

Leukotriene receptor antagonists in the treatment of asthma: an update

Leukotriene receptor antagonists (LTRAs), such as montelukast and zafirlukast, have been demonstrated in a number of studies to possess bronchodilating and anti-inflammatory properties, that make these drugs ideal candidates for the treatment of asthma. The last updating of the GINA Guidelines for the diagnosis and therapy of asthma in 1998 recommended the use of LTRAs in the treatment of moderate and mild asthma. In patients with moderate asthma not completely controlled with moderate doses of inhaled corticosteroids, the addition of a LTRA is indicated as an alternative to either the increase of the inhaled corticosteroid dose or the addition of an inhaled long-acting β_2 -agonist. Both *in vitro* and *in vivo* evidence indicate that LTRAs possess an anti-inflammatory activity that is presumably complementary to that presented by corticosteroids. Moreover, clinical studies show that the addition of an LTRA, montelukast, is able to improve clinical and functional indexes in patients with asthma not controlled with inhaled corticosteroids, and to allow a reduction in corticosteroid dosage in patients with asthma well controlled by inhaled corticosteroids. In patients with mild persistent asthma monotherapy with an LTRA is indicated in alternative to a low-dose inhaled corticosteroid, an inhaled cromone, or an oral slow-release theophylline. Previous clinical studies in patients with mild to moderate asthma had demonstrated that monotherapy with LTRAs is able to improve airway function, asthma symptoms, use of as-needed medications, exacerbation rate, and quality of life, without evidence of tolerance with prolonged use. Recently, in a subgroup analysis of patients with mild persistent asthma, a 6-week treatment with oral montelukast or inhaled beclomethasone gave similar improvements in “rescue-free” days, days with well controlled asthma, FEV₁, blood eosinophils, beta-agonist use, and nocturnal awakes due to asthma.

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Introduction

Leukotrienes (LTs) are unsaturated fatty acids generated by action of the 5-lipoxygenase (5-LO) enzyme on the cell membrane-bound arachidonic acid (AA). Two classes of LTs are derived from the 5-LO pathway, the nonpeptide LTs LTA₄ and LTB₄, and the cysteinyl-LTs LTC₄, LTD₄ and LTE₄. *De novo* synthesis of LTs in response to a variety of stimuli, including the IgE mediated, type I immunological reaction, is made in many cell types, both resident cells, such as mast cells, and infiltrating cells, such as eosinophils. Once secreted extracellularly LTs act on specific receptors, after which they are rapidly degraded, with a very short half-life. In particular, the activation of the recently cloned Cys-LT₁ receptor, whose expression has been demonstrated on bronchial smooth muscle cells and various inflammatory cell types in the lung, is responsible for the bronchoconstrictive and proinflammatory actions, including increased microvascular permeability with oedema formation and increased mucus secretion, possessed by cysteinyl-LTs (1).

Pharmacological research for the identification and development of anti-LT drugs started between the end of the 1970s and the beginning of the 1980s, soon after the discovery by Samuelson and his group at the Karolinska Institute in Sweden of the chemical nature and potent activity of LTs. In particular, cysteinyl-LTs were demonstrated to be the chemical constituents of the *slow reacting substance of anaphylaxis*, already known since 1940 as a mixture of unidentified chemical mediators released in response to various stimuli, including anaphylactic reactions, and characterized by slow, but potent, long-acting contracting activity on smooth muscle cells.

Since 1987 clinical studies on various compounds with anti-LT properties were initiated, and just 10 years later the first anti-LT drugs zileuton, pranlukast, zafirlukast, and montelukast were almost contemporarily commercialized. Zileuton blocks the synthesis of LTs by inhibiting the 5-LO enzyme, whereas pranlukast, zafirlukast, and montelukast are all orally active cysteinyl-LT receptor antagonists (LTRA). Zafirlukast

and montelukast are the only anti-LT drugs available in Europe. Recommended adult doses are 20–40 mg twice daily for zafirlukast, and 10 mg once daily for montelukast. Only montelukast is licensed for use in children, with a 5-mg dose for children 6–12 years of age and a 4-mg dose (only in USA) for children 2–5 years of age.

A number of studies have demonstrated that LTRAs show bronchodilating and anti-inflammatory properties, that make these drugs ideal candidates for the treatment of asthma (2). In asthmatic patients with airway obstruction LTRAs exert a bronchodilating effect manifesting as an increase in FEV₁ of 10%–15% over baseline value; the bronchodilation appears rapidly – a few hours after administration – and is maintained throughout the treatment period, suggesting the absence of tachyphylaxis (2). Asthmatic patients treated with LTRAs also show a reduction in diurnal and nocturnal asthma symptoms, a 30–35% reduction in the as-needed use of bronchodilator drugs, and a diminished number of asthma exacerbations (2). Moreover, LTRAs present a number of experimental and clinical effects that indicate some anti-inflammatory activity. In fact, they are capable of blunting both the early and late bronchoconstrictive response and the cellular inflammatory response to inhaled allergen, and to prevent the exercise induced and the aspirine induced bronchoconstriction, without evidence of tolerance with prolonged use (2). Finally, long-term treatments with LTRAs are able to reduce both the blood and sputum eosinophilia in both adult and children with asthma (2).

The aim of the present article is to review briefly some recent evidence supporting the use of LTRAs in the treatment of moderate and mild persistent asthma, as recommended by the last 1998-revision of the NIH/WHO Guidelines for the diagnosis and care of patients with asthma (3).

Moderate asthma

According to the 1998-updating of the GINA Guidelines, those asthmatic patients who still complain about symptoms and present airway obstruction despite regular use of low to moderate doses of inhaled corticosteroids should be treated by one of the following:

- increase in the dose of inhaled corticosteroid;
- addition of an inhaled long acting beta₂-agonist;
- addition of an oral LTRA (3).

The rationale supporting the introduction of an LTRA in these cases is based first on some studies evaluating the effect of corticosteroids on LTs production. In fact, although *in vitro* studies indicate that corticosteroids are capable of reducing the cysteinyl-LTs synthesis, presumably by increased expression of

lipocortin and consequent inhibition of the phospholipase enzyme responsible for releasing AA from the cell membrane phospholipids (4), *in vivo* studies show that clinical doses of systemic methylprednisolone have no effect on LTC₄ level in bronchoalveolar lavage (BAL) fluid, nor on *ex vivo* synthesis of LTC₄ from BAL cells in asthmatic patients (5). In addition, a one week treatment with oral prednisone, 60 mg/day, does not influence the urinary LTE₄ levels both before and after allergen inhalation in patients with allergic asthma (6). On the other hand, as noted above, LTRAs show some anti-inflammatory activity and, in this context, montelukast is able to prevent in asthmatic patients both the early and late asthmatic response to inhaled allergen (7) and to reduce with long-term treatments the eosinophil levels both in the blood (8) and in the airways (9).

On a clinical ground, in a randomized, controlled study, oral montelukast, 10 mg once daily for 12 weeks, added in patients with asthma not controlled with inhaled beclomethasone, 200 µg bid, has been demonstrated to improve significantly diurnal and nocturnal asthma symptoms, airway function, blood eosinophilia, asthma exacerbation rate, and global physician evaluation (10).

Finally, in a randomized, placebo controlled, 12 week study on patients with asthma well controlled by regular treatment with inhaled corticosteroids, the addition of montelukast is significantly superior to the addition of placebo in allowing a reduction in corticosteroid dosage, without altering the asthma control in these patients (11).

Taken together, these experimental and clinical data suggest that LTRAs possess an anti-inflammatory activity, that is presumably complementary to that presented by corticosteroids. Thus, LTRAs should be considered in the regular treatment of patients with moderate asthma in association with inhaled corticosteroids, with the aim of either improving the asthma control, or reducing the inhaled corticosteroid doses (3).

Mild persistent asthma

According to the stepwise approach employed in the NIH/WHO Guidelines for diagnosis and treatment of asthma, the definition of mild persistent asthma includes a normal or near-normal lung function (FEV₁ > 70% of predicted), frequent but not daily asthma symptoms, and only occasional interference with normal activity of daily life (3). Mild persistent asthma represents an important burden for the national health services, in that it affects as much as 40–45% of all patients with persistent asthma.

A regular anti-inflammatory treatment is recommended for mild persistent asthma, in order to minimize daily and nocturnal asthma symptoms and use of rescue medications. Possible alternatives include:

- a low-dose inhaled corticosteroid;
- an oral LTRA;
- an inhaled cromone;
- an oral slow-release theophylline (3).

With regard to LTRAs, a randomized, double-blind, placebo controlled study in patients with mild to moderate asthma has demonstrated that oral zafirlukast, 20 mg bid for 6 weeks, was able to induce an 11% increase in FEV₁, as compared to placebo, and that this increase was evident since the first day and maintained until the end of treatment, suggesting absence of tolerance towards the bronchodilator effect of the drug (12). In the same study, a reduction of asthmatic symptoms, a 30% decrease of as-needed bronchodilators, a reduction of asthma exacerbations, and an improvement of quality of life was obtained with zafirlukast (12).

In a similar clinical study conducted in patients with mild to moderate persistent asthma, oral montelukast, 10 mg once daily for 12 weeks, gave comparable clinical and functional results (13). Moreover, a 3-week washout period showed, as expected, a progressive decrease in FEV₁ in patients who had been treated with montelukast; however, this decrease did not exceed the placebo FEV₁ value, thus suggesting a lack of rebound effect for bronchodilation by montelukast (13).

A randomized, controlled study comparing directly oral montelukast, 10 mg once a day, with inhaled beclomethasone, 200 µg twice a day, for 12 weeks has demonstrated inhaled beclomethasone to be slightly superior to montelukast in improving clinical and functional indexes in patients with mild to moderate asthma (14). However, in an open, extension trial in which the majority of the patients included in the initial study were treated with the same study drug – montelukast or beclomethasone – for further two years, clinical and functional improvements obtained with montelukast were maintained until the end of the trial (15). In contrast, the beclomethasone group showed throughout the study period a progressive decline in clinical and functional parameters, and, in particular, a decrease in FEV₁ towards a value that, at the end of the trial, was not different from that given by montelukast (15). A progressive fall in compliance to the treatment is the most likely explanation for the decline in effectiveness presented by beclomethasone, confirming that compliance is difficult to obtain in patients performing long-term inhalation treatment.

Finally, an oral LTRA, montelukast and an inhaled corticosteroid, beclomethasone dipropionate have very recently been compared in mild persistent asthma in a study presented at the last American Thoracic Society Meeting, held in Toronto, May 2000 (16). The study was a subgroup analysis of patients with mild persistent asthma (FEV₁ > 70% of predicted; as-needed use of inhaled beta₂-agonists < 6 days per week), who had completed two randomized, double-blind, 6 week studies comparing oral montelukast, 10 mg once daily (38 patients) with inhaled beclomethasone, 200 µg twice daily (30 patients). The results show that both drugs induce significant improvements, as compared to baseline, in a number of clinical and functional indexes, with no difference between montelukast and beclomethasone treatment (16). In particular, “rescue-free” days were 24.4% and 23% of the total study period, days with well controlled asthma were 73.4% and 69.2%, FEV₁ increased over baseline 10.2% and 10.9%, blood eosinophils decreased from baseline 40 and 30 cells/ml, beta₂-agonist use decreased 25.2% and 33.1%, and nocturnal awakes decreased 1.1 and 0.8 nights/week for montelukast and beclomethasone, respectively (16). In summary, these data show that a regular treatment either with oral montelukast or with inhaled beclomethasone is capable of inducing similar improvements in patients with mild persistent asthma.

Conclusions

LTRAs have been recently introduced as antiasthma drugs. In a number of studies, LTRAs have been demonstrated to have bronchodilating and anti-inflammatory properties. Regular treatments with LTRAs have been proved to be beneficial in asthmatic patients by improving airway function, asthma symptoms, as-needed use of rescue medications, and quality of life. At present, international guidelines for asthma management recommend that LTRAs should be used for regular treatment in patients with moderate asthma not completely controlled by inhaled corticosteroids in order to improve the asthma control, in patients with moderate asthma well controlled by inhaled corticosteroids in order to try to reduce the dose of inhaled corticosteroid, and, as monotherapy, in patients with mild persistent asthma in order to reduce airway inflammation and minimize symptoms and use of rescue medications.

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