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The use of antileukotrienes in Paediatrics

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Abstract. – **Allergic diseases include a variety of different illnesses (rhinitis, conjunctivitis, asthma, urticaria, dermatitis) whose physiological and pathological basis is the release of chemical mediators such as histamine, PAF (platelet activating factor), metabolites of arachidonic acid and chemotactic factors from mastocytes, basophils and eosinophils. The numerous drugs used for allergy treatment now include the new pharmacological category of cysteinyl leukotriene antagonists. The cysteinyl leukotrienes (LTC4, LTD4 and LTE4) are chemical mediators of the inflammation involved in the pathogenesis of asthma, the biological effects of which are bronchial constriction and an increase in both mucus secretion and vascular permeability. Recent studies carried out above all on adult patients suggest that antileukotrienes can play an important part not only in the acute phase but also in controlling the chronic development of bronchial asthma. Antileukotrienes have also been successfully used by some authors to control atopic dermatitis and urticaria. Though further controlled testing will be required, these applications broaden the possible range of treatments for allergic disease in all its many aspects.**

Key Words:

Bronchial asthma, Atopic dermatitis, Antileukotrienes.

Introduction

Coined by Von Parquet in 1906, the term "allergy" comes from the Greek aleos (change of original state) and indicates the possibility that an encounter between an organism and a foreign substance (allergen) will result in an impairment of specific response to display intensification (hypersensitivity) or diminution (immunity) on subsequent contact.

"Atopy", meaning "strange" illness and again derived from Greek, is used to denote allergic diseases that appear to be of hereditary or family origin and are accompanied by a tendency to produce high quantities of IgE, e.g. rhinitis, asthma, and atopic dermatitis, as opposed to "non-atopic" diseases of delayed hypersensitivity such as contact dermatitis.

Allergic diseases include a variety of different illnesses (rhinitis, conjunctivitis, asthma, urticaria, dermatitis) whose physiological and pathological basis is the release of chemical mediators such as histamine, PAF (platelet activating factor), metabolites of arachidonic acid and chemotactic factors from mastocytes, basophils and eosinophils.

Biological, immunological and pharmacological research into the chemical mediators of inflammatory and allergic reactions was characterized in the twentieth century by exceptional experimental results leading to significant progress in the treatment of allergic diseases. Drugs like antihistamines have made it possible to obtain greater control over symptoms and the clinical situation in the acute phase as well as an improved quality of life for allergic patients.

Antileukotrienes

Attention has also focused in recent years on the new pharmacological category of cysteinyl leukotriene antagonists denoted by the suffix "lukast" (Montelukast, Pranlukast and Zafirlukast)[1]. The cysteinyl leukotrienes (CysLTs) LTC4, LTD4 and LTE4 are chemical mediators of inflammation involved in the pathogenesis of bronchial asthma[2]. Their history dates back all the way to the 1940s, when Kellaway, Feldberg and Thehewie described the biological properties of the "slow reacting substance of anaphylaxis" (SRS-A), a molecule released by the lung of a guinea pig isolated and permeated with cobra poison. SRS-A proved capable of causing a slow and prolonged contraction of the smooth musculature of the guinea pig's ileum with pharmacological characteristics different from those of histamine[3-5]. Subsequent investigation

demonstrated that this lipid substance was a mixture of at least three molecules derived from arachidonic acid, namely the leukotrienes C4 (LTC 4), D4 (LTD4) and E4 (LTE4). Arachidonic acid is a normal constituent of the phospholipids of the cellular membrane. In activated cells, various enzymes belonging to the family of phospholipase A2 are capable of hydrolizing arachidonic acid from phospholipids and making it available for further conversion into biologically active metabolites (eicosanoids). After migrating onto the nuclear membrane, 5-lipoxygenase acts together with the 5-lipoxygenase activating protein (FLAP) to produce LTA4, an unstable intermediary that is quickly converted into LTC4 by LTC4 synthetase and into LTB4 by LTA4 hydrolase. LTC4 synthetase introduces a residue of glutathione onto the lipid structure of the LTA4. The gradual remodelling of this peptide component by a Y-glutamil transpeptidase and a dipeptidase leads to the formation of LTD4 and LTE4 respectively.

Most of the biological effects of CysLTS (bronchial constriction and an increase in both mucus secretion and vascular permeability) are mediated by the activation of two specific receptors, namely CysLT1 and CysLT2. Human Cys-LT1 has recently been cloned and has been detected on bronchial smooth muscle cells, pulmonary macrophages, eosinophils and monocytes[6]. The expression of Cys-LT1 on various inflammatory and immunocompetent cells suggests that CysLTs may play a part in the alteration of immune responses, modulation of chronic inflammation and remodelling of airways observed in bronchial asthma. There is a great deal of clinical evidence that these molecules induce the formation and maintenance of the eosinophilic infiltrate by fostering the recruitment and inhibiting the apoptosis of these cells[7]. CysLTs also foster the proliferation of smooth muscle cells and the epithelial cells of the respiratory system. Preliminary data suggest hat these substances perform “priming” functions on human pulmonary macrophages by triggering the secretion of pro-inflammatory cytokines[6]. The second type of receptor, Cys-LT2, is predominantly expressed on the vascular smooth musculature, and it is therefore possible that the effects of CysLTs on endothelial cells are also mediated by this receptor. While further studies will be needed to test this hypothesis, if the results are confirmed, it is probably that receptor antagonists active both on Cys-LT1 and on Cys-LT2 will display a more powerful anti-inflammatory effect than the antagonists currently available.

As a whole, these results suggest that CysLTs can play an important part not only in the acute phase but also in controlling the chronic development of bronchial asthma, thus expanding the pharmacological profile and range of treatments. This also opens up the possibility of their long-term use in treating asthma and other allergic diseases (e.g. atopic dermatitis).

Clinical applications of antileukotrienes

Greater knowledge of the biosynthesis of leukotrienes and recognition of their role in the pathogenesis of asthma have led to the formulation of a series of clinical research protocols regarding the treatment of asthma patients. Although most studies involving antileukotrienes have so far focused primarily on adults and adolescents, with few studies confined exclusively to subjects of paediatric age, the therapeutic results appear to be particularly encouraging in cases of infantile asthma[8].

These research protocols provide for the use of antileukotrienes with different categories of patient. The first clinical studies with anti-LT assessed their effect with respect to a placebo. Adults with slight to moderate asthma treated with different doses (10, 20 and 40 mg a day) of Zafirlukast for 6 weeks displayed clinical improvement as regards consumption of bronchodilators and respiratory functionality in proportion to the dose taken and significantly superior to the placebo[9]. Identical results were obtained in two separate studies on adolescents and adults treated for 13 weeks with doses of 20 mg twice a day[10,11].

The greater effectiveness of Montelukast (evening dose of 10 mg) as regards pulmonary functionality and circulating eosinophils with respect to the placebo was demonstrated by a twelve-week multi-centre study on asthmatic adults[12,13].

The first clinical study with anti-LT on paediatric-age subjects also confirmed the superiority of Montelukast with respect to the placebo[8]. The administration of 5 mg

doses of Montelukast every evening for eight weeks led to significant differences in terms of average increase in FEV1 (8.2% vs 3.5%), reduced consumption of bronchodilators, fewer asthmatic exacerbations, improved quality of life, and reduction of peripheral eosinophils. On the other hand, no differences were registered as regards such clinical parameters as diurnal/nocturnal symptoms and the need for systemic steroids to control attacks. As in the studies on adults, Montelukast proved effective both for patients treated with topical steroids (about 30%) and for those taking only bronchodilators as needed. The anti-inflammatory effect of the anti-LT shown in experimental studies and documented by the reduction of eosinophils in various clinical studies was recently confirmed in a study focusing on NO in asthmatic children[14]. Treatment with Montelukast for 2 weeks proved to produce a significant reduction in the concentration of NO exhaled with respect to the placebo. The effect was discernible on the second day of treatment and proved to be independent of treatment with inhaled steroids.

One important aspect of anti-LT regards their role in the treatment of medium-severe asthma together with other anti-inflammatory drugs. Though few data are available as yet, they appear to suggest a supplementary effect in combination with inhaled steroids.

The data available on the effect of anti-LT in the prevention of exertion-induced asthma indicate levels of protection varying between 40% and 80% of the patients, both adults and children, depending on the criterion selected[15]. This degree of protection is similar to that offered by oral cromolyn but less than that offered by beta-2 agonists. The administration of Montelukast to children aged from 6 to 14 about 20 hours before a exercise testing led to a significant attenuation of bronchial constriction with respect to the placebo. The administration of Zafirlukast (doses of 5, 10, 20 and 40 mg) to children of school age four hours before a exercise testing also proved to offer a higher level of protection than the placebo, although it was not possible to identify an optimal dose. The data available in the literature indicate that the antileukotrienes currently in use are reasonably safe. Most of the adverse events reported are in fact of slight importance (cephalalgia, gastrointestinal disorders, pharyngitis) and display no significant differences with respect to the placebo. It is recommended that serum transaminases be checked in patients at risk, such as those taking hepatotoxic drugs at the same time. Cases have been reported in steroid-dependent asthmatic adults of a syndrome similar to the Churg-Strauss (allergic vasculitis and granulomatosis) arising concomitantly with the decrease in the dose of systemic steroids administered[16]. At present it is not clear whether the anti-LT are somehow involved in the pathogenesis of this condition or, as is more probable, these are actually cases of the Churg-Strass syndrome masked by treatment with cortisones. Recent studies show that in subjects of paediatric age (children aged over 6), daily 5 mg doses of Montelukast provide effective supplementary asthma treatment for patients with persistent asthma of a slight to moderate level for whom insufficient control is provided both by the inhalation of corticosteroids and by the taking of beta-adrenergic agonists with a short span of action “as needed”[17]. This drug is also recommended for the prophylactic treatment of asthma when the predominant component is bronchial constriction induced by physical exertion[17]. The therapeutic results appear to be particularly encouraging. At present, however, there is no information as to how antileukotrienes are able – by themselves or together with other medicines – to influence the chronic course of asthma or to interfere with the impairment of immune response that is the underlying cause of asthma and allergic diseases in general. Neither is information available on the effect of antileukotrienes on the remodelling of airways. In any case, the experimental findings suggest that there are good grounds for the use of antileukotrienes in the long-term treatment of bronchial asthma. The high degree of tolerability and the absence of major side effects, as hitherto confirmed by medium-term clinical studies, constitute a further reason to assess the effectiveness of chronic treatment with antileukotrienes. The results of long-term clinical trials now underway will provide answers to these questions. For the time being, however, it is reasonable to expect that they will expand the pharmacological profile and the range of treatments.

New therapeutic prospects for the use of antileukotrienes

Particular interest attaches to the use of anti-LT to treat atopic dermatitis in children. Atopic dermatitis (AD) is a disorder of multifactorial origin distinguished in clinical terms by intensely itchy eczematous lesions of a chronic-recurrent nature, xerosis and cutaneous hyper-reactivity. As the appearance and location of the rash differ in relation to the patient's age, there are three classically recognized phases of development. In the first phase (babies), the rash is located mainly on the cheeks, on the forehead at the level of the retro-auricular and sub-auricular groove, on the scalp, and only secondarily on the trunk and the extensible surface of the limbs. In the second phase (infants), the lesions display greater lichenification and are located symmetrically, above all on the elbow creases, the popliteal cavities, the wrists, the ankles, the hands, and the lateral region of the neck. In the third phase (adolescents), there is a marked degree of lichenification and the areas affected can include the neck and face as well as the creases and extremities of the limbs. In each phase, the major symptom is itchiness, accompanied by agitation and sleeplessness, especially in small children. In a large proportion of cases, AD is associated with high levels of total IgE, airborne and/or alimentary allergen-specific IgE, and extracutaneous clinical manifestations of atopy, especially allergic rhinitis and bronchial asthma.

AD affects a growing proportion of the general population, currently between 10% and 15%, and very often makes its first appearance in childhood, with 50% of cases occurring in the first year of life and another 30% between the first and the fifth. As the most common form of allergy among subjects of paediatric age, it is often indicative of an atopic constitution. The clinical expression of the disorder is influenced by various factors – both non-specific (cutaneous hyper-reactivity) and specific (allergic sensitization) – but an important role is also played by reduced sebaceous secretion, hidrosis, susceptibility to staphylococcal infections, hypersensitivity to histamine and a low pruritic threshold in relation to thermal, physical and psychological (stress) stimuli. The presence of IgE-mediated allergic sensitization is demonstrated in over 50% of children with AD (80% present high values of total IgE and over 60% specific IgE with respect to trophoallergens and airborne allergens). These children often come from families with a history of other allergic diseases, thus confirming the predominant role of the genetic component in atopy. The course of the disorder is characteristically chronic and recurrent with alternating phases of improvement and worsening of symptoms. Given these elements, it is important that the allergy should be diagnosed as soon as possible and that tests should be carried out for various foods and inhalants so as to obtain prognostic information on the child's allergic future and take prompt measures of environmental and, if necessary, pharmacological protection.

At present there are no clinical studies of paediatric-age subjects demonstrating the effectiveness of antileukotrienes in the treatment of atopic dermatitis. The clinical trials on Montelukast as a therapeutic agent in adult atopic dermatitis could, however, also be extended to subjects of paediatric age. The study recently carried out by D.J. Yanase reports a modest but significant improvement in dermatitis after a four-week period of treatment[19]. Eight patients suffering for over a year with persistent atopic dermatitis diagnosed in accordance with the Hanifin criteria were divided into two randomly selected groups. The first received 10 mg of Montelukast a day for 4 weeks followed by another 4 weeks of placebo after a two-day washout. The second group instead received the placebo first and then the drug, again in double-blind conditions. The pharmacological treatment led to a significant decrease in peripheral eosinophilia. The study by Dambra et al. shows the effectiveness of Montelukast treatment in producing a clinical improvement also in patients with chronic idiopathic urticaria[19].

In conclusion, the results of numerous experiments and the experience built up through clinical use subsequent to the introduction of antileukotrienes onto the market make it possible to assign these drugs an important role in the panorama of strategies for the treatment of infantile asthma. They combine anti-inflammatory properties with safety in use and ease of administration. Given such qualities, these drugs can be expected to play an increasingly important role in the treatment not only of asthma but also of rhinitis and atopic dermatitis in children.

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