EDITORIAL

Which patients with asthma could benefit from using anti-leukotriene drugs: an evidence based review

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Asthma is characterized by airway inflammation, bronchial hyperresponsiveness and airway obstruction. Many mediators and cytokines have been found involved in the pathogenesis of asthma. Leuktrienes are produced via the 5-lipoxygenase pathway of arachidonic acid metabolism. Monocytes, alveolar macrophages, and peripheral blood neutrophils preferentially generate leukotriene B4 (LTB_4), whereas eosinophils, mast cells and basophils preferentially generate the cysteinyl leukotrienes (CysLTs) (LTC_4, LTD_4 and LTE_4).[1]

The CysLTs have been strongly implicated in the pathogenesis of asthma and allergic rhinitis. They are potent bronchoconstrictors and have many proinflammatory effects, such as the recruitment and activation of eosinophils, increased vascular permeability and stimulation of airway mucus secretion.[2]

The CysLTs bind to the leukotriene receptors CysLT1 and CysLT2. Most of the actions of the CysLTs are believed to be mediated through the CysLT1 receptor. The advent of the leukotriene modifiers including the CysLT1 receptor antagonists provided a relative new class of antiasthma drugs.[3] Their exact place in the treatment of asthma has been gradually evolving in the past years. They are now explicitly considered in the international guidelines on the diagnosis and treatment of asthma. In the present review, the place of antileukotrienes in the treatment of asthma in adults is shortly reviewed and the results of a recently published systematic review on the role of the CysLT1 receptor antagonist montelukast as add-on therapy to inhaled corticosteroids are commented upon.

Use of leukotriene modifiers in the treatment of asthma The leukotriene modifiers include the CysLT1-receptor antagonists montelukast, pranlukast and zafirlukast and the 5-lipoxygenase inhibitor zileuton. Clinical trials with these drugs have demonstrated a small and variable bronchodilator effect, reduced symptoms, improved lung function, reduced airway inflammation and asthma exacerbations (TABLE 1).[4]

The leukotriene modifiers are now one of the controller medications that can be used in the treatment of asthma. It is of interest to note that leukotriene modifiers are especially effective in clinical models of allergen-induced airway changes, and in patients with exercise-induced bronchoconstriction or aspirin-sensitive asthma.[5-7] Leukotriene modifiers have been used as an alternative to inhaled steroids in the treatment of adult patients with mild persistent asthma. In clinical trials they were found to have an antiasthmatic effect comparable to that of a low dose of inhaled steroids (i.e. 200–400 µg beclomethasone).[1,8] A possible advantage is that these drugs are given orally and that they have additional effects on allergic rhinitis, a disease that is very frequently associated with asthma. Leukotriene modifiers can also be used as add-on therapy to inhaled steroids: in this situation they may reduce the dose of inhaled steroids required by patients with moderate to severe asthma and they may improve control in those patients whose asthma is not controlled with low or high doses of inhaled steroids.[4] The place of the leukotriene modifiers in the treatment of asthma according to the 2006 GINA guidelines is summarized in TABLE 2.

Montelukast as add-on therapy to inhaled corticosteroids in the treatment of mild to moderate asthma: a systematic review Many clinical trials have shown CysLT1 receptor antagonists to be effective in asthma therapy. As inhaled corticosteroids (ICS) are more effective in reducing asthma

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TABLE 1 Summary of the antiasthmatic effect of leukotriene receptor antagonists

Prevention of bronchoconstriction induced
1 by allergen
2 by exercise and cold air
3 by aspirin and other non-steroidal antiinflammatory drugs
Treatment of chronic asthma
1 short-term: bronchodilator effect
2 improvement of lung function in persistent asthma
3 lower use of rescue bronchodilators and lowering of symptom scores
4 reduced exacerbations
5 antiinflammatory effects (including reduction of the amount of eosinophils in peripheral blood and induced sputum)

TABLE 2 Place of leukotriene modifiers in the treatment of adult asthma, according to the 2006 GINA guidelines[a]

STEP 1: as-needed reliever medication
STEP 2: reliever medication + 1 controller
leukotriene modifiers are an alternative to low-dose inhaled steroids
they are particularly appropriate for patients who are unable or unwilling to use inhaled steroids, or who experience intolerable side effects, such as persistent hoarseness from inhaled steroid treatment and those with concomitant allergic rhinitis
STEP 3: reliever medication + 1 or 2 controllers
the add-on to low-dose inhaled steroids is one of the alternatives for low-dose inhaled steroids + long-acting β_2-agonists
STEP 4: reliever medication + ≥2 controllers
possible add-on to medium-to high-dose inhaled steroids + long acting β_2-agonists or to medium-or-high dose of inhaled corticosteroids
STEP 5: reliever medication + additional controller options

a The highlighted option is also highlighted in GINA material (GINA 2006)

exacerbations, they remain the first choice in asthma management. The efficacy of CysLT1 receptor antagonists as add-on therapy to ICS was evaluated in two relative recent Cochrane Reviews: they were found to be active in this setting, but less than long acting β_2-agonists.[9,10]

Montelukast is the most widely prescribed CysLT1 receptor antagonist. In a systematic review published by S. Joos et al. from the Department of General Practice and Health Services Research of the University of Heidelberg, an evaluation was done of the studies investigating add-on therapy with montelukast in patients with asthma who remained symptomatic on inhaled steroids[11] (http://www.iqwig.de accessed on 25 October 2008). The authors retrieved 13 studies meeting all of the inclusion criteria: investigation of montelukast as add-on therapy to inhaled corticosteroids (ICS) in adults and adolescents (≥12 years) with mild to moderate asthma and language of the publication (English, German, Dutch, French, Spanish or Portugese). The studies had to evaluate at least one of the predefined outcomes: asthma symptoms, exacerbations with or without emergency treatment, hospitalization and/or outpatient treatment, adverse events, activities of daily living, disease related quality of life, treatment satisfaction, physical capacity, asthma related mortality and total mortality. It is of importance to note that, in contrast to the previous Cochrane reviews, in this systematic review short-term trials with duration of less than 12 weeks were excluded.

Overall the findings of this systematic review indicate that montelukast/ICS was clinically more effective than ICS monotherapy. The combination montelukast/ICS was however clinically less effective than the combination salmeterol/ICS in the 12 week trials. A separate analysis of active controlled 48 week trials showed comparable proportions for patients with at least 1 exacerbation in both groups.

Conclusion Antileukotriene drugs are now considered as an alternative to low dose of inhaled steroids in step 2 and as an alternative to long acting β_2-agonists for add-on to inhaled corticosteroids in step 3 and 4 of the GINA guidelines. The systematic review reported by S. Joos et al. from Heidelberg underscore the value of montelukast in the step 3 and 4 of the 2006 guidelines. As the contribution of different asthma mechanisms (inflammation and bronchial hyperresponsiveness) differs among different patients (or in individual patient over time) benefit of any drug in an individual patients may differ as well and individualized therapy is frequently needed.[12]

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