immunotherapeutic modality has been studied. This modality is based on the immunostimulatory action of an oligodeoxynucleotide (ISS-ODN) which, when conjugated with an allergen (AIC), shows marked immunogenic activity and low allergenicity, as demonstrated in previously sensitized rats that showed greater cytokine production from Th1- than from Th2-lymphocytes. This effect was maintained for at least one year[13-15].

A contraindication to immunotherapy is severe asthma. The severity is often due to polysensitization with an excessive increase in serum IgE levels. As an alternative, good results have been obtained with an anti-IgE recombinant humanized monoclonal antibody, omalizumab, which reduces serum IgE levels, the incidence and intensity of dyspnea, and the need for medication. This drug is also effective in allergic rhinitis and has been shown to prevent the development of asthma[16,17]. The disadvantages of this treatment are the routes of administration, intravenous or subcutaneous, and the need to repeat doses indefinitely at an average of every two weeks. Very high IgE levels are a contraindication because of the risk of producing immunocomplexes.

Although not exhaustive, this review of the current state of research leads to the conclusion that we are facing a new strategy, in the medium term, for the treatment of asthma and other allergic diseases.

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REFERENCES

1. Menzies-Gow A, Flood-Page P, Sehmi R, Burman J, Hamid Q, Robinson DS, et al. Anti-IL-5 (mepolizumab) therapy induce bone marrow eosinophil maturational arrest and decrease eosinophil progenitors in the bronchial mucosa of atopic asthmatics. J Allergy Clin Immunol 2003;111:714-9.
2. Leckie PJ, Brincke A, Khan J. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness and the late asthmatic response. Lancet 2000;356:2.144-4.
3. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-Interleukin-5 partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 2003;167:199-204.
4. Del Pozo V, Rojo M, Rubio ML, Cortegano I, Cardaba B, Gallardo S et al. Gene therapy with galerctin-3 inhibits bronchial obstruction and infammation in antigen-challenged rats through interleukin-5 gen down-regulation. Am J Respir Crit Care Med 2002;166:732-7.

5. Debets R, Savelkoul HFJ. Cytokine antagonists and their potential therapeutic use. Immun Today 1994; 15:455-8.
6. Barnes PJ. Cytokine modulators as novel therapies for airway disease. Eur Resp J 2001;18 (Suppl 34):67s-77s.
7. Barnes JP. Cytokine-directed therapies in asthma. Allerg Intern 2003;52:53.
8. Romagnani S. The role of lymphocytes in allergic diseases. J Allergy Clin Immunol 2000;105:399-408.
9. Kowalski ML, Jutel M. Mechanisms of specific immunotherapy of allergic diseases. Allergy 1998;53: 485-92.
10. Akdis CA, Blazer K. Mechanisms of allergen-specific immunotherapy. Allergy 2000;55:522-30.
11. Mohapatra SS, Nicodemus CF, Schou C, Valenta R. Recombitant allergens and epitopes. ACI News 1994;6:45-8.
12. Chapman MD, Smith AM, Vailes LD, Arruda LK, Dhanaraj V, Pomés A. Recombinant allergens for diagnosis and therapy of allergic diseases. J Allergy Clin Immunol 2000;106:409-18.
13. Tighe H, Takabayashi K, Schwartz D. Conjugation of protein to immunostimulatory DNA results in a rapid, long-lasting and potent induction of cell-mediated and humoral immunity. Eur J Immunol 2000;30:1939-47.
14. Horner AA, Tacabayashi K, Zubeldia JM, Raz E. Immunostimulatory DNA-based therapeutics for experimental and clinical allergy. Allergy 2000;57 (Suppl 72):24-9.
15. Horner AA, Takabayashi K, Beck L, Sharma B, Zubeldia JM, Baird S et al. Optimized conjugation ratios lead to allergen immunostimulatory oligodeoxynucleotide conjugates with retained immunogenicity and minimal anaphylactogenicity. J Allergy Clin Immunol 2002;110:413-20.
16. Hamelmann E, Rolinck-Werninghaus C, Wahn U. From IgE to anti-IgE: Where do we stand? Allergy 2002;57:983-94.
17. Busse W, Corren J, Lanier BQ, McAlary, Fowler-Taylor A, Cioppa GD. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-90.