

New perspectives in the treatment of allergic rhinitis and asthma in children

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Purpose of review

Allergic rhinitis and asthma are some of the most prevalent chronic diseases in children. Meticulous evaluations of the therapeutic options and interventions are needed to control this burden. The central pathogenic mechanism is an immediate hypersensitivity reaction, followed by interventions in the allergic cascade. Once inflammation is established, potent anti-inflammatory agents or mediator antagonists could help control the phenomenon and reduce the characteristic symptoms related to severity.

Recent findings

Monoclonal antibody against IgE has demonstrated its efficacy in reducing the symptoms of asthma and rhinitis. In difficult-to-treat asthma patients it allows a reduction in the dose of inhaled steroids, the number of exacerbations, emergency visits and hospitalizations. Its broad implementation is limited by its high cost because adverse events are not a concern. Specific sublingual immunotherapy gave promising results in clinical trials, while modifying immunoglobulins and cytokine profiles, also inducing T-cell tolerance. Safety issues of subcutaneous immunotherapy have been surpassed by the sublingual route, with equivalent efficacy. The new inhaled steroid ciclesonide is effective in established inflammation, is activated only in the respiratory system, and has negligible systemic effects.

Summary

Robust evidence on the efficacy and safety of several novel therapies in rhinitis and asthma is available.

Keywords

allergic diseases, children, ciclesonide, omalizumab, specific sublingual immunotherapy

Abbreviations

HPA	hypothalamic pituitary adrenal
QoL	quality of life
SIT	specific immunotherapy
SLIT	sublingual immunotherapy

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1528-4050

Introduction

The vast majority of countries around the world consistently display an increase, although variable in magnitude, in the prevalence of allergic rhinitis and asthma [1^{••}]. Genetic, socioeconomic and environmental conditions are probably responsible for the differences among countries. The average result is that there are increasing numbers of children with allergic diseases worldwide.

Asthma is a chronic inflammatory disease that affects people of all ages, with a prevalence that ranges from 3% to over 30% in children [1^{••}]. Asthma should be considered in some way allergic in nature, as the low circulating IgE levels found in more severe asthma patients do not rule out the possibility that most of them are sensitive to aeroallergens, and biopsies from fatal asthma show an elevated presence of FcεRI-positive cells within the lamina propria [2].

New guidelines emphasize as their main objective gaining control of asthma. This approach means controlling symptoms, limitation of activities, sleep disturbance, lung function and the use of rescue medication [3^{••}]. A 'total' control of the disease can be achieved in more than a third of patients, and good control can be achieved in a large proportion of them, when an appropriate treatment is given [4]. The Global Asthma Insights and Reality surveys have, however, shown that in Europe, Asia and the United States, patients with more severe symptoms had a lower use of preventive medication and a higher intake of quick relief medication, thus suggesting scarce asthma control despite the availability of effective therapies [5]. Ideally, the development of local guidelines considering regional factors that influence the behaviour of physicians and patients is desirable. Also, the availability of simple tools to improve the diagnosis and follow-up of asthma and its co-morbidities, such as allergic rhinitis [6], is needed.

Curr Opin Allergy Clin Immunol 7:201–206. © 2007 Lippincott Williams & Wilkins.

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Current Opinion in Allergy and Clinical Immunology 2007, 7:201–206

Allergic rhinitis is an inflammatory disease of the nasal mucosa, affecting between less than 1% to almost 40% of children, according to International Study of Asthma and Allergies in Childhood (ISAAC) studies [7] considered in the Allergy Rhinitis and its Impact on Asthma (ARIA) document [8]. A very recent report by Galassi *et al.* [9] showed a progressive increase of allergic rhinitis, currently affecting over 30% of Italians up to 14 years of age; even more interestingly, in the past 5 years an increase of 5%. If this is the trend, in 2020, we may expect to have one out of two people of that age having rhinitis. With this prevalence, allergic rhinitis is becoming the most common chronic disease in the paediatric population. On the other hand, this increase in allergy prevalence should not be restricted to the young population. Linneberg [10] reported that the allergy epidemic might be spreading to old age.

The impact of allergic rhinitis on the quality of life (QoL) is not negligible. In addition, allergic rhinitis predisposes to co-morbidities such as conjunctivitis, sinusitis and otitis media, and, most remarkably, allergic rhinitis is a strong independent risk factor for the development of asthma [8,11•].

In the management of allergic rhinitis, the first line medications are new generation antihistamines. Nonetheless, their effect on nasal blockage is only partial, so topical corticosteroids are preferred in the case of persistent blockage [8,12]. In this regard, new drugs with improved safety and efficacy are emerging. Among them, ciclesonide is one of the most promising [13•,14•]. Focusing on the allergic inflammation, and interfering with the triggering reaction will result in abrogating clinical expression and a reduction in complications. Omalizumab blocks serum IgE and, therefore, reduces clinical symptoms and allows a progressive downregulation of the specific receptor in basophils and mast cells [15].

The role of allergens is well accepted, but their total avoidance is impractical in the majority of sensitizations. As a result, specific immunotherapy (SIT) remains an important approach as a biological response modifier. SIT is effective in the treatment of allergic rhinitis [16], and should be considered when there is a constant need for pharmacotherapy and allergen avoidance is not possible. The safety concerns have sometimes limited the use of injection immunotherapy, but the introduction of the sublingual route of administration has almost totally overcome this problem, especially in the paediatric population [17,18•].

In the present review, established interventions will not be considered, such as the efficacy of long-acting B2 agonists in combination with inhaled steroids for asthma control [4]. Instead, the mechanisms of action as well as

the safety and efficacy of the new therapies are analysed, providing the specialist with the most up-to-date knowledge in the field.

The control of airway inflammation: inhaled corticosteroids

Inhaled corticosteroids exert a broad spectrum of anti-inflammatory actions. In particular, they inhibit the transcription factors activator protein 1 and nuclear factor κ B, in consequence decreasing the production of the inflammatory mediators IL-1 β , tumour necrosis factor α , granulocyte-macrophage colony-stimulating factor, IL-4, IL-5, IL-8 and eotaxin, possibly by inhibiting histone acetylation. They reduce the survival of eosinophils and lymphocytes, and promote the differentiation of regulatory CD25⁺CD4⁺ T cells [19•].

Only 10–20% of the inhaled corticosteroids can reach the lungs, whereas a large fraction is deposited in the mouth and pharynx. This fraction is directly absorbed or absorbed after swallowing, and can reach the systemic circulation. The fraction of inhaled corticosteroids absorbed in the blood, if not extensively metabolized at the first pass, can exert systemic metabolic/endocrine effects. For these reasons, considerable efforts have been made to improve delivery devices and the formulation of the drug to reduce systemic availability and increase lung deposition.

Budesonide is almost 90% and fluticasone almost 100% metabolized in their hepatic first pass. Knowing that, the Childhood Asthma Management Program (CAMP) study evaluated whether budesonide could have a systemic effect in asthmatic children, evaluating the growth rate concomitantly with pulmonary function and bronchial hyperresponsiveness. In that study a better control of asthma with respect to placebo and nedocromil was shown, associated with a transient and small reduction in growth [20]. Agertoft and Pedersen [21] studied the long-term effect of budesonide on adult height, and found that patients could reach a normal height, but with a transient (although significant) delay in the first years of treatment.

The ideal inhaled corticosteroid must have a great pulmonary tissue deposition, a high receptor affinity, and the lowest systemic availability to avoid adverse effects.

Ciclesonide

Ciclesonide is a steroidal pro-drug that is converted into its active metabolite, desisobutyryl-ciclesonide, by the esterases of the respiratory system. The esterification is reversible, and the formulation is available as a solution in a metered dose inhaler with hydrofluoroalkane, giving particles of 1–2 μ m that easily deposit in the lungs.

These properties confer to the drug an excellent safety profile [22]. Evaluations of the effect of ciclesonide on the hypothalamic pituitary adrenal (HPA) axis have been performed with negative results, even at over 10 times the therapeutic dose [13[•]].

Ciclesonide in asthma

Inhaled corticosteroids are effective in controlling asthma, their exacerbations, hospitalizations and the need for systemic steroids. Ciclesonide is not an exception. Gelfand *et al.* [14[•]] evaluated more than 1000 asthmatic children, and found a significant improvement in pulmonary function, symptoms score and albuterol use as a rescue medication, and also no HPA axis modification. Furthermore, ciclesonide was shown to be more effective than budesonide in terms of improving forced expiratory volume in 1 s, peak expiratory flow and forced vital capacity [23]; and was equivalent to fluticasone in asthmatic children when comparing pulmonary function, rescue medication and symptom-free days [24]. In a small sample of adult asthma patients, ciclesonide and fluticasone at high doses were comparable in efficacy, but fluticasone (and not ciclesonide) significantly modified HPA axis parameters [25].

Long-term studies are needed to obtain comparable results with the rest of the inhaled corticosteroids in terms of growth and bone mineral density in children; however, a significant effect seems unlikely because there are no demonstrated systemic effects.

Ciclesonide in allergic rhinitis

When nasally applied, the safety of ciclesonide was demonstrated in the clinical setting, both in adults and adolescents. With regard to its efficacy in allergic rhinitis, it has been shown that the effects of 100–200 µg doses were significantly different from that of placebo, but smaller doses were ineffective [26,27]. Further evaluations comparing ciclesonide with the available nasal steroids will provide more information on efficacy.

Interfering with allergic mechanisms: anti-IgE antibody

Elevated total and specific IgE levels are commonly found in allergic diseases such as asthma and allergic rhinitis. The pivotal mechanism of the allergic cascade involves the allergen binding of two molecules of specific IgE attached to its receptor FcERI on mast cells and the surface of basophils. The anti-IgE (omalizumab, xolair) is a chimeric monoclonal antibody that binds the Fcε3 domain of free circulating human IgE, thus impeding the binding of IgE to the specific receptors [28]. Free serum IgE forms, with the antibody, small heterotrimers and hexamers that are easily cleared from the circulation. The final result is a decrease in the serum of free IgE, independent of their specificity, and the almost complete

absence of IgE from the surface of mast cells and basophils. In addition, a significant reduction in FcERI on circulating basophils after omalizumab has been reported [2,15].

Omalizumab in asthma treatment

Several studies have reported the reduction of inflammatory mediators such as IL-5, IL-6, IL-8, IL-10, IL-13 and soluble interstitial cell adhesion molecule, as well as eosinophil levels [2,15]. These alterations correlate with clinical observations such as a reduction in asthma exacerbations and steroid use, an improvement in asthma control and QoL.

The SOLAR study [29] evaluated more than 400 children and adult patients with asthma and allergic rhinitis, and after 7 months of treatment, those randomly assigned to the study drug improved their QoL significantly in both asthma and rhinitis symptoms, and experienced fewer exacerbations of asthma; adverse events were even fewer than in placebo controlled patients.

Patients with more severe asthma seem to have more benefits with this therapy; a significant reduction of the exacerbations and emergency visits characteristic of this group has been reported [30]. Also a significant reduction in exacerbations and steroid requirements has been shown in moderate to severe asthmatic patients aged 12–75 years [31,32].

In children aged 6–12 years with moderate to severe asthma, Milgrom *et al.* [33] found a significant reduction or withdrawal of inhaled corticosteroid use in the omalizumab group compared with placebo, associated with a significant reduction of exacerbations and hospitalizations. There was no significant change in spirometry controls, but parameters that must be considered for asthma control were all in favour of omalizumab.

Omalizumab in allergic rhinitis treatment

Anti-IgE decreased the expression of FcERI on dendritic/mast cells in nasal tissue, reducing the nasal allergic response, with significant benefits in terms of symptoms and QoL as a consequence [34[•]]. As mentioned before, the SOLAR study [29] clearly demonstrated that in patients with co-existing allergic respiratory diseases, the efficacy and safety of anti-IgE is considerable. Although some studies also involved patients aged 12–18 years of age [35,36] and showed a significant clinical benefit of omalizumab in rhinitis, there has so far been no study on allergic rhinitis specifically designed for children. Moreover, further research is needed to determine the effects of anti-IgE in allergic rhinitis in order to prevent its development and progression to asthma [37].

Modifying the natural course of allergic disease: allergen immunotherapy and sublingual immunotherapy

SIT is the only treatment capable of modifying the natural history of allergic diseases and of preventing new sensitizations. The immunological mechanisms of action involve a decrease in specific IgE, an increase in specific IgG, and the modification of the cytokine profile as well as lymphocyte modulation (anergy or suppression) [16]. Its efficacy in allergic rhinitis is without doubt. With regard to asthma treatment there were safety concerns because of the potential risk of anaphylaxis or asthma exacerbations. In a systematic review in the Cochrane database, Abramson *et al.* [38] concluded that this risk must be considered. Immunotherapy reduces asthma symptoms, the need for asthma medication, and improves bronchial hyperreactivity, similar to inhaled corticosteroid.

Taking into account the potential of SIT to modify the course of allergic disease and the efficacy and safety of anti-IgE, a combination of the two treatments was proposed and utilized in children [39]. Omalizumab is not allergen-specific but decreases circulating IgE, thus helping to prevent the potential side effects of SIT. On the other hand, SIT acts in a specific manner and modifies the biological response. The main result of this trial was that the combination therapy produced a reduction in symptoms and rescue medication usage greater than 80% [39].

With injection SIT, there is a remote but real risk of severe, even fatal, adverse events that are more difficult to treat in children. For this reason, the official guidelines state that an age of less than 5 years is a relative contraindication to injection SIT [16]. The sublingual route of administration is now considered a viable alternative to the subcutaneous route mainly because of its very satisfactory profile [17,40,41]. The safety of sublingual immunotherapy (SLIT) in children has been convincingly demonstrated in several postmarketing surveys [42,43], and also in very small children (less than 5 years of age) the rate of adverse events was negligible [44].

The mechanisms of action of SLIT are similar to those described for the injection route, and involve an immune deviation towards T-regulatory cells, secreting transforming growth factor beta and IL-10 [45,46].

Sublingual immunotherapy in asthma

The number of studies performed in paediatric asthma and rhinitis is constantly increasing.

A meta-analysis conducted in a paediatric population of mite-sensitive asthma patients [47], reported that SLIT showed low to moderate clinical efficacy, although stat-

istically significant, being recommended together with environmental protection measures. A recent meta-analysis of SLIT in asthmatic patients (including adults and children) [48^{*}] showed that there was a significant improvement in asthma symptoms, pulmonary function, bronchial hyperresponsiveness and relief medication use, in seven studies with more than 800 patients.

The efficacy of SLIT has been clearly demonstrated, and the safety profile is equally strong. No serious adverse event has been reported with aeroallergen-specific SLIT, and non-specific local and gastrointestinal complaints were the most frequent adverse events reported. Itching, throat irritation, nausea and abdominal ache were usually mild, with no need to stop treatment. The incidence of these adverse events has been reported in less than 10% of intervention groups [17,40].

Sublingual immunotherapy in allergic rhinitis

In a previous meta-analysis Wilson *et al.* [49] had insufficient data in children to support any conclusion on the efficacy of SLIT. The meta-analysis was recently repeated [18^{*}], including a larger number of patients, and the efficacy of SLIT in children with allergic rhinitis was clearly demonstrated. The implementation of SLIT in this particular group of patients could prevent the onset of asthma [50] and new sensitizations, besides the possibility of maintaining its beneficial effect for years after discontinuation, but more conclusive data on these aspects are definitely needed.

Conclusion

It should be borne in mind that there is so far no single curative therapy for allergic diseases, and physicians have a wide range of effective therapeutic options. Nonetheless, research and experimental clinical results have increased our therapeutic tools, and some definitive conclusions can be drawn.

First, it is agreed that the first option in asthma treatment is inhaled corticosteroids. In this regard, because of the virtual absence of systemic effects, ciclesonide represents an important advance.

Second, even with multiple drugs, there are patients who cannot control their asthma, having side effects because of high doses of inhaled corticosteroids, hospitalizations, frequent exacerbations and the need for systemic steroids. In these cases, omalizumab has clearly been shown to offer a substantial benefit. Further research is needed to determine whether anti-IgE could alter the natural progression of allergic diseases.

Third, SIT is the unique intervention that now has this potential, because it has been demonstrated that inhaled corticosteroids, even at the very beginning as a preventive

therapy, are unable to alter the progression of allergic diseases [51^{*}]. The safety and efficacy of SLIT makes it a first-line therapeutic option, together with pharmacotherapy and preventive measures. Finally, the ideal treatment of allergic diseases must combine immunological and pharmacological therapies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 220–221).

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