MINI-REVIEW

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Leukotriene receptor antagonists: clinical potential in allergic rhinitis*

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SUMMARY

Leukotrienes are potent pro-inflammatory mediators that have been shown to play a prominent role in the pathophysiology of asthma and associated allergic disorders including allergic rhinitis (AR) and atopic dermatitis (AD). In the treatment of these disorders, topical corticosteroids (TCS) are currently the most important anti-inflammatory agents, however, long-term application of TCS is associated with side-effects. Moreover, corticosteroids appeared not to inhibit the release of leukotrienes in humans in vivo. Therefore, leukotriene receptor antagonists (LTRAs) have been introduced into clinical practice and these specific oral drugs are currently registered as additive therapy in mild to moderate persistant atshma not controlled by inhaled corticosteroids. As for other allergic disorders, including AR, until recently only a few placebo-controlled studies with LTRAs have been performed. These (preliminary) data provide a basis for optimism, but clearly more long-term studies are needed to evaluate their clinical effectiveness, especially as add-on therapy.

Key words: leukotrienes, leukotriene receptor antagonists, allergic rhinitis, anti-inflammatory drugs

INTRODUCTION

In chronic inflammatory diseases, maintenance therapy is specially targeted at suppressing the chronic inflammation, and the subsequent prevention of exacerbations. Therefore, it is important that this long-term treatment does not induce many or serious side effects.

The role of leukotrienes and leukotriene receptor antagonists (LTRAs) in asthma

After more than twenty years of research, it has now been established that cysteinyl leukotrienes (cysLTs: LTC_4, LTD_4 and LTE_4) play a predominant role in the pathophysiology of asthma (Sampson, 1996). These broncho-active substances produce bronchospasm, being more than 1000x more potent than histamine on a molar base (Smith et al., 1985), mucosal oedema and 'plugging' of the airways, and also possess pro-inflammatory properties, chemoattracting eosinophils into target tissues (Sampson, 1996). During the last years, there is increasing evidence that these pro-inflammatory mediators are also involved in the development of structural changes within the airways, the so-called airway remodelling (Wang et al., 1993; Panettieri et al., 1998), which may finally give rise to serious clinical symptoms. All these broncho-active and pro-inflammatory effects are mediated by stimulation of specific receptors in target tissues, the so-called $CysLT_1$- and $CysLT_2$-receptors (Gorenne et al., 1996), which have recently been characterized in human airways and several inflammatory cells.

Extensive pharmacological research has resulted in the development of potent leukotriene receptor antagonists (LTRAs), which are capable of preventing the effects of cysLTs through specific blockade at the $CysLT_1$-receptor (Drazen et al., 1999). LTRAs possess a dual mechanism of action, both anti-inflammatory and bronchodilator, which makes them suitable candidates for the treatment of asthma (Drazen et al., 1999; Diamant and Sampson, 1999). Moreover, increasing evidence has been provided, from various large studies in both adults and children (from 2 years and older), that these oral anti-asthma drugs have relatively few side-effects (Drazen et al., 1999; Knorr et al., 1998), which even in much higher doses have not been significantly different from placebo. Recently, the LTRAs zafirlukast and montelukast have been registered in several European countries. Zafirlukast is a twice daily tablet in doses of 10, 20 and 40 mg (12 years and older). Montelukast is a once daily oral formula in doses of 10 mg for adults and in chewable tablets of 5 mg for children between 6-14 years and of 4 mg for children of 2-5 years old. Currently, in various European countries, these compounds have been registered as complementary therapy for mild to moderate persistent asthma, for adults and children (≥6 years), especially

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when exercise-induced complaints are involved (Bousquet, 2000). Combining LTRAs with mild to moderate doses of inhalational corticosteroids (ICS) has been shown to provide better asthma control than the use of both treatments separately, both in terms of clinical symptoms and inflammatory parameters (Laviolette et al., 1999; Simons et al., 2001).

Allergic rhinitis (AR)

Allergic rhinitis is one of the most common chronic atopic disorders. Although it can be manifest without clinical symptoms of asthma, it affects the majority of asthmatic patients. AR is characterized by nasal itching, sneezing, rhinorrhoea and nasal congestion, and is often associated with conjunctivitis and pharyngitis. Recent evidence has been provided that asthma and AR share a common pathophysiological background, with similar inflammatory mechanisms in which cysLTs have been shown to be involved (Howarth, 2000). These observations have lead to the concept of "one airway, one disease" (Meltzer, 2000). Hence, not unexpectedly, treating patients with AR resulted in fewer exacerbations of their concomitant asthma and consequently, in fewer hospital admittances (Ronberg et al., 1998).

Histopathologically, AR is characterized by a chronic inflammation of the nasal mucosa, with accumulations of mast cells, eosinophils and basophils (Howarth, 2000). Upon stimulation, these inflammatory cells are capable of producing pro-inflammatory mediators, including leukotrienes. Indeed, cysLTs have been found in enhanced concentrations in nasal lavages following provocations with allergen, cold, dry air, and aspirin (in aspirin-sensitive asthma) (Howarth, 2000). Moreover, similarly to studies in asthma, following intranasal application, cysLTs have been shown to induce long-lasting mucosal oedema by increasing the vascular permeability, and protein-containing exudations (Mygind et al., 2000 and refs therein). These effects can be measured in a laboratory setting by means of rhinomanometry, showing an enhanced upper airway resistance (Howarth, 2000). Based on these findings, several studies are now investigating the clinical potential of (add-on) therapy with LTRAs in allergic rhinitis.

Treatment of allergic rhinitis (AR)

Currently, the most important pharmacological strategies against AR consist of H_1-receptor antagonists (antihistamines) and topical cortricosteroids (TCS) (van Cauwenberge et al., 2000). However, antihistamines do not prevent nasal congestion, whereas TCS are not accepted by all patients and may cause some side effects like crusting when applied on regular basis. Hence, there is a need for alternative therapies that can prevent AR-symptoms in combination with mild side effects. In this context, several studies have addressed the clinical effectiveness of LTRAs in AR in the past few years.

H_1-receptor antagonists

Both systemic and topical H_1-receptor antagonists have clinical effectiveness in the treatment of AR, providing improvements of most of the nasal symptoms, including nasal itching, sneezing and rhinorrhoea (Howarth, 2000). Unfortunately, these drugs hardly affect nasal congestion. This is in agreement with the findings of a recent Japanese study, which showed that histamine only plays a minor role in the pathophysiology of mucosal swelling in rhinitis (Numata et al., 1999). Maintenance therapy with most of the H_1-receptor antagonists induces only few side effects: some compounds possess sedative properties, whereas a minority may produce cardiac arrhythmias.

Sodium cromoglycate (SC)

The precise mechanism of action of cromones is not yet clarified, although there is evidence that these agents may inhibit the degranulation and subsequent mediator release from mast cells in the nasal mucosa. They can be delivered by either oral or topical route and no clinically relevant side effects have been reported thus far (Cos, 1967). Although two studies in AR showed similar effectiveness of cromones and H_1-receptor antagonists (Lindsay-Miller and Chambers, 1987; Orgel et al., 1991), overall, the clinical potential of cromones has been questioned, especially when compared with TCS and H_1-receptor antagonists (Bousquet et al., 1993). Moreover, the compliance of drugs requiring four to six administrations daily is doubtful. Therefore, sodium cromoglycate cannot be considered a major therapeutic option in the treatment of AR, although it has some potential in the prophylaxis of conjunctivitis or in mild or early rhinitis.

Intranasal corticosteroids

Several placebo-controlled clinical studies both in adults and in children have shown that regular treatment with topical corticosteroids (TCS) reduces all nasal symptoms. Comparative studies demonstrated that TCS are more effective in the treatment of AR than systemic or topical H1-receptor antagonists or topical sodium cromoglycate (Svensson et al., 1998; Bousquet et al., 1993). In addition, the superiority of TCS over H_1-receptor antagonists has been confirmed by a recent meta-analysis (Weiner et al., 1998). Reducing nasal congestion in combination with additional anti-inflammatory properties, makes TCS first choice treatment in perennial allergic rhinitis, when nasal congestion is the major symptom, and in long-standing disease (Holm et al., 1999). TCS have a relatively slow onset of action (~12 h), while their maximum effectiveness develops over days and weeks. In case of extreme nasal congestion, nasal corticosteroids may not easily reach the mucosa, and hence, it may be advisable to apply a (topical) decongestant or systemic steroids for up to one week. In general, treatment with TCS is prescribed on a regular basis and, in severe cases, should be started before the beginning of the pollen season for maximal clinical effect. The current intranasal preparations are well tolerated and can be used on a long-term basis without mucosal atrophy. Topical steroids may occasionally cause local side effects, such as crusting, dryness, and minor epistaxis. Nasal perforations due to prolonged use of TCS have been mentioned only anecdotically.

Effects of oral LTRAs in allergic rhinitis (AR)

Until recently, only a few studies have investigated the clinical effectiveness of LTRAs in the treatment of AR (Meltzer, 2000; Donnelly et al., 1995; Pullerits et al., 1999; Meltzer et al., 2000). In 1995, one of the first studies has been published reporting on the effects of different doses of the LTRA zafirlukast on symptoms of seasonal allergic rhinitis (Donnelly et al., 1995). From this two-day, placebo-controlled, parallel study in 164 patients with AR, already 2 hours upon ingestion, zafirlukast (1x20 mg, 1x40 mg, or 1x 100 mg daily) provided dose-dependent protection against symptoms of seasonal rhinitis with on average better symptom scores for nasal congestion, sneeze, and rhinorrhoea than placebo. Moreover, this effect appeared to last for 24 hours (Donnelly et al., 1995). In another placebo-controlled, 3-armed study in 33 patients with seasonal AR, the effect of a 50-days treatment with zafirlukast (2x20 mg daily) has been compared with intra-nasal beclomethasone (2x 200 μg daily) (Pullerits et al., 1999). In contrast with beclomethasone, in this study zafirlukast failed to produce significant improvement in AR-symptoms or a reduction in activated eosinophils in nasal biopsies. These negative findings may be at least partly explained by the small sample size in this study. In another placebo-controlled study in asthma, clinical effectiveness of the LTRA montelukast (1x 5 mg daily, for 8 weeks) was evaluated in 336 children. In this study, montelukast not only improved asthma control but it was also noted that it significantly reduced symptoms of AR as compared with placebo (Knorr et al., 1998).

Despite increasing evidence that leukotrienes are pivotal pro-inflammatory mediators in the pathophysiology of asthma and AR, they are not the only mediators involved in these disorders (Numata et al., 1999). In a recent multi-center, parallel, placebo-controlled study in 460 patients with seasonal AR, the effect of 2-weeks treatment with the combination of the H_1-receptor antagonist loratadine and the LTRA montelukast was evaluated on all AR symptoms (Meltzer et al., 2000). Patients were randomized in one of the 4 study-arms: placebo, loratadine, montelukast, or the combination of loratadine and montelukast. In this study the combination of loratadine and montelukast appeared to produce the best protection against AR symptoms, while both active monotherapies did not differ from placebo (Meltzer et al., 2000).

CONCLUSION

As in the case of asthma, application of LTRAs in the treatment of AR is rational on pathophysiological basis. Until recently, there are only few studies performed applying LTRAs in AR, showing conflicting data, whereas the combination of an LTRA and an H_1-receptor antagonist provided an overal relief of rhinitis symptoms, when both monotherapies were not different from placebo. Hence, long-term studies in large numbers of patients are needed to determine the clinical effectiveness of (additive) therapy with LTRAs in the treatment of AR.

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