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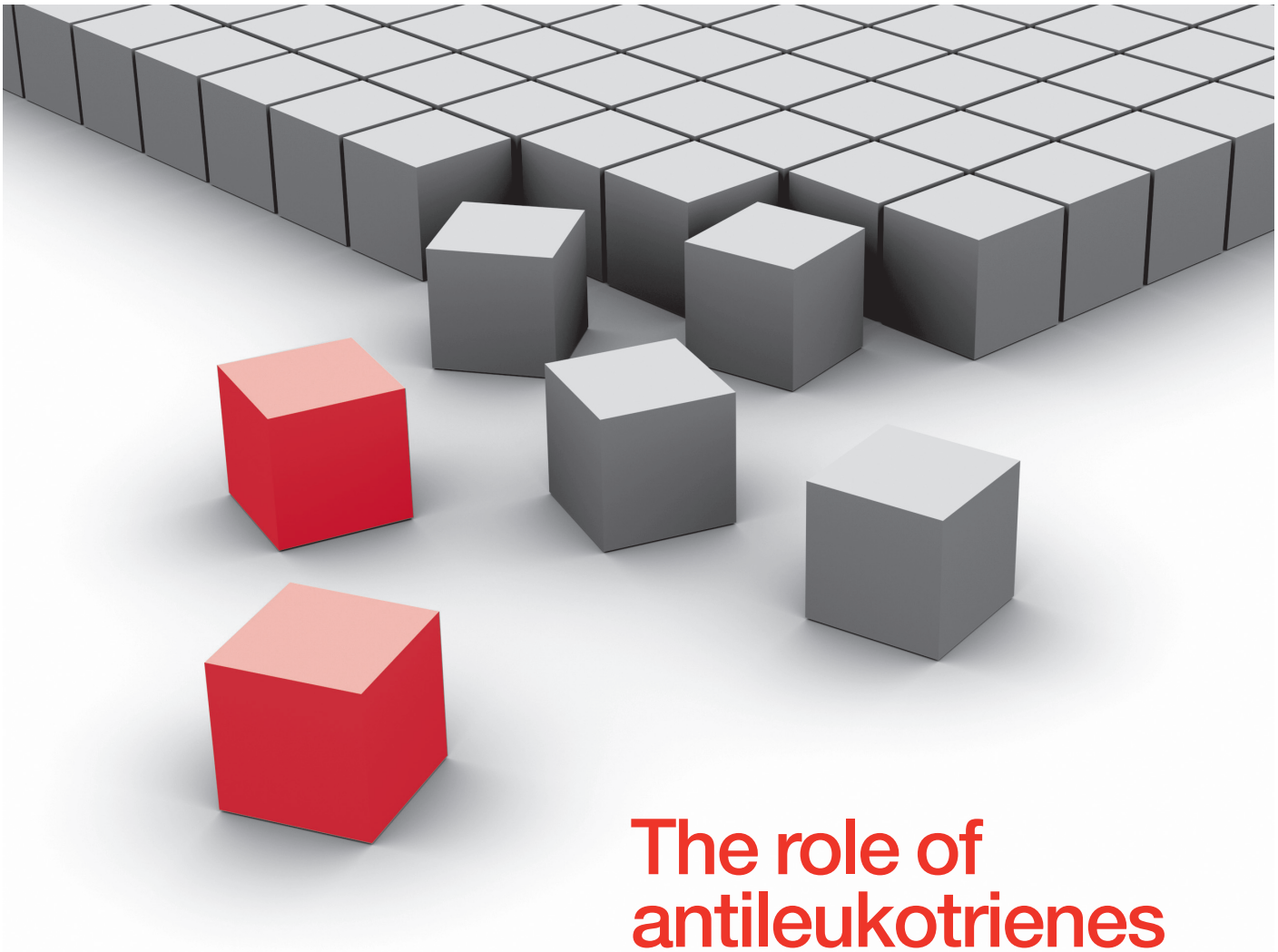

The role of antileukotrienes in children

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Summary

Objetives: To review the role of antileukotrienes in children. **Material and methods:** A search was carried out in MEDLINE for observational studies, clinical trials and systematic reviews that evaluated the role of antileukotrienes in the management of asthma in children. In addition, we also consulted current clinical practice guidelines on the management of asthma, the Cochrane library, documents from the European Medicines Agency (EMEA) on indications, and recommendations of the Food and Drug Administration (FDA) on matters of safety of these agents. **Results and conclusions:** The only therapeutic indication of antileukotrienes is in the management of asthma. In persistent asthma randomized controlled trials have shown that antileukotrienes are more effective than placebo, but less than inhaled steroids. In exercise-induced asthma, leukotrienes proved to be a useful alternative to short-acting beta 2 agonists. Given the current evidence with regard to clinical benefits, the prescription of these agents has exceeded its corresponding role. This may be due in part to the ease in use when compared to other agents employed in the treatment of asthma. Antileukotrienes are well tolerated among the majority of the population. Currently the FDA is carrying out a study to evaluate the safety of montelukast and its association with changes in behaviour and suicidal thoughts.

Introduction

Antileukotrienes are drugs used in the treatment of asthma and have been available in the market for 10 years now. The prescription of these agents have exceeded their corresponding role given the current evidence of their clinical benefits. This may be due to their ease in use when compared to other agents employed in the management of asthma. In the treatment of **persistent asthma**, randomized controlled trials have shown that antileukotrienes are more effective than placebo, but are less effective than inhaled corticosteroids (IC). In **exercise-induced asthma**, antileukotrienes are more effective than placebo and are an alternative to short-acting beta 2 agonists[1].

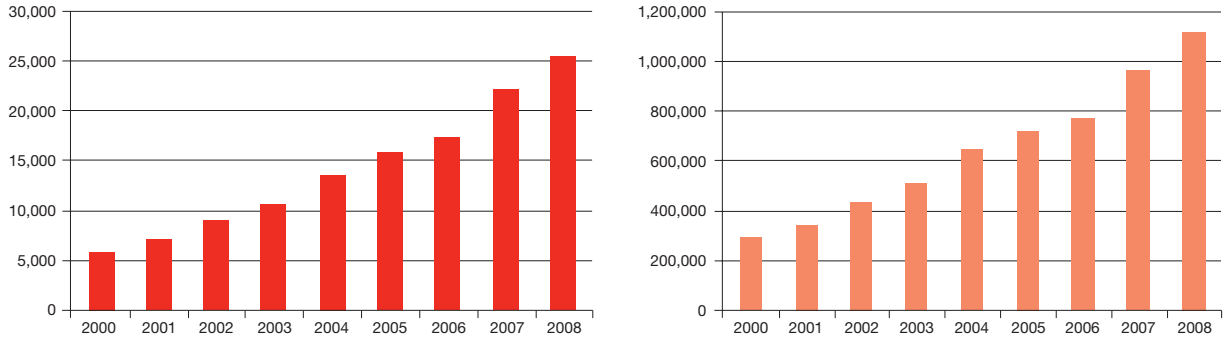
Antileukotrienes are well tolerated by the majority of the population[1]. Currently the FDA is carrying out a study on the safety of montelukast and its association with changes in behaviour and suicidal thoughts[2].

Inhaled corticosteroids are currently the cornerstone in the treatment of persistent asthma in children as well as in adults. However the potential risk of adverse effects has led to the search for other alternatives. Antileukotrienes appeared some years ago and showed effectiveness in improving the control of asthma.

Leukotrienes are potential inflammatory substances released by different cells, including mastocytes, and eosinophils. They adhere to specific receptors in respiratory airways producing bronchoconstriction, mucous secretion and vascular permeability and accumulation of eosinophils. As antileukotrienes block this union, and act at a different site from steroids, it was hoped that additional therapeutic benefits would be attained. However different trials and systematic reviews have concluded that their efficacy is inferior to inhaled corticosteroids, thus resulting in a poor alternative[1,3].

In Navarre, the use of antileukotrienes has greatly increased over the last few years, exemplified by an expense of a little over a million euros in the year 2008.

Figure 1. Antileukotriene prescription in Navarre, 2000-2008.



YEAR	2000	2001	2002	2003	2004	2005	2006	2007	2008
Prescriptions [■]	6,100	7,194	9,186	10,898	13,850	16,006	17,771	22,188	25,766
Cost (euros) [■]	290,119	342,245	434,211	513,304	650,673	720,680	774,469	963,396	1,118,483

Antileukotrienes available in Spain. Indications

Currently there are two antileukotrienes available on the market in Spain: montelukast and zafirlukast. In September 2007, the pharmaceutical manufacturer of montelukast made an application of arbitration to harmonise differences in the technical information existing in different countries with regard to, among other aspects, the authorised indications[3]. This arbitration referred to the 4 mg dose of montelukast. The European commission emitted a decision in July 2008[4].

The current approved indications of the commercialised antileukotrienes in Spain are:

Montelukast 4 mg

It is indicated in asthma as an **add-on therapy from 6 years of age** in patients with **mild to moderate persistent asthma** not controlled sufficiently with inhaled steroids and in patients where short-acting beta 2 agonists applied as rescue medication do not offer sufficient control of symptoms.

In addition, this agent could be used as **an alternative** to low dose inhaled steroids **in patients from two years of age** with **mild persistent asthma**, with no recent history of severe asthma but have required oral steroids, and who are unable to use inhaled steroids.

Moreover, montelukast is indicated in children **above 2 years of age** as prophylaxis for asthma whose main component is bronchoconstriction induced by exercise.

Montelukast can be administered in children from 6 years of age. Experience in children from 6-12 months is limited. Safety and efficacy under 6 months of age is not well known.

During the process of arbitration, to justify the indication for **combined treatment in children between 6 months and 2 years**, the manufacturer presented data on pharmacokinetics, safety and an extrapolation to this age group of data on the efficacy demonstrated in older children (2-5 years and 6-14 years of age). The effect of montelukast on asthma was considered modest, but constant throughout the spectrum of endpoints and coherent with results obtained in studies carried out in adults and older children.

The *Committee for Medicinal Products for Human Use* (CHMP) considered that this data was not very solid and thus, requested that the company include the following warning in the drug information leaflet of the product:

Antileukotrienes are indicated in the treatment of asthma.

"The data on efficacy resulting from clinical trials in children between 6 months and 2 years with persistent asthma is limited. The response of patients treated with montelukast after 2-4 weeks should be evaluated. Treatment should be suspended if no response is observed."

With regard to children between 2 and 5 years, the data offered by the company did not require the inclusion of the above mentioned warning.

The CHMP considered that the use of montelukast as **monotherapy from 2 years of age** was sufficiently supported by evidence from clinical trials and agreed to maintain this indication.

In the case of exercise-induced asthma, it is difficult to evaluate the limitation of activity in very small children (under 2 years of age), and therefore the CHMP considered that the indication in this case should be for children of 2 years or above.

Moreover the CHMP suggested that the company include the following paragraph in the drug information leaflet:

"In patients between 2 and 5 years of age, **bronchoconstriction induced by exercise** could be the predominant manifestation of persistent asthma that requires treatment with inhaled corticosteroids. Patients should be examined after 2-4 weeks of treatment with montelukast. If no satisfactory response is attained then an additional or different approach to management should be considered."

Zafirlukast

This agent is indicated in the prevention and chronic treatment of asthma in addition to maintenance therapy in those asthmatic patients in which rescue short-acting beta 2 agonists do not achieve adequate control of the disease. More so, it is indicated in patients with mild or moderate persistent asthma that are not adequately man-

aged with inhaled corticosteroids. It has not been evaluated in children under 12 years of age.

This bulletin will review the role of montelukast in pediatrics, given that it is the most employed antileukotriene and the only one authorised from 6 years of age.

In 2008, 2,258 pediatric patients were treated (3% of the children) in Navarre with antileukotrienes, of which 68% had a history of asthma (code R-96).

Clinical efficacy of montelukast in pediatrics

Compared to placebo

Montelukast has been compared in children with placebo in different randomised double-blind trials. The severity of persistent asthma was either mild or moderate. The results of these trials have shown improvements in multiple parameters: asthmatic symptoms during the day (cough, wheezing, difficult breathing and limitation in activity), symptoms during the night, percentage of days free of symptoms, need for beta 2 agonists or oral corticosteroids, global evaluations and levels of eosinophils in blood. The improvement in FEV1 from the basal state was significantly greater with montelukast when compared to placebo[5].

Other trials using endpoints such as bronchial hyperreactivity after metacholin challenge test[6], or the detection of levels of exhaled nitric oxide[7] (inflammatory marker) showed significantly greater efficacy of montelukast against placebo. Some authors consider that the information offered by nitric oxide in the course of the asthmatic condition is scarce and contradictory, and thus should only be limited to research for now[8].

One trial[9] randomly distributed 689 patients between **2 and 5 years** with either montelukast or placebo, with the main aim of determining the safety profile of the former. The conclusions of the authors were that montelukast is effective, generally well tolerated and with no clinically significant adverse effects.

In the management of asthma, antileukotrienes have shown to be more effective than placebo, safe and well tolerated.

Comparison with inhaled corticosteroids

Various trials have compared treatment with antileukotrienes with inhaled corticosteroids in patients with mild to moderate persistent asthma. The majority of the comparisons have been made between montelukast and fluticasone. The general conclusion is that inhaled steroids are the most effective anti-inflammatory agent and are the elective treatment option in any grade of asthma. In general the magnitude of the anti-inflammatory effects of antileukotrienes are lower than that obtained with steroids[10].

One trial compared budesonide in suspension for nebulizer with montelukast in 394 children between **2 and 8 years** with mild asthma or recurrent wheezing during a period of 52 weeks[11]. The primary endpoint was time up to the need to add the first drug due to worsening of asthma. Secondary endpoints included time up to first exacerbation, rate of exacerbations during the 52 week study period and endpoints on daily pulmonary function (objective, peak expiratory flow, PEF and subjective questionnaires). In this trial no significant differences were observed between the groups with regard to the primary endpoint. However, other secondary endpoints did show statistically significant differences favourable to budesonide. For example, the rate of exacerbations after 52 weeks (1.23 exacerbations per person-year vs 1.63 for montelukast, p=0.034) and measurements of pulmonary function (PEF).

The authors pointed out that the lack of significance in the primary endpoint could be due to two factors: the severity of the disease was mild and compliance with medication equal or above 80% was low in both groups. In addition, the authors comment that the administration of budesonide in nebulizer could prove more uncomfortable than the oral administration of montelukast, which in many occasions could make the antileukotriene the preferred choice.

Another study compared montelukast with low dose fluticasone (50 mcg b.i.d) for 12 weeks in 342 children with persistent asthma between **6 and 12 years of age**[12]. Fluticasone was significantly more effective than montelukast in the improvement of pulmonary function, asthmatic symptoms, and in the need to use rescue salbutamol for quick relief. Both drugs showed similar safety profiles. Parents and physicians showed greater satisfaction with fluticasone.

One trial compared montelukast with fluticasone in 994 children between **6 and 14 years** (median = 9 years) with mild persistent asthma[13]. The randomised double-blind and non-inferiority multicenter trial had a follow-up period of 12 months. It compared 5 mg daily montelukast with 100 mcg twice a day fluticasone. The primary endpoint was percentage of days without medication, the basal level at 64%. The results showed non-inferiority of montelukast when compared to fluticasone (84% vs 86.7%). Patients treated with montelukast presented more asthmatic attacks (32.2% vs 10.5%) and needed more oral steroids (17.8% vs 10.5%) than those treated with fluticasone.

Another study compared three types of drugs in 285 children between **6 and 14 years** of age with mild to moderate asthma for 48 weeks[14]. The groups were 100 mcg b.i.d fluticasone, 100 mcg fluticasone / 50 mcg salmeterol (morning) and 50 mcg salmeterol (at night) and montelukast. The primary endpoint was days with controlled asthma. The results of the group of fluticasone in monotherapy were 64.2%, combined fluticasone 59.% and montelukast 52.5%. The differences between fluticasone in monotherapy and montelukast were statistically significant.

Another trial compared montelukast with fluticasone in mild to moderate persistent asthma in 144 children between **6 and 17 years** for a 16 week period[15]. The primary endpoint was days with controlled asthma. The results of the study showed favourable significance for fluticasone, both in the primary endpoint as well as in results in pulmonary function and biomarkers. Response to fluticasone was better when basal conditions of the patients were worse (less days with controlled asthma and more use of salbutamol). A better response to montelukast was not associated with any basal characteristic. This concurs with other studies that neither have managed to identify any predictive basal characteristic of a better response to montelukast.

One observational study compared montelukast with fluticasone in 3,674 children between **4 and 17 years**[16]. The results of the study showed that children treated with montelukast suffered greater failure rates in adherence to treatment (OR = 2.55; CI95%, 2.19-2.96) and a higher number of hospital admissions due to asthma (OR = 1.99; CI95%, 1.15-3.44) when compared to children treated with fluticasone. As an observational study, no solid conclusions can be derived from it.

Antileukotrienes are not a first choice option in monotherapy. Its efficacy in mild persistent asthma is lower than inhaled corticosteroids.

Different comparative trials showing greater efficacy of inhaled corticosteroids when compared to antileukotrienes make them the elective treatment of asthma. Data available on 2 year-old children is still very limited.

Exercise-induced asma. Montelukast vs placebo.

A double-blind placebo controlled multicenter cross-over study in which 27 patients between 6 and 14 years of age participated (median = 12 years), showed with statistical significance that montelukast protected child patients against exercise induced bronchoconstriction[17].

Its use in younger children is based largely on these data, taking into account the pharmacokinetics of montelukast (rapid absorption) and the data available from adults that show a rapid appearance of effects.

In exercise-induced asthma, the treatment of choice before exercise still is short-acting beta 2 agonists.

APPROVED INDICATIONS	QUESTIONS TO CONSIDER
Monotherapy: They are an alternative to ICs in low doses in children from 2 years and in those that do not use ICs.	In what occasions can antileukotrienes be used as the elective choice in children from 2 years, instead of ICs?
Additonal therapy: Patients from 6 months. in treatment with ICs plus rescue short-acting beta 2 agonists and inadequate control.	If adequate control is not achieved, what is the better option, increasing the IC dose, or adding on an antileukotriene? When combined treatment is applied with ICs besides rescue beta 2 agonists, what option is better, adding a long-acting beta 2 agonist or an antileukotriene?
Prophylaxis in exercise-induced bronchoconstriction, from 2 years of age.	Are antileukotrienes the elective choice or are they just an alternative to the most effective elective treatment option?

Questions that can help establish the role of montelukast in pediatrics

According to the authorised indications of montelukast other questions can be posed to establish its role in therapy.

Can we predict a more beneficial response with montelukast according to the characteristics of the patient?

Monotherapy

When can antileukotrienes be employed as the first choice in treating children from 2 years of age instead of inhaled corticosteriods (IC)?

According to the product information, antileukotrienes have only proved to be an alternative to low doses of ICs. According to comparative trials antileukotrienes represent a poor alternative to ICs.

Different guidelines for the treatment of asthma (North American[18], Canadian[19], and British[20]) point out that in the case of uncontrolled asthma in patients under treatment with rescue short-acting beta 2 agonists, ICs are the recommended choice at low doses.

The use of antileukotrienes should be considered when ICs cannot be administered (difficulty to use the inhaled form, problems with oral candidiasis) or when the oral route is necessary.

Of the 2,268 children treated in Navarre with antileukotrienes in 2008, 25% were under monotherapy.

Additional therapy to inhaled corticosteroids

If adequate control is not achieved, then what would the best option be: increase corticosteroid dose or add a antileukotriene to therapy?

There is no upper limit from which it would be better to combine a new drug or continue increasing doses of ICs. We can say that, in children, with doses of budesonide of 400 mcg daily or above (or its equivalent) adverse effects are more frequent.

A randomised, blind, prospective controlled study published in 2006 compared the administration of 400 mcg inhaled budesonide with 200 mcg inhaled budesonide plus 5 mg montelukast in children with moderate persistent asthma. The trial had a follow-up of 12 weeks. There were no statistically significant differences between the 2 groups neither in pulmonary function tests (FEV1-forced expiratory volume in the first second, PEF-peak expiratory flow) nor in subjective endpoints (measured through questionnaires) at the onset, during follow-up and at the end of the trial. Children treated with montelukast plus ICs had more exacerbations than those treated with higher doses of ICs (33% vs 9.1%, $p<0.01$).

The conclusion of the authors was that in children with moderate persistent asthma, control of asthma with montelukast as add-on therapy to low dose budesonide is inferior than with a medium dose (400 mcg daily) of budesonide alone.

No dose of ICs from which combined treatment should be initiated has been established. Whenever possible it seems adequate to reach doses of 400 mcg daily of budesonide or its equivalent before adding on an antileukotriene to therapy.

What is better, adding on a long-acting beta 2 agonist to the inhaled corticosteroid or adding on an antileukotriene?

The are limited studies carried out in pediatrics that compare montelukast with long-acting beta 2 agonists in the management of persistent asthma.

In 2006, the Cochrane library updated its review on this issue[21]. The objective was to compare the efficacy and the safety profile of asthmatic patients that remained symptomatic despite the use of ICs. Controlled and randomised trials carried out in patients with recurrent asthma were considered (6-79 years) who received long-acting beta 2 agonists (salmeterol or formoterol) or an antileukotriene (montelukast or zafirlukast) combined with ICs for a minimum of 28 days. The review concluded that on adding a long-acting beta 2 agonist, there was a significantly greater protection against exacerbations (RR = 0.83; CI95%, 0.71-0.97), an improvement in pumonary function and symptoms, in the use of rescue medication, quality of life and satisfaction when compared to the antileukotriene. The risk of abandoning treatment due to any cause was significantly lower with IC plus long-acting beta 2 agonist than with IC plus antileukotriene (RR = 0.83; 95%CI, 0.73-0.95).

Although one trial included children and the majority allowed the inclusion of adolescents[3] (up to 15 years), we cannot extrapolate the conclusions of this review to children.

One study carried out in 2003[22], with 23 children between 6-15 years treated with 400 mcg daily inhaled budesonide compared the effect of adding placebo, montelukast, or salmeterol to the habitual treatment. In this trial, montelukast did not show significant differences against placebo, while salmeterol was significantly better than placebo, with regard to the FEV1.

But not all studies reach the conclusion that it is better to add on a long-acting beta 2 agonist instead of an antileukotriene[23,24]. These trials, included patients from between 14-15 years up to adult age and who were treated with 200 mcg daily fluticasone and with montelukast vs salmeterol. The authors concluded that both options presented comparable benefits, especially in the reduction of the number of exacerbations.

Another study[25] carried out with 48 children between 7 and 11 years concluded that the addition of montelukast to a 400 mcg daily dose of budosenide was more effective than the addition of a long-acting beta 2 agonist (formeterol) or a two-fold increase in the dose of budesonide to control the exhaled nitric oxide levels in the asthmatic children. Nevertheless, there were no significant differences in FEV1 between the groups, after 2 months of treatment.

If no response is observed after 2-4 weeks of treatment with the antileukotriene then the agent must be discontinued.

The British guidelines (2008) recommend adding a long-acting beta agonist as a first option in combined treatment to the standard doses of ICs in children over 5 years, and an antileukotriene in those children between 2 and 5 years. The American guidelines (2007) recommend adding a long-acting beta 2 agonist in children above 5 years of age, while in those under 5 years the guidelines do not show any preference for an antileukotriene or a long-acting beta 2 agonist as additional treatment. The Canadian guideline (2005) does not make any reference to age and considers that, if asthma remains uncontrolled despite standard doses of ICs, then either an antileukotriene or a long-acting beta agonist should be added.

It is worth pointing out that there exists great controversy in the safety issue of long-acting beta 2 agonists, not only with regard to the SMART study but also due to a meta-analysis that showed an increase in mortality related to asthma in patients that used these agents. However the increase in mortality occurred mainly in those patients treated with long-acting beta 2 agonists without ICs[26].

No clinical indicators have been found that show a better response with the use of antileukotrienes.

Data on children is very limited, and is based on studies with small samples of patients and the results obtained are contradictory. Therefore, no clear recommendations can be made.

Based on the data available from adults, when combined treatment becomes necessary, then long-acting beta 2 agonists lead to greater improvement in pulmonary function and symptoms and a reduction in exacerbations, when compared to antileukotrienes.

However despite the lower efficacy of antileukotrienes against long-acting beta 2 agonists, in combination with CIs, the former may prove safer in the long term. In any case one should not forget the association of Churg Strauss syndrome that appears rarely with antileukotrienes[27].

In children under the age of 5 years, the guidelines recommend adding an antileukotriene to medium doses of ICs before employing a long-acting beta 2 agonist.

Figure 2 shows the proportion of children treated with antileukotrienes in combination with other antiasthmatic drugs in Navarre in 2008.

Exercise-induced asthma

Are antileukotrienes the elective choice or are they an alternative to the first choice of treatment in exercise-induced asthma?

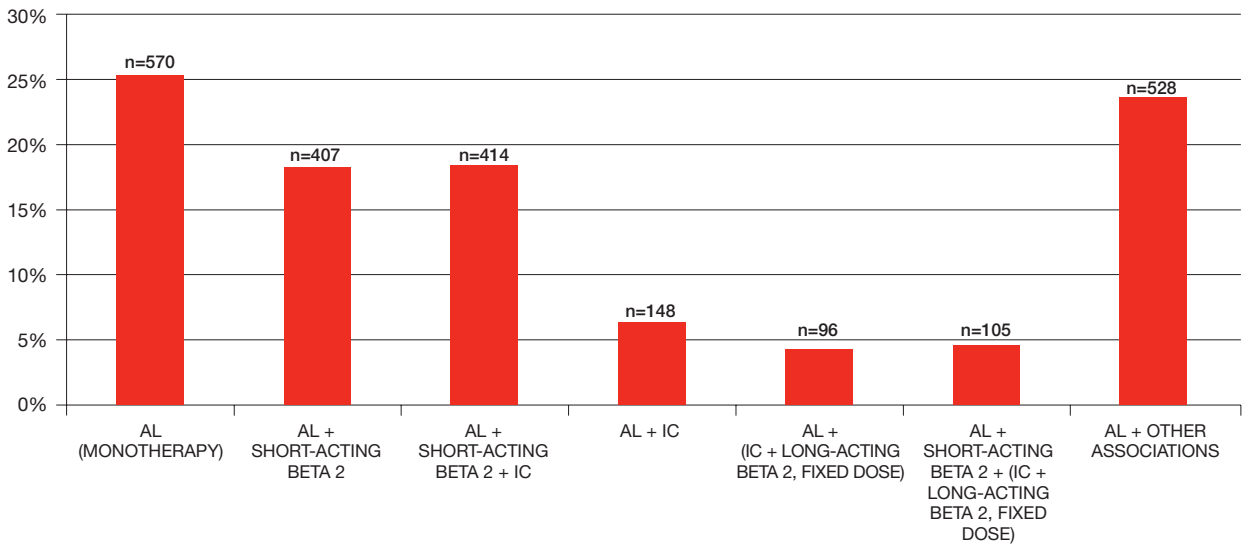
Bronchospasm induced by exercise is frequent in asthmatic children which produces certain limitations during the exercise of some physical activities in children with mild to moderate asthma. Exercise induced bronchoconstriction can be the only symptom of asthma in some people, but can also appear due to a lack of control of asthma.

Traditionally short-acting beta 2 agonists have been employed in the pre-treatment of exercise-induced asthma. Long-acting beta 2 agents are sometimes preferred to increase the duration of protection. Short-acting beta 2 agonists offer protection of up to 2 hours while long-acting agents prevent attacks for up to 12 hours.

A recent study compared treatment with salbutamol with montelukast added on to the habitual treatment in children with mild to moderate asthma[28]. The study was a prospective, randomised, cross-over, double-blind trial. Seventeen children with mild to moderate asthma between 7 and 17 years participated and treatment was randomised for 3-7 days on oral montelukast or inhaled salbutamol, 15 minutes before the onset of exercise. The authors found that the pre-treatment with inhaled salbutamol was much more effective than pre-treatment with montelukast in the prevention of bronchospasm induced by exercise, defined as a reduction of ≥15% in the FEV1 from the basal level. Moreover in this study, none of the children that received salbutamol suffered bronchospasm compared to 55% of the patients who received montelukast which presents a minimum reduction of 15% in the FEV1 after exercise.

The conclusion of the study is that the administration of short-acting beta 2 agonists such as salbutamol is significantly more effective than montelukast in the pre-treatment of patients to prevent

Figure 2. Proportion of children treated with antileukotrienes.



exercise-induced bronchospasm. The failure of montelukast to protect nearly 50% of the children with bronchospasm increases the doubts on its usefulness.

The most adequate pre-treatment of exercise-induced asthma is the use of short-acting beta 2 agonists. Antileukotrienes can represent an alternative in very small children that may have difficulty in using inhalers or in those patients in which a short-acting beta 2 agonist does not provide complete protection[1,6].

Is there any subgroup of children that responds better to the treatment options for asthma?

Not all treatments for asthma are effective in all patients and there is a heterogenous response to the different treatments, whether there are beta 2 agonists, ICs or antileukotrienes.

A study published in 2003 evaluated the characteristics of patients that are susceptible to obtain a better response to treatment with montelukast[29].

The study included patients that had participated in two randomised clinical trials with montelukast: children between **2 and 5 years** (n=689) and between **6 and 14 years** (n=336). The children were randomly distributed for montelukast and placebo and were followed up for 12 weeks (children between 2 and 5 years) and 8 weeks (children between 6 and 14 years). In both groups data was recorded on the following: age, race, sex, weight, height, family history of asthma, personal history in relation to allergens, frequency of asthmatic symtoms, eosinophilia and the concomitant use of CIs. The effect of montelukast was evaluated as follows: days without asthma, the change in forced expiratory volume in one second (FEV1), the number of asthmatic attacks and a variety of secondary symptoms.

The results of the study was that in children between 2-5 years, there was no evidence that treatment with montelukast was modified by the presence of any of the variables included in the study. The same happens in children between 6 and 14 years, in which the effect of montelukast did not produce significant changes in FEV1 according to the patients basal characteristics.

Another study evaluated the response to fluticasone vs placebo in 305 children between **12 and 47 months** with asthma[30]. The endpoints under study were days without symptoms and exacerbations according to various characteristics such as age, frequency of symptoms, family history of asthma, personal history of rhinitis or eccema and previous history of exacerbations. The authors concluded that those children with frequent symptoms, a family history of asthma or both characteristics showed a better response to fluticasone.

Different studies have shown that some clinical indicators can predict a better clinical response to ICs compared to antileukotrienes. Intra-individual analysis reveal that certain basal characteristics, such as low pulmonary function levels, greater use of bronchodilators and greater levels of exhaled nitric oxide, are related to a differentially better response to ICs than to montelukast[31].

A study carried out in 144 children between 6 and 17 years evaluated the response to montelukast or to fluticasone according to certain basal characteristics of the patient[32]. The study also evaluated whether the asthmatic patients responded to one of the medications when no response was observed with the other medication. Children with mild to moderate persistent asthma were included and were randomly distributed to one of the 2 cross-over sequence, with 8 weeks of 100 mcg fluticasone twice a day and 8 weeks of 5 or 10 mg montelukast depending on their age. This multicenter, double-blind study had a follow-up period of 18 weeks. Response was measured according to improvement in FEV1 and its relation to basal characteristics of the patient.

The result was that 17% of the patients responded to both drugs, 23% responded to fluticasone alone, 5% to montelukast alone, and 55% did not show a response to any of the drugs.

A favourable response to fluticasone alone was associated with higher levels of exhaled nitric oxide, eosinophilia and Ig E, and low levels of pulmonary function. Response to montelukast was only associated with very small children and those with a shorter duration of the asthmatic condition.

The conclusion of the authors was that the response to montelukast and to fluticasone varies considerably. Children with a low pulmonary function or high levels of allergic inflammatory markers should receive ICs. In the rest of the cases, any of the two treatments, ICs or antileukotrienes can be employed.

A study mentioned earlier by Zeiger[16] confirmed these results with other parameters of asthma management, such as days with controlled asthma, values in questionnaires of symptom control, use of salbutamol, exhaled nitric oxide and the

value of PEF in the morning. The authors concluded that the level of exhaled nitric oxide could predict more favourable clinical and pulmonary response to ICs compared to antileukotrienes. However, the measurement of exhaled nitric oxide is not accepted by all authors as an indicator of asthma control.

Efforts to determine clinical indicators of a response to antileukotrienes have not been very successful. Results from clinical trials in children between 2-14 years indicate that there are no differences in the response to montelukast with regard to age, sex or race. In general, neither were other predictive characteristics of asthma (family history of asthma, eosinophilia and personal history of allergy) predictive of any response. However, one trial has demonstrated that very small children and those with a shorter duration of disease respond to montelukast. A favourable response to ICs was observed in children with frequent symptoms, low levels of pulmonary function or a family history of asthma.

Safety

The safety profile of montelukast represents another issue to bear in mind. In general, montelukast proved safe and well tolerated in clinical trials. In 2007 however the manufacturer updated the information on montelukast by including the adverse reactions observed after its commercialisation, which included fear, depression, suicidal thoughts, anxiety and suicide. The FDA is also evaluating the safety profiles of other commercialised antileukotrienes. To do so, the FDA has since March 2008 started a study on the safety of montelukast, more specifically on its relation to suicidal thought and behaviour.

In January 2009, the FDA published a preliminary report on the issue. It pointed out that given the current evidence, no definitive recommendation could be made with regard to the adverse effects of montelukast on mood and behaviour. Thus, the FDA comments that it will continue with its analysis of the data and that a number of months will pass before any conclusion may be reached.

For the moment the FDA petitions all health professionals who employ antileukotrienes in their practice to declare any adverse effect found.

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Conclusions

Clinical trials in the child population are scarce.

In the case of antileukotrienes, the trials carried out in children are very limited, with a small number of participants and, in general, are also of low quality[33,34]. The conclusions on the use in children are often an extrapolation of data from adults.

The clinical trials have shown that the efficacy of antileukotrienes is moderate.

The current evidence indicates that antileukotrienes are not the first choice in the treatment of asthma in monotherapy. Its efficacy in persistent mild asthma is inferior to ICs. They prove to be a poor alternative to the use of low dose ICs.

In combined therapy with ICs, the evidence available in children does not permit any solid recommendation, given that the data is contradictory. In general, moderate doses of ICs are recommended (400 mcg per day of budesonide or the equivalent) before commencing combined therapy. According to British (2008) and American (2007) guidelines on the management of asthma, the first option of combined therapy with inhaled corticosteroids will depend on the age of the child: if the child is more than 5 years, the guidelines recommend adding a long-acting beta 2 agonist. If, however the child is under 5 years, the British guidelines recommend adding an antileukotriene, while the American guidelines offer, at the same level, a long-acting beta 2 agonist and an antileukotriene.

Due to its oral route of administration, some authors consider that antileukotrienes are more adequate for those asthmatic patients that have difficulties in the use of inhaled medication or patients who cannot use inhaled corticosteroids.

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