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EDITORIAL

Omalizumab: Just what we needed

Although asthma has been known for a long time, there are still many gaps in our knowledge of its etiology and physiopathology or, more precisely, of the different phenotypes that conform what we know as asthma (for/of a better term).

Since the 1930s, when theophylline (a stimulator of catecholamine release) was first synthesized, the history of asthma has been linked to successive physiopathological/pathogenic findings. In effect, between 1950 and 1980, the management of asthma was centered on bronchoconstriction, and in 1960 beta-2-adrenergic receptor agonists were developed for the induction of bronchial muscle relaxation. In the 1970s and 1980s, with the introduction of the inhalatory corticosteroids, which allowed for a lesser use of systemic corticosteroids, inflammation became the focus of attention, followed shortly afterwards by airway remodeling.

In the late 1990s, drugs were developed that selectively inhibit binding of the cysteinyl leukotrienes to their receptors, thereby reducing the actions of these mediators (bronchoconstriction, increased mucus production and eosinophil chemotaxis). Since these drugs can be administered via the oral route, they allow us to adopt a joint approach to rhinitis and asthma (common airway concept), and can reach the small airways (which are not accessible to the conventional inhalatory drugs) through the bloodstream. Some drug substances have been abandoned along the way or are now little used, due to their narrow therapeutic margin (theophyllines) or scant activity-effectiveness (chromones, anticholinergic agents).

This scenario of new drug developments every 10–20 years has also been characterized by modifications of the drug formulations. In this sense, long-acting beta-2-adrenergic receptor agonists have been developed, as well as the combination of the latter with inhalatory corticosteroids in one same inhaler device, propellant modifications, or inhalatory corticosteroids of smaller particle size in order to allow the drug to reach the medium and small caliber airways. Nevertheless, it must be remembered that none of these treatments are able to cure asthma. Rather, the existing therapies offer symptoms relief and counter inflammation while they are being used, but the disease continues its natural course once treatment is discontinued – with

possible progression to “bronchial remodeling” if no treatment is provided.

Since asthma is an inflammatory condition with an underlying immunological basis, the treatments used for allergic or extrinsic asthma must be targeted to the cause in order to be truly effective and to modify the natural course of the disease. Etiological treatment includes two key elements:

- Allergen avoidance, which in the real life scenario has not been shown to be effective¹ in improving the parameters of asthma, although some studies have reported partially beneficial results following intensive measurements over a period of one year.²
- Immunotherapy in its different variants, which to date has been the only treatment capable of slowing the progression of asthmatic inflammation, preventing the development of new sensitizations, and avoiding the progression of rhinitis to asthma.³ However, the success of immunotherapy depends on correct indication of the treatment in patients sensitized to the predominant components of the vaccine, and this requires a precise diagnosis based on the study with recombinant formulations.

Despite the above, a subgroup of asthmatic patients continue to suffer chronic symptoms and exacerbations despite the available treatment modalities, including high-dose inhalatory corticosteroids, long-acting beta-2-adrenergic agonists, and leukotriene antagonists. Such poorly controlled asthma constitutes a public health problem, affecting the quality of life of the patients and their families, and causing a loss of school and working hours. It moreover implies visits to the emergency service and hospital admissions. This all implies high direct and indirect costs.⁶ Indeed, severe asthma represents 5% of the total cases of asthma but consumes over 50% of the healthcare resources associated with the disease.

In these patients, and because of the lack of new treatment options, physicians tend to apply health education measures (checking the technique and adherence to therapy, discarding comorbidities, etc.), with variable results. Given this lack of new therapies, the latest incorporation to the therapeutic armamentarium for uncontrolled severe

asthma appears to be just what we needed: the humanized monoclonal antibody omalizumab. This drug would constitute the third major contribution to etiological treatment of the disease by specifically blocking IgE – a key element in allergic diseases. The first pivotal studies with omalizumab were carried out in the opening years of this century, and the drug was first marketed in the United States in 2003, and in Europe in 2005. The use of omalizumab in application to uncontrolled severe asthma in patients from 6 years of age has been warranted by different guides, such as the ICON, or the NICE guide.

In the present issue of *Allergologia et Immunopathologia*, Vieira et al.,⁴ present the results of a descriptive study in the real life (clinical practice) setting of a Portuguese hospital. The study includes 15 adults (13 females) with uncontrolled severe asthma despite combination therapy in the form of >1000 µg/day of budesonide (or equivalent) plus long-acting beta-2-adrenergic agonists, who received omalizumab during 1–3 years. The authors describe the short-term impact (during the first 4 months of treatment) and the results 1–2 years after omalizumab therapy referred to quality of life, asthma control and parameters such as the need for medication, lung function, the number of asthma attacks, or unscheduled visits.

One of the main objectives of the study was application of the Asthma Life Questionnaire (ALQ) to assess the effect of omalizumab upon 6 quality of life domains (activities and sleep, symptoms, triggering factors, healthcare system use, medication and psychological condition). Quality of life generally improved, though some of its domains considered individually showed no significant improvements. The authors also observed improvements in a secondary study objective: the assessment of asthma control based on the Asthma Control Test (ACT).

The results referred to the secondary objectives were heterogeneous. The number of asthma attacks and unscheduled visits due to asthma decreased considerably, though this may have been because the patients reported for treatment with omalizumab on a scheduled basis and did not require unscheduled visits. This aspect could improve adherence to therapy and also influence the decrease in daily inhalatory corticosteroid doses and the need for oral corticosteroids observed in the study. Lung function as assessed by FEV1 improved significantly, but not so the FeNO test.

It should be remembered that omalizumab is indicated in asthmatics who are not controlled (frequent symptoms, the need for oral corticosteroid cycles, frequent asthma attacks, visits to the emergency service or admissions) despite the administration of step 3 or higher treatment, with sensitization to perennial allergen/s, elevated IgE, and FEV1 <80%. Although the patients included in this study (women with a mean duration of asthma of 36 years) do not present the same profile as asthmatic children treated with omalizumab in our pediatric allergy and/or pneumology units, the findings of the authors imply a radical change in clinical practice, since this drug has made it possible for many patients to achieve control the disease.

It would be advisable to have results referred to asthmatic children treated with omalizumab, with less evolved asthmatic disease and a more ductile immune system, in which the results consequently could be expected to be even

more favorable than in adults. Another issue that has not been resolved to date is the optimum duration of such treatment. While we remain in wait of results from long-term studies conducted in the real life setting, Lowe and Renard⁵ have used mathematical models to postulate that both the serum levels of IgE and production of the immunoglobulin decrease exponentially over 5 years of therapy, followed by stabilization thereafter, and that this effect persists for at least 15 years.

On the other hand, new perspectives are opened for the use of omalizumab in diseases other than allergic asthma, some of which have already been included in the Summary of Product Characteristics, such as chronic urticaria,⁶ while others probably will be included in the future, such as atopic dermatitis,⁷ rhinitis,⁸ food allergy,⁹ and even intrinsic asthma.¹⁰ Lastly, the drug might find use as a coadjuvant to subcutaneous or oral immunotherapy with foods.¹¹

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