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Treating asthma: is there a place for leukotriene receptor antagonists?

Zuzana Diamant[a,*], Thys van der Molen[b,c]

[a]*Centre for Human Drug Research, Zernikedreef 10, 2333 CL Leiden, The Netherlands*
[b]*University of Groningen, Department of General Practice, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands*
[c]*University of Aberdeen, Department of General Practice, Westburn road, AB 252 AY Aberdeen, Scotland*

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Summary Asthma is a chronic disorder, characterized by airway hyperresponsiveness (AHR), airway inflammation and airway remodelling. Evidence has been provided for a relationship between pathophysiology, airway inflammation and remodelling. Moreover, these asthma features have been shown to respond to anti-inflammatory therapy. According to current guidelines, monitoring of asthma is predominantly based on symptoms and lung function data. However, these parameters appeared as poor indices for asthma control. Alternatively, asthma control relates well to exacerbations and (anamnestic) surrogate biomarkers of airway inflammation. Hence, appropriate treatment of asthma should primarily target the airway inflammation.

According to current guidelines for asthma management, anti-inflammatory therapy with inhaled corticosteroids (ICS) is the cornerstone in the treatment of persistent asthma. To further optimize asthma control, add-on therapy with long-acting β_2-agonists (LABA) or leukotriene receptor antagonists (LTRA) should be combined with low to high doses of ICS. While the first combination focuses on optimal control of symptoms and lung function, the second provides a more complete suppression of the airway inflammation.

In this paper we discuss treatment of asthma according to current guidelines versus new insights, addressing practical issues.

*Corresponding author. Tel.: +31 71 5246466; fax: +31 71 5721470.
E-mail address: z.diamant@gems.demon.nl (Z. Diamant).

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Introduction

The hallmark of asthma comprises chronic airway inflammation affecting both the large and the small airways.[1] Airway inflammation induces increased 'twitchiness' of the airways to various (a) specific stimuli, the so-called airway hyperresponsiveness (AHR), which subsequently causes the signs and symptoms of asthma.[2] Apart from this chronic inflammatory process, there are structural changes throughout the entire airway wall and beyond found already early in asthma. This process is termed 'airway remodelling' and currently there is a dilemma going on whether it is a protective or rather a detrimental process within the airways (Fig. 1).[3,4]

Treatment of asthma according to current guidelines versus new insights

Practical issues

According to current guidelines, monitoring of asthma is predominantly based on symptoms and lung function data.[5,6] However, these parameters appeared poor indices for asthma control.[7,8] Alternatively, asthma control has been shown to be related to exacerbations and surrogate biomarkers of inflammation.[8,9] A recent study comparing two management strategies in patients with mild-to-moderate persistent asthma for 12 months, showed that treatment aimed at controlling the airway inflammation yielded better asthma control reducing the frequency of severe exacerbations over 65% as compared with treatment aimed at improving symptoms and lung function only.[9] As compared with the reference group, the sputum eosinophil counts and the exhaled NO were significantly reduced and corresponded with an increased PC_{20}(methacholine) in the sputum management group.[9] Interestingly, although patients in both treatment groups had similar asthma characteristics, superior asthma control in the sputum management group was achieved at similar inhaled corticosteroids (ICS) doses.[9] These findings are in keeping with previous observations by Sont and colleagues comparing a treatment strategy aimed at improving AHR strategy with the reference strategy aimed at improving symptoms and lung function in patients with mild-to-moderate persistent asthma for 24 months.[8] As compared with the reference strategy-treated patients, those treated according to the AHR strategy had significantly lower exacerbation rates corresponding with reduced eosinophil numbers in bronchial biopsies.[8]

What are the consequences of the new insights for general practice? In general practice, only a few workers can afford the time and investment of measuring markers of airway inflammation, including exhaled nitric oxide (eNO), sputum eosinophils, or a methacholine/histamine PC_{20} for the assessment of AHR for monitoring their patients' asthma. However, there are various anamnestic indices of a worsening asthma control suggestive of increased airway inflammation, often not spontaneously brought up by patients, which may provide a useful and reliable alternative (Table 1).[10] These 'anamnestic surrogate markers of airway inflammation' can be helpful guides in the management of asthma.

This brings us to the following therapeutical issues: how can we optimize asthma control? Are there other options, apart from doubling the dose of ICS? Why is a combination of ICS and long-acting β_2-agonists (LABA) often not 'good enough'? We will discuss these topics in the view of recent clinical studies in asthma and will provide some useful background information.

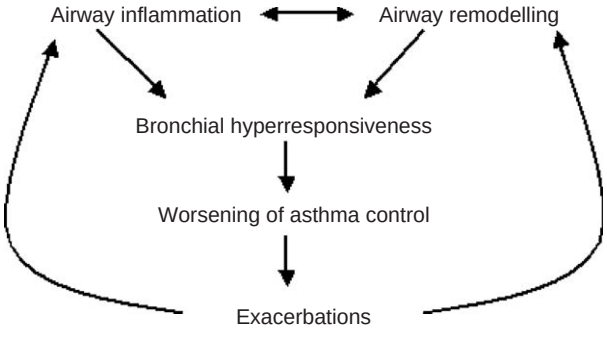

Figure 1 Relationship between the key features of asthma.

Therapeutic options to optimize asthma control

Doubling the dose of ICS

According to current guidelines, anti-inflammatory therapy with ICS represents the cornerstone of the treatment of persistent asthma.[5,6] Indeed, adequate (long-term) treatment with ICS has been shown to effectively improve several markers of airway inflammation, including asthma exacerbation rates, exhaled NO, airway eosinophils

Table 1 Anamnestic parameters related to increased AHR/airway inflammation and loss of asthma control.

Increase in asthma signs and symptoms following exposure to (a)specific stimuli (e.g. weather changes, cold, cigarette smoke, parfume, allergens, etc)
Exercise-induced bronchoconstriction
Nightly awakenings due to worsening of asthma
Increased use of rescue bronchodilators

and AHR.[8,9,11,12] However, being the case with almost all maintenance therapy, ICS may induce both local (e.g. hoarseness, candida infections of the laryngo-pharynx) and long-term use in high daily doses (adults: $>1000\,\mu g$/day; children: $>800\,\mu g$/day) even systemic side effects (e.g. osteoporosis, cataracta lentis).[13] Besides, even high doses ICS could not completely abolish all aspects of the airway inflammation in asthma.[14,15] In accordance with these findings, two recent studies failed to demonstrate the benefit of doubling the dose of ICS on the exacerbations rate in subjects with mild-to-moderate persistent asthma.[16,17] These long-term placebo-controlled studies were performed in 290 and 390 patients, respectively, with mild-to-moderate persistent asthma, during 6 and 12 months, respectively.[16,17] As compared to placebo, preventively doubling the dose of ICS in patients at risk for an exacerbation failed to affect the overall exacerbation rate in both studies.[16,17] Obviously, increasing the ICS dose per se does not offer ultimate control for every type of asthma. Hence, more potent compounds or complementary treatment modalities are needed.

Add-on therapies

The above-mentioned studies have lead to the concept of achieving optimal asthma control with the 'lowest possible' doses of ICS, applying add-on therapy in the treatment steps 3 and 4.[5,6] Presently, there are two main add-on options: (1) LABA resulting in further improvement of the airway function by potent bronchodilation or (2) leukotriene receptor antagonists (LTRA) offering complementary suppression of the airway inflammation (Table 2).[5,6,18,19] Clinical and pathophysiological implications of both add-on options will be discussed.

Add-on therapy with long-acting β_2-agonists

Most important findings from recent clinical trials

In a multi-center study in 852 patients with mild-to-moderate persistent asthma, adding a LABA (formoterol, $12\,\mu g$ b.i.d.) to a lower ICS dose (budesonide $100\,\mu g$ b.i.d.) produced a similar improvement in various asthma parameters including similar reduction in mild exacerbations rate as the four-fold higher ICS dose alone (budesonide $400\,\mu g$ b.i.d; average decrease of exacerbations of 40% and 37%, respectively).[18] However, the ultimate reduction in exacerbation rate (by on average 62%) was achieved by combining LABA (formoterol, $12\,\mu g$ b.i.d.) with the higher ICS dose (budesonide $400\,\mu g$ b.i.d).[18] Other studies have confirmed these data,[20,21] including the so-called GOAL study. In this recent multi-center study in patients with mild-to-moderate persistent asthma, (near) total asthma control was achieved adding the LABA salmeterol to half the dose of ICS.[22] Unfortunately, no surrogate markers of inflammation have been included in these or other similar studies with LABA to provide substantial pathophysiological support to the data.[18,20–22]

Mechanism of action

LABA are potent bronchodilators providing a quick, long-lasting spasmolytic effect. Although there is some evidence of reducing eosinophils and mast cells in bronchial biopsies especially when added to ICS,[23,24] LABA do not seem to possess clinically relevant anti-inflammatory properties per se (Table 2). Despite 7 days pre-treatment with salmeterol, no protective effects could be demonstrated against allergen-induced airway

Table 2 LABA versus LTRA: most important properties and effects.

Long-acting β_2-agonists (LABA)
Inhaled formulation (local activity)
Long-acting, potent bronchodilation
No clinically relevant anti-inflammatory effects
Leukotriene receptor antagonists (LTRA)
Oral compounds (systemic activity)
Anti-inflammatory effects, complementary to inhaled corticosteroids
Mild bronchodilator effects (as a result of anti-inflammatory effects)

inflammation in subjects with atopic asthma.[25] In addition, 6 weeks of treatment with this potent bronchodilator, failed to provide any improvement on parameters of airway inflammation, despite a significant improvement in symptoms and lung function in subjects with persistent asthma.[26] Hence, LABA provide instant relief of symptoms and improvement of lung function, but do not affect the underlying airway inflammation. Hence, early introduction of LABA may mask the airway inflammation.

Add-on therapy with leukotriene receptor antagonists

Background information

Cysteinyl leukotrienes (cysLTs: LTC_4, LTD_4 and LTE_4) are bronchoactive mediators, that are released within the airways following activation of asthma-related inflammatory cells and that cannot be blocked by corticosteroids.[15] These mediators play an important role in the inflammatory process of asthma [27] and in associated allergic syndromes.[28,29] Their effects are mediated through stimulation of specific CysLT-receptors that have been demonstrated within human airways.

Mechanism of action

In the 1980s, the anti-leukotrienes have been developed. The first compounds of this novel class of anti-asthma drugs have been worldwide registered in the second half of 1990s. The mechanism of action of the LTRA is based on counteracting the effects of cysLTs at their receptor site (CysLT1-receptor) within the airways. This results in a dual effect: (a) suppression of the airway inflammation and as a result (b) mild bronchodilator properties (Table 2).[27,30] Both effects are superimposed on the effects of ICS and short-acting β_2-agonists, respectively, underlining a different mechanism of action.[27,30] In several studies, LTRA have been shown to improve symptoms and lung function parameters. Moreover, they have been shown to possess bronchoprotective properties, reducing the AHR and providing partial protections against airway-narrowing stimuli including exercise, allergen and aspirin.[27,30] In addition, being oral compounds, LTRA possess systemic activity, and hence suppress the airway inflammation throughout the entire airways, even beyond the reach of inhaled formulae, including the upper and small airways. In patients with allergic rhinitis (AR) ($>50\%$ of the asthma patients suffer of AR), the combination of LTRA and an H_1-receptor antagonist was equally effective as the golden standard therapy with topical corticosteroids.[31] There is now substantial evidence of the beneficial (add-on) effects of LTRA coming from many controlled clinical trials; the most important ones will be discussed subsequently.

Clinical studies and controversies

Many studies have demonstrated improvements of asthma control following addition of an LTRA to low dose of ICS in both adults and children (management step 2).[32,33] Apart from improving symptoms and lung function, add-on therapy with LTRA particularly produced a significant reduction in asthma exacerbations and inflammation parameters. In the so-called COMPACT-study (management step 3), 12 weeks of treatment with a moderate dose of ICS (budesonide 800 μg/day) combined with the LTRA montelukast (1×10 mg) produced similar beneficial effects as doubling the ICS dose (budesonide 1600 μg/dag).[34] These beneficial effects have been demonstrated on various parameters of asthma, including symptoms, lung function parameters, nightly awakenings, and the frequency of exacerbations.[34] Moreover, both treatments have been shown to be safe, except for a higher incidence of airway infections in the budesonide 1600 μg arm.[34] In another study in 581 patients with asthma, adding montelukast to the existing dose of ICS, enabled 81% to taper off and 61% to discontinue the ICS without losing asthma control.[35] In a recent placebo-controlled study in 639 patients with mild to severe persistent asthma (management steps 2–4), adding montelukast for 16 weeks reduced the exacerbation frequency by on mean 35% irrespective of the ICS dose (400–1600 μg/day).[19] Conclusively, recent data confirm and underscore the complementary anti-inflammatory activity of LTRA in asthma.

However, there are also some studies that could not demonstrate any (additive) effects of LTRA in asthma.[36–38] In the placebo-controlled study by Robinson and colleagues, adding montelukast for 2 weeks to high doses of ICS/oral corticosteroids was obviously too short to establish any additional improvement in patients with moderate to severe persistent asthma (management steps 3 and 4).[36] Apart from the short treatment period in these patients, the disputable study design (i.e. no washout-period in a study testing anti-inflammatory therapy) could also account for the negative findings. These study bias have been reported in

the accompanying editorial.[39] Two other studies by Fish and Nelson, respectively,[37,38] which are in fact identical, compared the bronchodilator effects of the combination anti-inflammatory therapy/long-acting bronchodilator (ICS/LABA) with that of a combination of two anti-inflammatory compounds (ICS/LTRA).[37,38] Hence, taking into account the mechanisms of action of all compounds tested, the results of both studies could already be foretold, especially in an asthmatic population with a reversible lung function (reversibility $>12\%$). Interesting, however, are the results of two other studies comparing the effects of the same combinations on different outcome parameters of asthma.[40,41] In the first study, both combinations appeared equally effective in improving symptoms and lung function in patients with mild-to-moderate persistent asthma.[40] However, the combination ICS/LTRA showed superior effectiveness in suppressing inflammation both within the airways and in peripheral blood.[40] Similar results were reported in a study in 1490 patients with mild-to-moderate persistent asthma in whom the effect of both combinations during 48 weeks have been tested on symptoms, lung function parameters, exacerbation rate and peripheral eosinophils.[41] Both combinations showed similar effectiveness in preventing asthma exacerbations. However, this appeared to be achieved through different mechanisms of action: ICS/LABA mainly improved symptoms and lung function, whereas ICS/LTRA appeared superior in suppressing features of inflammation.[41]

Adverse events

Although in the past 8 years, LTRA have already been prescribed to over 25 million patients with asthma worldwide, including 6,4 million young children, only few adverse events related to their use have been reported. The majority of the reported adverse events have been described as 'mild' and present as headache, gastro-intestinal discomfort, and in the very young children as thirst (Table 3). Rumours about a possible relationship between LTRA and the occurrence of Churg-Strauss Syndrome could be refuted. This syndrome has been shown to become manifest in patients in whom (very) high doses of (inhaled) corticosteroids could be stopped while using LTRA.[42] In all reported cases, the Churg-Strauss Syndrome appeared to be pre-existent and relapsed due to withdrawal of the corticosteroids.[42] As is the case with all novel systemic therapy, we should always remain alert towards potential new adverse events at all times.

What add-on therapy should be applied, when and why?

In the past years, many studies and reports have addressed the so-called therapeutic step (2)-3-dilemma i.e. should we (first) add an LABA or an LTRA to the ICS? The results of the most important randomized clinical trials are summarized in Table 4 and have been discussed previously. Given the different mechanisms of action of LABA and LTRA, the choice in fact means: 'optimising the lung function' or 'optimising the airway inflammation suppression'. It does not come as a surprise, that the combination ICS/LABA mainly produces complementary improvement of lung function, whereas the combination ICS/LTRA predominantly results in complementary suppression of inflammation. Table 5 summarizes the recommended use of LTRA in asthma according to GINA[5].

Conclusions and recommendations

According to current guidelines, optimal treatment of persistent asthma consists of adequate suppression of the airway inflammation.[5,6] The ICS are the cornerstone in the treatment of persistent asthma in the lowest possible, effective dose.[5,6] Based on recent controlled studies in asthma, add-on therapy to low/middle doses of ICS has proved to be at least as effective as doubling the dose of ICS (Table 5).[18,41] Currently, there are two main options for add-on therapy in steps (2)-4 in asthma: LABA and ICS either separately or in one device, or the combination of oral leukotriene receptor antagonists (LTRA) and ICS.[5,6] Although both combinations have produced comparable improvement of various asthma parameters, including symptoms and exacerbation rates, both combinations achieve this in a different manner. While the combination ICS/LABA focuses on improving the lung function, ICS/LTRA's main objective is complementary suppression of the airway inflammation. These differences in effects result from a different mechanism of action: bronchodilator versus bronchoprotective cq. anti-inflammatory effect and local versus systemic activity (Table 2).

Table 3 Adverse events related to LTRA.

Head ache
Gastro-intestinal dyscomfort
Thirst (in the ages of 2–5 years)

Table 4 Therapeutic step 3-dilemma: ICS/LABA versus ICS/LTRA.

Asthma severity	Combination therapy	Outcome parameters	Best combination	[References]
Mild-moder.	ICS*/LABA	Symptom scores	ICS/LABA	[37]
Persistent ($n = 948$)	vs. ICS*/LTRA	Lung function	ICS/LABA	
Mild-moder.	ICS**/LABA	Symptom scores	ICS/LABA	[38]
Persistent ($n = 447$)	vs. ICS**/LTRA	Lung function	ICS/LABA	
Mild-moder.	ICS†/LABA	Exacerbations	Both	[41]
Persistent ($n = 1490$)	vs. ICS†/LTRA	Blood eosinophils	ICS/LTRA	
		Symptom scores	Both	
		Lung function	ICS/LABA	
Moderate	ICS‡/LABA	symptom scores	Both	[40]
Persistent ($n = 20$)	vs. ICS‡/LTRA	Lung function	Both	
		Airway inflammation	ICS/LTRA	

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LTRA, leukotriene receptor agonists.
*Doses ICS: low-middle doses ICS.
**Doses ICS: low-high doses ICS.
†Doses ICS: low doses ICS.
‡Doses ICS: low-middle doses ICS.

Table 5 Recommended use of LTRA in asthma (adults and children) according to GINA.

Step 1:	as monotherapy in mainly exercise-induced bronchoconstriction
Step 2:	add-on to low dose of ICS
Step 3:	add-on to middle dose of ICS
Step 4:	add-on to high dose of ICS

Hence, to make the right choice between both add-on therapies, one needs to ask oneself the following questions: First, 'do I want to achieve a better asthma control, and how will I do this?' And second, 'is my primary goal complementary suppression of the airway inflammation or do I mainly aim for improving the lung function?' Although in the daily practice monitoring of the airway inflammation/hyperresponsiveness is often impossible, some anamnestic indices may provide a usuful guide to adequate asthma control (Table 1). Nevertheless, in patients with persistent asthma in whom active airway inflammation is the main issue, treatment should primarily focus on supressing the airway inflammation, which implicates that LTRA should be added to their ICS (Tables 2 and 4). These patients can be identified by their increased airway responsiveness to (a)specific irritants, increased asthma complaints during exercise, nightly awakenings, etc (Table 1). All these complaints are suggestive of an increased airway responsiveness caused by active airway inflammation. Should we first add a LABA, we will encounter a considerable improvement of symptoms and lung function that in fact will mask the underlying airway inflammation. However, in some cases (steps 3 and 4), optimal asthma control may be achieved by combining all treatment modalities. Future studies should confirm this option.

Summary

Asthma is a chronic inflammatory disorder of the airways. Hence, asthma management focuses on suppressing the airway inflammation by (1) prevention, i.e. avoiding a(specific) irritants and (2) anti-inflammatory therapy. Inhaled corticosteroids (ICS) are the cornerstone in the treatment of persistent asthma, and the lowest possible, effective dose of ICS should be applied. To this end, current guidelines advocate the use of add-on therapy in management steps (2), 3 and 4. Currently, there are 2 main options for add-on therapy: long-acting β_2-agonists (LABA) and leukotriene receptor antagonists (LTRA), both having a different mechanism of action. LABA come as an inhaled formula and produce potent, longstanding bronchodilation (without anti-inflammatory properties), while LTRA are oral compounds, and hence act systemically, possessing mainly anti-inflammatory effects. Based on recent, controlled trials in asthma, we have made an attempt to explain why optimising the suppression of airway inflammation should precede optimising the lung function in patients with persistent asthma.

References

1. Busse WW. Inflammation in asthma: the cornerstone of the disease and target of therapy. *J Allergy Clin Immunol* 1998;**102**:S17–22.
2. Boulet LP. Physiopathology of airway hyperresponsiveness. *Curr Allergy Asthma Rep* 2003;**3**:166–71.
3. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 2001;**164**:S28–38.
4. McParland BE, Macklem PT, Pare PD. Airway wall remodeling: friend or foe? *J Appl Physiol* 2003;**95**:426–34.
5. Global initiative for asthma: global strategy for asthma management and prevention. *NHBLI/WHO workshop*, NIH Publication; 1998, 2002.
6. British Thoracic Society guidelines for asthma. *Thorax* 2003;**58**(Suppl I):i1–i94.
7. Teeter JG, Bleecker ER. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. *Chest* 1998;**113**:272–7.
8. Sont JK, Willems LN, Bel EH, et al. Clinical control and histopathological outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL study group. *Am J Respir Crit Care Med* 1999;**159**:1043–51.
9. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;**360**:1715–21.
10. Bjermer L. History and future perspectives of treating asthma as a systemic and small airways disease. *Respir Med* 2001;**95**:703–19.
11. Ward C, Pais M, Bish R, Reid D, Feltis B, Johns D, Walters EH. Airway inflammation, basement membrane thickening and bronchial hyperresponsiveness in asthma. *Thorax* 2002;**57**: 309–16.
12. Kharitonov SA, Barnes PJ. Nitric oxide in exhaled air is a new marker of airway inflammation. *Monaldi Arch Chest Dis* 1996;**51**:533–7.
13. Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefler SJ. Inhaled corticosteroids: past lessons and future issues. *J Allergy Clin Immunol* 2003;**112**:S1–40.
14. Louis R, Lau LCK, Bron AO, Roldaan AC, Radermecker M, Djukanovic R. The relationship between airways inflammation and asthma severity. *Am J Resp Crit Care Med* 2000;**161**:9–16.
15. Dworski R, Fitzgerald GA, Oates JA, et al. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am J Respir Crit Care Med* 1994;**149**:953–9.
16. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Canadian asthma exacerbation study group. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;**59**:550–6.
17. Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomised controlled trial. *Lancet* 2004;**363**:271–5.
18. Pauwels RA, Löfdahl C-G, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formeterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;**337**:1405–11.
19. Vaquerizo MJ, Casan P, Casatillo J, Perpina M, Sanchis J, Sobradillo V, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;**58**:204–10.
20. Lemanske RF, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol. *J Am Med Assoc* 2001;**285**:2594–603.
21. O'Byrne PM, Barnes PJ, Rodriquez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;**164**: 1392–7.
22. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. (GOAL Investigaters Group). Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control Study. *AM J Respir Crit Care Med* 2004;**170**(8):836–44.
23. Wallin A, Sandstrom T, Cioppa GD, Holgate S, Wilson S. The effects of regular inhaled formoterol and budesonide on preformed Th-2 cytokines in mild asthmatics. *Respir Med* 2002;**96**:1021–5.
24. Wallin A, Sue-Chu M, Bjermer L, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol* 2003; **112**:72–8.
25. Calhoun WJ, Hinton KL, Kratzenberg JJ. The effect of salmeterol on markers of airway inflammation following segmental allergen challenge. *Am J Respir Crit Care Med* 2001;**163**:881–6.
26. Roberts JA, Bradding P, Britten KM, et al. The long-acting beta2-agonist salmeterol xinafoate: effects on airway inflammation in asthma. *Eur Respir J* 1999;**14**: 275–82.
27. Diamant Z, Sampson AP. Anti-inflammatory mechanisms of leukotriene modulators. *Clin Exp Allergy* 1999;**29**:1449–53.
28. Howarth PH. Leukotrienes in rhinitis. *Am J Respir Crit Care Med* 2000;**161**:s133–6.
29. Fauler J, Neumann Ch, Tsikas D, et al. Enhanced synthesis of cysteinyl leukotrienes in atopic dermatitis. *Br J Dermatol* 1993;**128**:627–30.
30. Sampson AP, Pizzichini E, Bisgaard H. Effect of cysteinyl leukotrienes and leukotriene receptor antagonists on markers of inflammation. *J Allergy Clin Immunol* 2003;**111**: S49–61.
31. Wilson AM, Orr LC, Sims EJ, et al. Antiasthmatic effects of mediator blockade versus topical cotricosteroids in allergic rhinitis and asthma. *Am J Respir Crit Care Med* 2000; **162**:1297–301.
32. Laviolette M, Malmstrom K, Lu S, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;**160**:1862–8.
33. Simons FE, Villa JR, Lee BW, Teper AM, Lyttle B, Aristizabal G, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr* 2001;**138**:694–8.
34. Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;**58**:211–6.
35. Price DB, Rouleau MY, Fletcher CP, et al. Use of montelukast in tapering inhaled corticosteroid therapy: an open-label 48-week trial. *Curr Ther Res* 2001;**62**:743–55.
36. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001;**357**:2001–11.
37. Fish JE, Israel E, Murray JJ, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest* 2001;**120**:423–30.

38. Nelson HS, Busse WW, Kerwin E, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *J Allergy Clin Immunol* 2000;**106**: 1088–95.
39. Pavord ID, editor. *Leukotriene antagonists and symptom control in chronic persistent asthma. Editorial. Lancet* 2001;**357**:1991–2.
40. Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. Evaluation of salmeterol or montelukast as second-line therapy for asthma not controlled with inhaled corticosteroids. *Chest* 2001; **119**:1021–6.
41. Bjermer L, Bisgaard H, Bousquet J, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *Thorax* 2003;**327**:891–5.
42. Kemp JP. Recent advances in the management of asthma using leukotriene modifiers. *Am J Respir Med* 2003;**2**: 139–56.