LEUKOTRIENE RECEPTOR ANTAGONISTS FOR THE TREATMENT OF ASTHMA

The Ontario Public Drug Programs (OPDP) and its expert advisory committee, the Committee to Evaluate Drugs (CED), recently re-evaluated the funding of leukotriene receptor antagonists for the treatment of asthma. Leukotriene receptor antagonists are drugs indicated for long-term asthma control and exacerbation prevention. This class of drugs includes montelukast (Singulair®) and zafirlukast (Accolate®). As a result of this review, the funding criteria for montelukast and zafirlukast have been revised.

Key Points

- **I nhaled corticosteroids are the most effective preventative therapy for persistent asthma in adults and children.**

- **For patients whose asthma is uncontrolled with an inhaled corticosteroid alone, the addition of a long-acting beta2-agonist is more effective than the addition of a leukotriene receptor antagonist.**

- **For adult patients whose asthma is poorly controlled despite treatment with an inhaled corticosteroid and a long-acting beta2-agonist, current evidence indicates that the addition of a leukotriene receptor antagonist is no better than placebo.**

- **In children who continue to experience asthma symptoms while on a low-dose inhaled corticosteroid alone, effective step-up treatment strategies include the addition of a long-acting beta2-agonist, the addition of a leukotriene receptor antagonist, or increasing the inhaled corticosteroid dose. Among these three options, add-on treatment with a long-acting beta2-agonist provides the highest likelihood of best response.**

- **Monitoring, patient education, and treatment adherence are integral components in the management of asthma. For example, any patient whose asthma is not responding well should have their medication inhalation technique checked.**

New Funding Criteria

Montelukast (Singulair®) 4mg tablet will continue to be listed on the Ontario Drug Benefit Formulary as a Limited Use benefit for the treatment of asthma in patients aged 2-5 years old.

Montelukast (Singulair®) 5mg and 10mg tablets and zafirlukast (Accolate®) 20mg tablet are now funded through the Exceptional Access Program (EAP) for the following groups of patients:

- For those asthma patients who cannot manage the use of an inhalation device despite assistance with a spacer (e.g. physically or mentally disabled patients or pediatric patients).

  OR

- For children and adolescents whose asthma cannot be controlled on inhaled corticosteroids alone and whose asthma remains uncontrolled despite using full dose inhaled corticosteroids with the addition of a long-acting beta2-agonist, and with assurance of good adherence and inhaler technique.

Information on the Exceptional Access Program (EAP) and details of the EAP criteria for leukotriene receptor antagonists can be found at:

http://www.health.gov.on.ca/english/providers/program/drugs/eap_mn.html

and

http://www.health.gov.on.ca/english/providers/program/drugs/pdf/frequently_requested_drugs.pdf

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CED Findings

1. **Inhaled corticosteroids (ICS) are the most effective preventative therapy for persistent asthma in both adults and children.**

   Available evidence clearly demonstrates that ICS are the preferred first-line treatment for persistent asthma.

   Results from published studies indicate that ICS are more effective than leukotriene receptor antagonists (LTRA) for first-line monotherapy of persistent asthma. Findings from a high quality systematic review comparing LTRA to ICS as first-line asthma therapy demonstrated that ICS were superior to LTRA for preventing asthma exacerbations, and for improving lung function, night awakenings, rescue medication use, symptom control and quality of life.\(^1\) The systematic review found no difference in the risk of side effects between ICS and LTRA.

   Moreover, a randomized controlled study showed that step-down to a LTRA from an ICS may result in a higher risk of treatment failure.\(^2\)

   **Children**

   The use of ICS as the preferred first-line treatment in both adults and children of all ages is well supported by clinical evidence.\(^3\) A recent study in children ages 6-14 years old with mild to moderate persistent asthma showed that ICS were superior to LTRA with respect to all measures of asthma control (e.g. asthma control days, exacerbation rate, and pulmonary function).\(^4\) Growth over the study duration of 48 weeks was not significantly different between the study group on ICS and the group on LTRA.

   A common concern with the use of ICS in children is its effect on growth. It is important to note that children treated with ICS attain normal adult height but at a later age, while uncontrolled or severe asthma adversely affects growth and final adult height.\(^3\)

2. **In patients whose asthma is inadequately controlled on ICS alone, the addition of a long-acting beta\(_2\)-agonist (LABA) is superior to the addition of a LTRA.**

   In patients whose asthma is not controlled on ICS monotherapy, findings from a good quality systematic review showed that the addition of a LABA provided greater improvement in exacerbation rates, lung function, symptom control, use of rescue medication, quality of life and patient satisfaction as compared to the addition of a LTRA.\(^5\) The systematic review also found that withdrawals of treatment due to adverse events were not significantly different between patients who received add-on therapy with LABA and those who received add-on with LTRA.

3. **For adult patients whose asthma is poorly controlled despite treatment with ICS and LABA, current evidence indicates that add-on therapy with LTRA is no better than placebo.**

   A large, rigorous clinical study in patients 15 years or older with poorly controlled asthma despite ICS monotherapy or combination ICS plus LABA found that add-on therapy with LTRA were no better than placebo at improving the rate of poor asthma control, asthma symptoms or quality of life.\(^6\)
4. In children who continue to experience asthma symptoms while on low-dose ICS alone, effective step-up treatment strategies include the addition of a LABA, the addition of a LTRA, or increasing the ICS dose. Among these three options, add-on treatment with a LABA provides the highest likelihood of a best response.

Three step-up regimens were evaluated in a clinical trial for children and adolescents (6-17 years old) whose asthma was poorly controlled on low-dose ICS alone. The three treatment strategies included: 1) increasing the dose of ICS; 2) adding LABA to ICS; and 3) adding LTRA to ICS. The study reported that the addition of a LABA was much more likely to provide a best response compared with the other two interventions. However, a significant minority of children had a best response with the addition of a LTRA or by increasing the ICS dose. These findings indicate that there is a subgroup of children who respond particularly well to LTRA step-up therapy. The study found no predictors for LTRA response.

5. Monitoring, patient education, and treatment adherence are integral components in the management of asthma.

One of the most common reasons for a poor response to asthma therapy is non-adherence to treatment, including using medication inhalers improperly. The reported rates of non-adherence to asthma medication regimens range from 30-70%. Patients should be assessed for asthma control, medication technique and treatment adherence at regular intervals. Education has been shown to increase treatment adherence and improve important clinical outcomes in patients with asthma.

6. Role of LTRA in specific patient subgroups

Although LTRA has been shown to be effective against placebo in certain patient subgroups (e.g. patients with concomitant allergic rhinitis, aspirin-intolerant asthma, and exercise-induced asthma), direct head-to-head comparison studies against alternative treatments are lacking to establish the relative place in therapy of LTRA in these conditions.

REFERENCES:
1. Ducharme et al. Antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database of Systematic Reviews 2004; (1): CD002314.