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REVIEW ARTICLE

Antileukotrienes in the treatment of asthma and allergic rhinitis

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Abstract

Objective: To compare leukotriene antagonists (LTA) to other groups of drugs used in asthma and allergic rhinitis treatment.

Sources: MEDLINE, LILACS and Cochrane Library. Keywords: leukotrienes, antileukotrienes, asthma treatment, allergic rhinitis treatment, asthma and allergic rhinitis. An attempt was made to group the main studies and reviews about this topic

Summary of the findings: LTA are more efficient than placebo and enhance the effects of inhaled corticosteroids. The association of inhaled corticosteroids with long-acting ß2 agonists is more efficient than the association of inhaled corticosteroids + LTA. Although use of LTA in acute asthma attacks and allergic rhinitis seems reasonable, more studies are needed to confirm this benefit. LTA reduce hospitalization time and the number of wheezing attacks in infants with acute viral bronchiolitis caused by respiratory syncytial virus, as well as recurrent wheezing after acute viral bronchiolitis. LTA are less efficient than intranasal corticosteroids for allergic rhinitis management. LTA are efficient in exercise-induced asthma, although they are not the first-line treatment.

Conclusion: Controlled and randomized studies show that inhaled corticosteroids are the drugs of choice to treat persistent asthma and allergic rhinitis. There is not enough evidence to recommend the use of LTA as first-line drug (monotherapy) in children with asthma (level I). For children who cannot use inhaled corticosteroids, LTA may be a good alternative (level II).

J Pediatr (Rio J). 2006;82(5 Suppl):S213-21: Asthma, exercise-induced asthma, rhinitis, antileukotrienes, montelukast, zafirlukast.

Introduction

Over the past decades, much progress has been made in understanding the pathophysiology and management of asthma and allergic rhinitis in childhood and adolescence. Four paradigms have been confirmed with certainty and widely disseminated: I) the prevalence of asthma and allergic rhinitis is increasing, II) they are clinically and functionally expressed as several phenotypes of varying severity, III) the inflammatory component, which results in clinical signs and symptoms, is very important and IV) inflammation may cause permanent changes in the airway structure (remodeling).[1-4] With the aim of achieving better control of those diseases, efforts have been made to find a drug, or group of drugs, that is able to combat airway inflammation. However, despite major advances, full control of symptoms is still not possible for many patients.

Studies demonstrating the anti-inflammatory activity of inhaled corticosteroids (IC) brought optimism. After that, in 1990, long-acting ß2 agonist bronchodilator (LABA) agents (formoterol and salmeterol) were developed, providing 12-hour bronchodilation. LABA were initially found to provide bronchodilation and bronchoprotection when used as monotherapy; however, they presented minimal or no anti-inflammatory effect. Later, when searching for optimized results in airway clearance, a synergic effect was verified between LABA and IC.

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In adults, the use of drugs containing LABA and IC has shown to be efficacious. It has been demonstrated that the combination of IC + LABA produces better asthma control than the use of IC alone; in addition, this combination results in fewer exacerbations, improvement in pulmonary function and better control of clinical symptoms than an increase in the daily IC dose alone. It is also clear that this combination is indicated for asthmatics with moderate to severe persistent asthma.[2-4] Such enthusiasm has led some research groups and guidelines to suggest the combined use of IC + LABA to treat patients with persistent asthma, including children, extrapolating the results obtained based on studies with adults. Consequently, the number of prescriptions of IC alone has been significantly reduced, whereas the number of prescriptions of IC + LABA has proportionally increased, as can be seen in children from Northern Europe.[1]

What do treatment guidelines recommend?

According to the Global Initiative for Asthma (GINA),[2] LABA should be used for moderate persistent asthma when there is no response to IC. British Thoracic Society (BTS)[3] guidelines suggest that LABA should be added to asthmatics whose symptoms are not controlled with IC. In the USA, the National Institutes of Health Guidelines for Diagnosis and Management of Asthma[4] recommend that LABA be used as adjuncts to anti-inflammatory therapy to produce longer-lasting symptom control especially of nocturnal symptoms, and prevent exercise-induced asthma. All these guidelines recommended association of drugs for individuals over 12 years old.

After 2000, concern was raised in the international scientific community about two facts: I) lack of controlled studies on the safety of associating LABA + IC in children and II) results of phase IV studies performed in adults to verify safety, effectiveness and efficacy of the LABA + IC association.

Several studies have shown that this association is efficient in the management of persistent asthma. However, it also presents a higher risk for undesirable outcomes such as development of tolerance and reduction in bronchodilator and bronchoprotective activity, arrhythmia, sudden death, hypopotassemia, worsening of asthma with increase in the number of exacerbations and increased risk of cardiovascular events.[5-8] Despite their small number, those side effects were not insignificant, preferentially affecting individuals of African descent. It was then argued that LABA in children should be used in special situations, in very severe cases and when there is no response to adequate doses of IC and/or leukotriene receptor inhibitors. Medical associations worldwide have recently published recommendations for LABA use:[9] I) they should not be used as monotherapy or as rescue medication (for these cases a short-acting ß2 agonist is recommended); II) they should not be used to replace IC; and III) the lowest possible dose should also be used. Based on those arguments and on meta-analyses and phase IV studies, several authors claim that there is little scientific evidence to support routine use of LABA in children, and that treatment guidelines for LABA use in children are extrapolated from studies in adults. Childhood asthma is different from adult asthma, and the results from studies in adults should not be extrapolated to children.

Countering these arguments, in 2006 Nelson et al. published a review study[10] and a study called SMART,[11] in which they list the main controversial points about using LABA, mainly salmeterol, defending the benefits of associating LABA and IC. Since those data were obtained from adults, caution is required when using LABA in children before phase IV studies confirm their efficacy and cost-benefit advantage Therefore, there is still a predominance of arguments questioning the use of LABA in children, recently discussed in two articles[1,12] that draw attention to the safety and risks of this group of drugs in children.

While the debate on the role of LABA in children continues, several phase IV studies have produced evidence to confirm that anti-inflammatory treatment should be the basis for any patient with persistent asthma (mild, moderate and severe). Among the anti-inflammatory drugs, IC are the basic choice to treat persistent asthma. In the absence of adequate response, they can be associated with LABA, LTA, theophylline or other anti-inflammatory agents. Short-acting ß agonist drugs, especially salbutamol, should be the rescue medication.

Martinez[12] draws attention to LTA safety as a good therapeutic option, mainly for patients with mild and moderate asthma in association with IC when there is no response to IC treatment alone. Additional phase IV studies are needed to confirm and consolidate these effects. According to Martinez,[12] if adequate LTA doses are used, LABA in children is indicated only for severe forms.

All these drug groups present a safety profile, usability, efficacy, effectiveness and actions on airway remodeling that allow adjustment both individually (LTA and IC) or in associations (LABA) (Table 1).

The community of professionals working and treating asthmatic children expects that new phase IV studies may bring a better understanding of the real role of each drug group in adequate asthma management. What most consensus statements affirm is that for patients whose asthma is not adequately controlled with IC, the options include associations with LABA, LTA, theophylline or increasing IC dose.

The main objective of this review is to inquire on the role of leukotriene antagonists in asthma and allergic rhinitis.

What are leukotrienes (LT) and leukotriene antagonists (LTA) and how they act

Several blood cells present in airways, and others that migrate there, release preformed (for example, histamine) and postformed substances (for example, LT) in response to atopic aggressions.

Leukotriene is the name given to the family of polyunsaturated eicosatetraenoic acids that are formed by enzymatic action in the phospholipid layer of a range of target activated cells. In airways and lungs, the main cells that release LT include neutrophils, eosinophils, mastocytes, macrophages, epithelial cells and vascular endothelial cells. LT are potent lipid mediators deriving from the phospholipid layer, which modulates a large number of intra- and extracellular processes. Leukotrienes have demonstrated antimicrobial action in host defense and play a role in diseases characterized by inflammation, cell proliferation and fibrinogenesis. There are two classes of leukotrienes, cysteinyl LT (Cys-LTs: LTC4, LTD4, LTE4) and LTB4, according to the presence or not of cysteine, respectively. These two types of LT act through two different specific receptors.[13] The activity of phospholipase on cell membrane phospholipids initiates a mediator cascade, as shown in Figure 1.

Cys-LT activity on airway structures has been documented by several investigators, including potent bronchoconstriction (much higher than that induced by histamine and methacholine), with subsequent changes in pulmonary function values, vasodilatation, increase in mucus secretion, reduction in mucus transport and eosinophil recruitment.[13-15]

The main effects of Cys-LT on airways can be seen in Figure 2.

The efforts to develop drugs to block the pro-inflammatory action of Cys-LT have produced two types of drugs: 5-lipoxygenase inhibitors and LTA. Zileuton decreases LT synthesis by blocking 5-lipoxygenase. Zafirlukast and montelukast, LTD4 antagonists, block leukotriene receptors and prevent these mediators from causing inflammatory reactions in the airways.

The effects of LTA are the opposite of those described for LT: LTA improve peripheral airway obstruction assessed by pulmonary volumes, air trapping,[16] airway resistance, specific conductance[17] and oscillometry.[18] They reduce the number of eosinophils in induced sputum[19] and in peripheral blood of asthmatic patients.[20] They reduce eosinophil migration to lungs.[14] They are capable of interfering with improvement of airway remodeling.[21]

Another major aspect to be considered for some asthmatic patients when evaluating LTA as potential therapy is the result of findings suggesting that use of oral corticosteroids, even in high doses, does not change LT concentrations in urine[22] and in airway secretions in asthmatics.[23] This suggests the existence of two pathways of inflammation control in airways and lungs, which occur in asthma and rhinitis: one is sensitive to corticosteroids and the other is sensitive to LTA. The fact that corticosteroids do not change urine LT concentrations also explains the more favorable action of the association of IC and LTA *versus* their independent use.

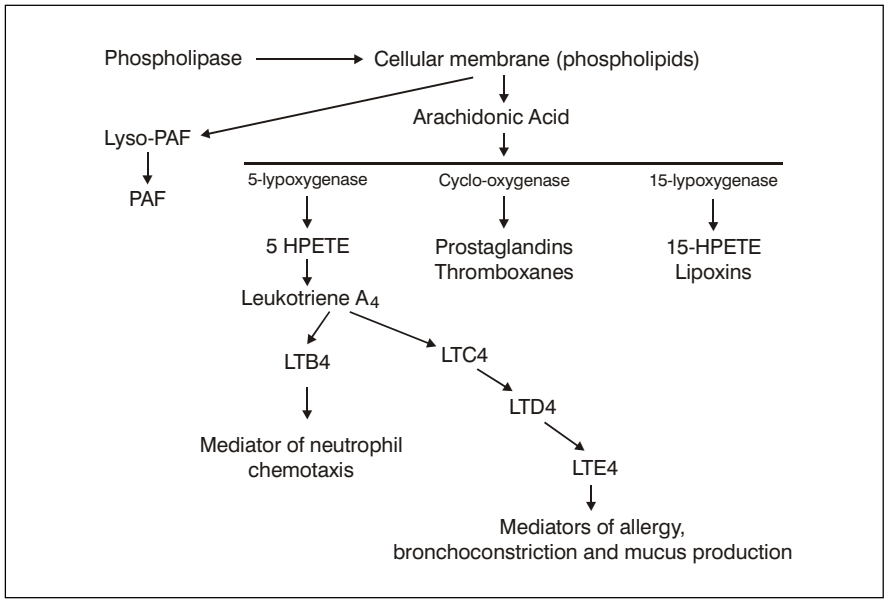
Studies on the role of LTA in asthma and allergic rhinitis

All international consensus statements have drawn attention to a more aggressive anti-inflammatory treatment in persistent asthma. Despite the use of other groups of anti-inflammatory drugs (ketotifen, nedocromil, disodium cromoglycate), IC are still the gold standard for the treatment of allergic rhinitis and persistent asthma. Unfortunately, the symptoms of several patients cannot

Table 1 - Considerations on drug groups for between-crisis asthma management in children

	Antileukotrienes	Inhaled corticosteroids	LABA
Safety	++++	++++	++
Usability	++++	++	++
Efficacy	++	++++	+++
Effectiveness	++	++++	+++
Remodeling	+++	++++	+++

+ = minimum; ++++ = maximum.



HPETE = Hydroperoxyeicosatetraenoic acid; LT = leukotriene; PAF = platelet activating factor.

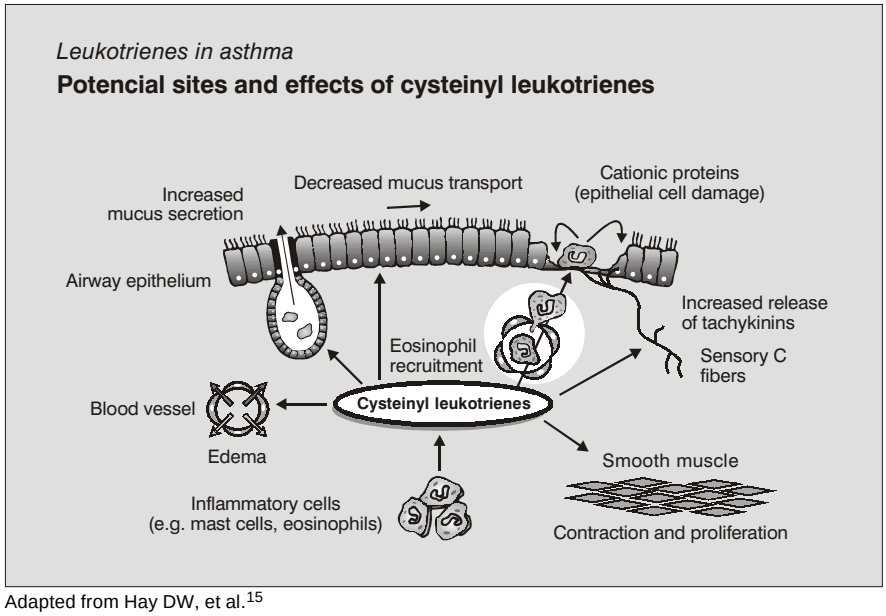
Figure 1 - Diagram of leukotriene formation

be controlled with IC alone. Another intriguing aspect is that all drugs and drug groups used in asthma and allergic rhinitis management present individual response variability.

LTA are a new class of anti-inflammatory drugs. They can be orally administered, once (montelukast) or twice (zafirlukast, pranlukast) daily with few side effects. Although they have less pronounced anti-inflammatory effects than IC, their efficacy has been demonstrated in some patients with asthma and allergic rhinitis.

Antileukotrienes *versus* placebo in asthma

The studies assessing LTA effects, comparing LTA to placebo, and the reviews that survey these studies show a clear statistical superiority of LTA, compared with



Adapted from Hay DW, et al.[15]

Figure 2 - Leukotriene actions on airway structures

placebo, with regard to improvement of asthma symptoms. Among these studies, Straube et al.[24] verified that in asthmatic wheezing infants aged between 10-26 months, montelukast determined significant improvement in inflammation, pulmonary function and symptom score compared with the placebo group.

Bisgaard et al.[25] investigated the role of montelukast in the prevention of wheezing attacks induced by viral infection in children with intermittent asthma aged between 2-5 years. The patients were randomized to receive montelukast or placebo for a 12-month period. The group with active treatment presented fewer symptoms and wheezing exacerbations.

A multicenter, double-blind and placebo-controlled study performed in children aged between 2-6 years from different countries and continents has also reported significant improvement in asthma signs and symptoms when montelukast was used.[26] Spahn et al.[17] have recently confirmed the effects of montelukast on peripheral airway obstruction and the concentration of eosinophilic cationic protein in children and adolescents with moderate asthma. Use of montelukast was associated with less air trapping, hyperinflation and resistance and higher values of spirometry and specific airway conductance as compared with placebo.

Antileukotrienes *versus* IC in asthma

Although the efficacy of LTA and IC to manage patients with persistent asthma was similar in some studies,[27] most studies show superiority of IC over LTA.[28,29]

Ducharme & Di Sálvio[29] analyzed the results of 27 recent studies comparing the efficacy of LTA versus IC to manage chronic persistent asthma in adults and children over 2 years. The review shows that IC at a dose of 400 µg/day (beclomethasone or similar) are more efficient than LTA; however, the dose equivalence for these two drug groups has not been determined yet. The authors conclude that IC monotherapy is the first choice for persistent asthma treatment.

Szefler et al.[30] showed that IC and LTA response varies among asthmatic patients. They performed a study to test whether a patient with poor response to a drug may respond better to another drug, in a cross-over comparison of the effects of inhaled fluticasone (FT) versus montelukast used alone and in alternate sequence. The authors used changes > 7.5% in forced expiratory volume at one second (FEV_1) as indicators of drug response. They verified that 17% of 126 participants (school children and adolescents) responded to both drugs, 23% only to FT, 5% only to montelukast and 55% did not respond to any drug. These results show what is also observed in the daily practice of physicians treating children and adolescents with asthma: some respond to a drug group, others do not, and sometimes it is necessary to combine drugs.

More recently, Zeiger et al.[31] comparatively analyzed FT efficacy (100 mg twice/day) versus montelukast (5-10 mg/night, dependent on age) in patients aged between 6-17 years with moderate persistent asthma. The group using FT had more favorable clinical and laboratory results than the group using montelukast alone, which indicates that IC are the first-line treatment for persistent asthma.

Addition of LTA to IC to treat asthma

The focus of the multicenter CASIOPEA[32] study was the comparison between budesonide + placebo and budesonide + montelukast in 639 patients with asthma for a 16-week period. The authors concluded that addition of montelukast to budesonide significantly improves asthma symptoms, more than using budesonide alone.

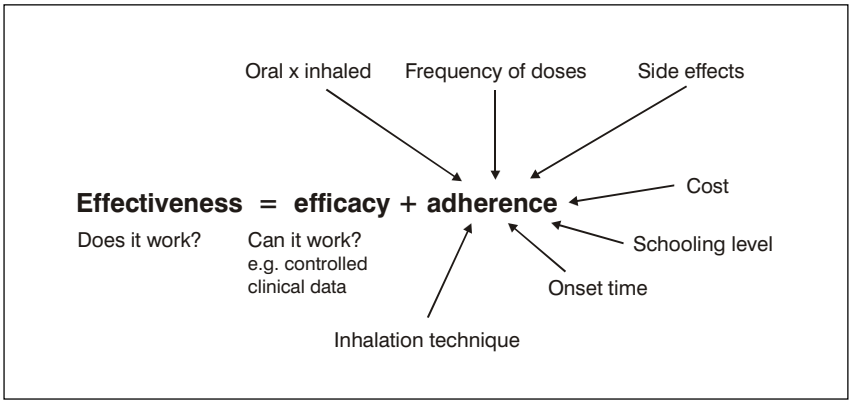


Figure 3 - Determinants of therapeutic effectiveness

LaViolette et al.,[20] in a 20-week double-blind, randomized and placebo-controlled study with asthmatic patients older than 15 years, also verified that montelukast associated with inhaled beclomethasone resulted in better control of inflammation in asthmatic patients than the use of isolated drugs. The multicenter, randomized, double-blind, parallel-group COMPACT[33] study was performed to compare the effects of inhaled budesonide (800 µg/day) + montelukast (10 mg/day) versus double dose budesonide (1600 µg/day) for 16 weeks of asthma treatment. The efficacy of both dose systems was similar in the outcomes used as markers of asthma improvement: need of using short-acting ß2 agonists, symptom scores, nocturnal awakening, asthma exacerbations, quality of life, number of eosinophils in peripheral blood and number of severe asthma attacks.

With the aim of comparing the efficacy of IC versus IC + LTA for the treatment of persistent asthma, Ducharme et al.[34] researched double-blind, randomized and controlled studies (27 in adults and two in children) published until 2003. Analysis of these studies led to the conclusion that addition of LTA results in improvement, although modest, in pulmonary function.

LTA associated with LABA versus IC associated with LABA

Patients with persistent asthma who do not improve with regular use of IC may require association of LABA or LTA.

A comparative study between montelukast + FT and salmeterol + FT to protect against asthma exacerbations in adults was performed by Bjermer et al.[35] for a 54-week period. Outcomes were similar in both groups. Both treatments were well tolerated, and eosinophilia at the end of the study was lower in the group using montelukast associated with FT. The authors concluded that addition of montelukast in patients whose asthma remains uncontrolled with FT promotes clinical control similar to that of the group receiving FT + salmeterol. The same authors published a study called IMPACT,[36] in which they compare the efficacy and safety of salmeterol + montelukast versus salmeterol + FT to prevent asthma attacks, improve quality of life, pulmonary function and reduce serum levels of eosinophil in 1,200 asthmatic adolescents and adults from 120 centers in several countries. The main discussion topic concerning the similar outcomes in both groups, according to those authors, is that addition of montelukast to IC represents an additive effect, whereas montelukast inhibits the effects of LT, which does not occur with IC. On the other hand, contrary to previous reports, Ringdal et al.[37] found that the association of FT + salmeterol was more efficacious than the association of FT + montelukast in asthmatic patients older than 15 years.

This efficacy relation was confirmed by Ram et al.,[38] who evaluated 13 randomized and controlled studies comparing associations of LTA + LABA *versus* IC + LABA in 5,895 adult asthmatic patients and concluded that in asthmatic adults improperly controlled with IC, addition of LABA is better than addition of LTA to I) prevent asthma exacerbations; II) improve pulmonary function; III) improve asthma symptoms; and IV) decrease the need of rescue medication (short-acting ß2 agonists).

Use of LTA in acute asthma

It is known that large amounts of LT are released and documented in the urine and in airway secretions of patients during acute asthma attacks. These high levels of LT have been found even in asthmatic patients undergoing treatment with IC and LABA.

Some authors have demonstrated and proposed that use of LTA associated with short-acting bronchodilators may be efficient to treat acute asthma, and that adding LTA may be beneficial in patients with severe asthma who do not improve with IC + LABA.[39] More studies are needed to confirm these benefits.

LTA versus intranasal corticosteroids in allergic rhinitis

Reviews and meta-analyses show that LTA are part of the therapeutic options for allergic rhinitis management.[40,41]

The systematic review performed by Rodrigo & Yañez[40] included 17 controlled studies in 6,231 adults. They concluded that LTA are more efficient than placebo and H1-histamine receptor antagonists, but less efficient than intranasal corticosteroids to control symptoms and improve quality of life of patients with allergic rhinitis. The order of increasing efficacy was: anti-H1, LTA associated with anti-H1 and intranasal corticosteroids.

LTA and wheezing in infants

High levels of LT have been found in secretions of infants after episodes of acute viral bronchiolitis (AVB) by respiratory syncytial virus (RSV).[42-44] Recurrent wheezing and airway hyperresponsiveness (AHR) may persist in these infants for many years. Therefore, Cys-LT are a rational target for the treatment of AVB by RSV and its sequelae. Over the past decade, some double-blind, randomized and placebo-controlled studies have demonstrated the efficacy of LTA in infants with AVB and in recurrent wheezing after AVB.[45]

In vitro studies have demonstrated that infection by RSV in epithelial cells induces expression of the 5-lipoxygenase gene (5LO), which plays a major role in LT

synthesis.[42,46] Bisgaard et al.[45] followed children aged between 3-36 months who were hospitalized due to AVB by RSV with no history of asthma. One group was given montelukast and the other received placebo in a double-blind, controlled and randomized study. During follow-up, the group that was actively treated had less wheezing exacerbation and less nocturnal cough. In another study involving 129 children with recurrent airway infections, AVB or recurrent wheezing, higher levels of Cys-LT were observed in respiratory secretions of children with AVB and recurrent wheezing than in children with upper airway infections (UAI).[44]

It is still unknown whether the amount of LT present in secretions of asthmatic patients having asthma attacks triggered by viral infection is different from that seen in attacks triggered by allergens. In children under 5 years with recurrent wheezing, montelukast, compared with placebo, proved to be more efficient in controlling wheezing attacks and improving clinical symptoms.[47]

Asthma is the most common chronic disease in childhood, and it has no cure yet. In a recent study assessing daily use of IC for 2 consecutive years in children, asthma symptoms and changes recurred after treatment was suspended. That means that IC did not affect the development of asthma in the third year when patients did not use IC. This was not observed for the association LTA + IC.[48] Therefore, long-term studies will be able to confirm whether or not addition of montelukast to IC in severe asthma is truly beneficial.

LTA doses and side effects

The recommended dose of montelukast is 4 mg/day for children under 6 years, 5 mg/day between 6 and 14 years and 10 mg/day over 14 years, in a single daily dose, preferentially at night. LTA, according to most studies, are well-tolerated. Side effects include headache, otitis, abdominal pain, pharyngitis, urticaria and nausea. Similar numbers of these side effects have been found in groups using placebo. The Churg-Strauss syndrome, initially described in patients receiving zafirlukast, but not montelukast, is today attributed to the interruption of corticosteroid treatment in patients with the syndrome who behaved as having severe steroid-dependent asthma. Montelukast crosses the placenta and passes into breast milk. There are no studies assessing risks and benefits in those situations.[13]

Becker et al. performed a study comparing the effects of montelukast and beclomethasone on growth of asthmatic school children. They verified reduction in growth rate caused by beclomethasone, whereas the group receiving montelukast did not present such changes.[49]

LTA in exercise-induced bronchial obstruction

Some asthmatic individuals present exercise-induced bronchial obstruction (EIB). Increased amounts of LT have been found in the urine of these patients after EIB.[50] Although prophylaxis, warm-up and use of bronchodilators before exercising is the ideal management, use of montelukast presents fast action to prevent EIB,[51] administered in the morning or at night.[52] In addition, montelukast mitigates immediate and late stages of [53] and may mitigate symptoms in children with long term EIB.[54] According to several international consensus statements and authors, IC are the basis for the management of patients with persistent asthma. It is proposed that the recommendation of drugs for asthma management follow criteria of effectiveness, efficacy and adherence (Figure 3).

Despite offering some advantages, such as oral therapy, single daily dose, few side effects, little interaction with food, approval for use in infants and anti-inflammatory action, LTA are far from being a panacea for asthma and should not be the first treatment choice, unless in selected cases. The best patients for LTA are infants and children under 5 years with effective clinical response after 4 weeks of treatment and those with asthma induced by non-steroid anti-inflammatory agents.

Main considerations on LTA in asthma and allergic rhinitis management

- LTA are more efficient than placebo.
- LTA increase IC potential.
- The association IC + LABA is more efficient than the association IC + LTA.
- Although use of LTA in acute asthma attacks and allergic rhinitis seems reasonable, more studies are needed to confirm the observed benefits.
- LTA are associated with reduced hospitalization time and number of attacks in infants with AVB by RSV and in recurrent wheezing after AVB.
- LTA are less efficient than IC for allergic rhinitis management.
- LTA are efficient in exercise-induced asthma, although they do not represent the first-line treatment.
- All drugs and drug groups used in asthma and allergic rhinitis management present individual response variability.

Conclusions

Asthma is a chronic disease and airway inflammation is the most important agent in symptom induction and maintenance. The use of anti-inflammatory agents is a permanent goal of asthma treatment. Although LTA are better than placebo, they are less efficient than IC to

control inflammation. Controlled and randomized studies provide evidence that IC are the choice drugs to treat persistent asthma. There is not enough evidence to recommend the use of LTA as first-line drug (monotherapy) in children with asthma (level I). For children who cannot use IC, LTA may be a good alternative (level II). In some patients, LTA curtail the inflammatory process of airways and lungs, with reduction in signs and symptoms and improvement in quality of life.

If a child's clinical symptoms or pulmonary function do not improve with a drug group, it is important to review environmental prophylaxis and adherence to drug use. If necessary, the dose should be increased or the drug group should be replaced with other drug groups following the order of efficacy.

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