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

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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 β2-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.

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Introduction

The hallmark of asthma comprises chronic airway inflammation affecting both the large and the small airways. 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. 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).

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. However, these parameters appeared poor indices for asthma control. Alternatively, asthma control has been shown to be related to exacerbations and surrogate biomarkers of inflammation. 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. As compared with the reference group, the sputum eosinophil counts and the exhaled NO were significantly reduced and corresponded with an increased PC20(methacholine) in the sputum management group. 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. 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. 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.

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 PC20 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). These ‘anamnestic surrogate markers of airway inflammation’ can be helpful guides in the management of asthma.

This brings us to the following therapeutic 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 β2-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.

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. 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
and AHR. 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: \(1000\) mg/day; children: \(800\) mg/day) even systemic side effects (e.g. osteoporosis, cataracta lentis). Besides, even high doses ICS could not completely abolish all aspects of the airway inflammation in asthma. In accordance with these findings, two recent studies failed to demonstrate the benefit of doubling the dose of ICS on the exacerbation rate in subjects with mild-to-moderate persistent asthma. 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. 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. 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. 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).

#### 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, perfume, allergens, etc) |
| Exercise-induced bronchoconstriction |
| Nightly awakenings due to worsening of asthma |
| Increased use of rescue bronchodilators |

#### Table 2

**LABA versus LTRA: Most important properties and effects.**

| Long-acting \(\beta_2\)-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) |

**Add-on therapy with long-acting \(\beta_2\)-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 µg b.i.d.) to a lower ICS dose (budesonide 100 µg 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 µg b.i.d; average decrease of exacerbations of 40% and 37%, respectively). However, the ultimate reduction in exacerbation rate (by on average 62%) was achieved by combining LABA (formoterol, 12 µg b.i.d.) with the higher ICS dose (budesonide 400 µg b.i.d.). Other studies have confirmed these data, 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. 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.

**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, 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 inflammation.

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. 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). Clinical and pathophysiological implications of both add-on options will be discussed.
inflammation in subjects with atopic asthma. 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. 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: LTC4, LTD4 and LTE4) are bronchoactive mediators, that are released within the airways following activation of asthma-related inflammatory cells and that cannot be blocked by corticosteroids. These mediators play an important role in the inflammatory process of asthma and in associated allergic syndromes. 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). Both effects are superimposed on the effects of ICS and short-acting β2-agonists, respectively, underlining a different mechanism of action. 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. 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 H1-receptor antagonist was equally effective as the golden standard therapy with topical corticosteroids. 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). 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). These beneficial effects have been demonstrated on various parameters of asthma, including symptoms, lung function parameters, nightly awakenings, and the frequency of exacerbations. Moreover, both treatments have been shown to be safe, except for a higher incidence of airway infections in the budesonide 1600 µg/dag arm. 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. 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). 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. 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). 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 had 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 GINA5.

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>
<thead>
<tr>
<th>Table 3</th>
<th>Adverse events related to LTRA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head ache</td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal dyscomfort</td>
<td></td>
</tr>
<tr>
<td>Thirst (in the ages of 2–5 years)</td>
<td></td>
</tr>
</tbody>
</table>
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 useful 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 suppressing 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 \(\beta_2\)-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.

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

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th>Combination therapy</th>
<th>Outcome parameters</th>
<th>Best combination</th>
<th>[References]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moder.</td>
<td>ICS(^*)/LABA</td>
<td>Symptom scores</td>
<td>ICS/LABA</td>
<td>[37]</td>
</tr>
<tr>
<td>Persistent ((n = 948)) vs. ICS/LTRA</td>
<td>Lung function</td>
<td>ICS/LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moder.</td>
<td>ICS(^*)/LABA</td>
<td>Symptom scores</td>
<td>ICS/LABA</td>
<td>[38]</td>
</tr>
<tr>
<td>Persistent ((n = 447)) vs. ICS(**)/LTRA</td>
<td>Lung function</td>
<td>ICS/LABA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moder.</td>
<td>ICS(^1)/LABA</td>
<td>Exacerbations</td>
<td>Both</td>
<td>[41]</td>
</tr>
<tr>
<td>Persistent ((n = 1490)) vs. ICS(^1)/LTRA</td>
<td>Blood eosinophils</td>
<td>ICS/LTRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent ((n = 20)) vs. ICS(^1)/LTRA</td>
<td>Symptom scores</td>
<td>Both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent ((n = 20)) vs. ICS(^1)/LTRA</td>
<td>Lung function</td>
<td>Both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent ((n = 20)) vs. ICS(^1)/LTRA</td>
<td>Airway inflammation</td>
<td>Both</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroids; LABA, long-acting \(\beta_2\)-agonists; LTRA, leukotriene receptor agonists.

\(^*\)Doses ICS: low-middle doses ICS.

\(^**\)Doses ICS: low-high doses ICS.

\(^1\)Doses ICS: low doses ICS.

\(^2\)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 |

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References


