Title: Leukotriene Receptor Antagonist (LTRA) for Asthma

Date: April 12, 2007

Context and policy issues:
Asthma is a chronic airways condition with symptoms varying from person to person and episode to episode. More than two million Canadians (over 12-year) have asthma and one in ten Canadian children have been diagnosed with asthma. Asthma is the most common chronic respiratory disease for Canadian adults and children, resulting in significant economic burden due to its associated hospitalization and clinical visits.

Pharmacotherapy is important part of the asthma management, where two groups of medications, relievers and controllers, are often used. The relievers are only for the symptomatic relief of intermittent asthma and should not be used on a regular basis while the controllers are administered regularly for long term asthma control and exacerbations prevention.

Leukotriene receptor antagonists (LTRA) are asthma controllers. It is seen as an alternative to inhaled corticosteroids (ICS) which are the mainstay of asthma maintenance therapy. There is evidence of superiority of LTRA over placebo in persistent asthma but compared with moderate-dose ICS. LTRA monotherapy did not show significant benefit. Besides LTRA, there are several other asthma controller medicines available, such as long-acting β₂–agonists (LABA) and theophylline.

The Canadian Asthma Consensus Reports published in 1999 and 2003 consistently recommended ICS as the first-line maintenance therapy. LTRA will be alternative to ICS only when patients who can not or will not use ICS. As add-on therapy, LTRA may be considered when asthma is not optimally controlled with moderate doses of ICSs after reassessing compliance, control of environment and diagnosis.
Since the Canadian recommendation was updated in 2003, increasing new evidence regarding LTRA and other controllers are available now. The purpose of this report is to identify these new evidences and provide a brief summary of them.

**Research questions:**
What is the clinical effectiveness of leukotriene receptor antagonists for the treatment of patients with asthma compared to LABA, inhaled corticosteroids, theophylline and placebo?

**Methods:**
A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results included RCTs between 2005 and the present, HTAs, systematic reviews and meta-analyses published between 2002 and the present, and were limited to English language publications only.

**Summary of findings:**
Our literature search resulted in 172 citations. Additional documents were located through grey literature sources. Abstract screening identified 31 randomized controlled trials (RCTs) and 8 reviews potentially relevant to our research question. These were reviewed in full text. At the end, five systematic reviews and twenty two RCTs were included in this report.

**Systematic reviews**

There are five systematic reviews identified:

- The latest Cochrane review by Ducharme et al in 2006, included 15 RCTs published up to March 2006, and compared LTRA+ICS with LABA+ICS for chronic asthma. The combined result showed that risk of exacerbations requiring systematic corticosteroids was significantly higher with LTRA+ICS. Patients receiving LABA+ICS also exhibited better outcomes compared to those receiving LTRA+ICS in terms of morning/evening PEFR, rescue-free days, symptom-free days, rescue $\beta_2$-agonists, quality of life, symptom score, night awakenings and patient satisfaction. The LTRA+ICS treatment resulted in a higher risk of withdrawals due to any reason. However, withdrawals due to specific reason such as adverse events, or poor asthma control, hospitalization, osteopenia, serious adverse events, overall adverse events, headache or cardiovascular events were similar between the two comparator groups. Overall, the review concluded that in asthmatic adults inadequately controlled on low doses of ICS, the addition of LABA is superior to addition of LTRA for preventing exacerbations requiring systematic steroids, and for improving lung function, symptoms, and the use of rescue $\beta_2$-agonists.
In 2004, a Cochrane review by Ducharme et al. compared LTRA+ICS to ICS alone. They searched literature up to August 2003 and included 27 trials. They found that LTRA + ICS would bring modest improvement in lung function, appear comparable to increasing the dose of ICS and was associated with superior asthma control after glucocorticoid tapering. However, they stressed that the power of the review is insufficient to confirm the equivalence of both treatment options (add-on LTRA and ICS alone) and the glucocorticoid-sparing effect can not be quantified at present.

In 2002, a similar Cochrane review was conducted by Ducharme et al examining the safety and efficacy of LTRA plus ICS compared to ICS alone. They searched the literature published up to September 2001 and found 13 qualifying trials. At that time, they stated that evidence is insufficient to firmly support the use of LTRA as add-on therapy to ICS.

Another Cochrane review by Ducharme et al. in 2004, compared LTRA as alternative first line agents to ICS. Out of 27 RCTs identified, 13 trials had high methodological quality and 20 were published in full text. The review found that patients treated with ICS were less likely to suffer an exacerbation requiring systemic steroids, achieved greater improvement in FEV<sub>1</sub>, and better outcomes in terms of symptoms, nocturnal awakenings, rescue medication use, symptom-free days, and quality of life. In addition, LTRA resulted in higher risk of withdrawals due to poor asthma control. However, side effect risks are not different between the two treatments. The overall conclusion was that ICS should remain the first line monotherapy for persistent asthma.

Another earlier Cochrane review by Ducharme et al. compared LTRA and ICS was published in 2002. It was based on 14 qualifying trials. Only RCTs comparing LTRA and ICS during a minimal 30-day intervention period in asthmatic patients aged 2 years and older were included. Their conclusion was that ICS at 400 mcg/day of beclomethasone-equivalent are more effective than LTRA for most asthma outcomes. More evidence is needed to determine the exact dose-equivalence of LTRA in mcg of ICS.

**RCTs:**

Twenty-two RCTs (Appendix) were found to be relevant to the research question. The sample size of these RCTs ranged from 49 to 994. Ten RCTs included children with asthma while the remainder included either adults alone or a combination of adults and children. The interventions varied and could be classed into two groups: monotherapy with LTRA and LTRA combination therapy. In the first group, LTRA was compared to placebo, low-dose theophylline, LABA, ICS, or LABA+ICS. In the second group, the LTRA combinations included, LTRA+ICS, LTRA+LABA, LTRA+ asthma reliever while the corresponding comparators included LABA+ICS, theophylline+ICS, high dose ICS or placebo + asthma reliever.
Of these RCTs, 10 were conducted in USA, 2 in India, 1 in Korea, 1 in Denmark, 1 in Poland, 1 in UK, 1 in Turkey, 1 in Japan, 1 in Australia, 1 in Brazil and Canada and 1 in multiple countries. Research funding was reported in 16 trials, among which seven were funded by the manufacturer, four partially or indirectly supported by the manufacturer, three by the National Heart, Lung and Blood Institute, one by the National Institutes of Health and one by the UK Asthma organization.

With respect to outcome measures, more than half of the trials examined forced expiratory volume in one second (FEV$_1$) and/or peak expiratory flow rates (PEFR). Other main primary outcomes in these trials included rate of asthma exacerbations, asthma symptom score, symptom-free days, lung function, quality of life, use of oral corticosteroids and etc.

Results of the RCTs showed:

**LTRA vs monotherapy**
- **LTRA vs. Placebo**
  - Four RCTs$^{9-12}$ (>50%) showed favorable outcomes in patients treated with LTRA, including higher asthma symptom score (either measuring activity limitations due to asthma$^9$ or severity of asthma symptom$^{10}$), improved maximum percent fall in FEV$_1^{10}$ and PEFR$^9$, better protection against exercise-induced bronchoconstriction (EIB)$^{11}$, lower rate of asthma exacerbations. Two$^{10,11}$ of these four trials had study samples of asthmatic patients with EIB.
  - In the remaining two trials,$^{13,14}$ LTRA group didn’t present significant asthma control overall.

- **LTRA vs. ICS**
  - Three RCTs$^{15-17}$ compared LTRA with ICS alone. LTRA may be a beneficial long-term treatment for asthma patients$^{15}$ because of it decreasing the serum IgE levels (note: reduction of free IgE level is a rational target in the treatment of allergic diseases$^{15}$). Also, it was not inferior to ICS in terms of the percentage of asthma rescue-free days (RFDs)$^{16}$ or even superior than ICS.$^{17}$
  - In the remaining six RCTs,$^{18-23}$ LTRA had less favorable outcomes than comparator groups in terms of FEV$_1$, symptom control,$^{19-22}$ pulmonary response,$^{20}$ lung function,$^{18,23}$ quality of life,$^{23}$ reduction in sputum eosinophils,$^{23}$ and adverse events.$^{21}$

- **LTRA vs. LABA**
  - Only one RCT$^{23}$ directly compared LTRA with LABA, reporting that LTRA had less benefit than LABA in terms of symptoms, reliever use, lung function, asthma control questionnaire, quality of life and patient global assessments. It also found that among patients receiving LTRA is the
relationship between patient-based variables (asthma questionnaire, quality of life, patient global assessments) and lung function significant.

- LTRA vs. Theophylline
  - One RCT,\[^{13}\] published in 2007, illustrated that neither LTRA nor theophylline lowered the PEFR for the patients with poorly controlled asthma despite improved lung function. However, for a subgroup of patients who did not use inhaled corticosteroids, theophylline was likely more effective than LTRA or placebo in terms of asthma symptom control. Also, it was observed as a safe and low-cost alternative asthma treatment.

LTRA monotherapy vs. combination therapy

- LTRA vs. ICS+LABA
  - One US RCT,\[^{17}\] published in 2006, reported that the combination of ICS and LABA achieved greater improvements in asthma compared to LTRA monotherapy in terms of the percent of asthma control days. Nevertheless, the growth of study children was similar in two comparator groups.

Add-on LTRA vs. combination therapy

- LTRA+ICS vs. LABA+ICS
  - In one four-way crossover RCT,\[^{24}\] the combination of LTRA and ICS was showed more effective than the combination of LABA and ICS in terms of reducing sputum eosinophil despite the benefit itself being modest. The patients in the study were being treated with the equivalent of <=400 µg/day beclomethasone dipropionate.

- LTRA+ICS vs. Theophylline +ICS
  - Two RCTs\[^{25,26}\] reported favorable outcomes for the combination of LTRA and ICS when compared with the combination of theophylline and ICS. Morning and evening PEFR increased in the group receiving LTRA+ICS compared with that in the group with theophylline +ICS.\[^{25}\] The incidence of clinical and laboratory adverse experiences had no significant difference between two treatment groups.\[^{25}\] The addition of LTRA to ICS led to greater improvement in pulmonary function test parameters.\[^{26}\]

- LTRA+ low dose ICS vs. High dose ICS
  - Two RCTs\[^{24,28}\] demonstrated that the combination of LTRA and low dose ICS had less benefit than high dose ICS. The reduction of sputum eosinophil count was more in the group with high does of ICS than in one
with the combination.\textsuperscript{24} No difference was observed between the groups in terms of FEV\textsubscript{1}, PEFR, asthma symptom score but more frequent exacerbations occurred in the combination treatment group so that the overall control of asthma with the combination therapy is inferior to that with high dose of ICS alone.\textsuperscript{28}

- LTRA+ asthma reliever vs. Placebo+ asthma reliever
  - One RCT\textsuperscript{29} showed additive clinical benefit provided by LTRA in mild to moderate acute asthma in pre-school-aged children when they were administered concomitantly with short-acting β\textsubscript{2}– agonist bronchodilators as the initial treatment. The observed outcomes included the pulmonary index score, respiratory rate, oral steroid need and hospitalization rate.

Limitations:
For LTRA, there are a number of available RCTs and relevant literature for review. Due to the volume of literature on this topic, we included only RCTs published since 2005. Thus RCTs published prior to 2005 were not sought. However, since this report included systematic reviews published since 2002, it is likely that the relevant RCT evidence would be captured in those reports.

LTRAs were used as monotherapy and combination therapy compared with many different interventions. This resulted in a variety of interventions for comparison among the many trials. Plus inconsistency due to the variety of clinical outcomes regarding asthma control, becomes complex to synthesize the evidence.

It should be noted that more than half of the included RCTs were supported fully or partially by manufactures while six RCTs did not report the funding source.

Conclusions and implications for policy and decision making:
The role of LTRA in the treatment of asthma has been widely discussed. The most recent available evidence presents various clinical benefits of LTRA, depending on study population, comparator treatments and outcomes of interest. Most RCTs, which compared LTRA monotherapy with ICS alone, were consistent with the Cochrane 2004 review in terms of their conclusion that ICS should remain the first-line maintenance therapy. Only one identified RCT\textsuperscript{24} that compared LTRA+ICS to LABA+ICS reported the contrasting results with comparison to the finding of Cochrane 2006 review\textsuperscript{4} that LTRA+ICS might be superior to LABA+ICS in some outcomes. As for other applications of LTRA, the evidence in our report was too limited and a comprehensive systematic review based on all available evidences is suggested.

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References:


7. Ducharme FM, Di Salvio F. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. Cochrane Database of Syst Rev 2004;(1):CD002314


**Appendix : Included randomized control trials of LTRA**

<table>
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<th>Authors; year; location; funder of study</th>
<th>Sample size, patient group</th>
<th>Intervention</th>
<th>Outcome measures and results</th>
<th>Conclusions</th>
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</table>
| Ja-Hyung Kim et al., 2005; Korea; unknown funding source | N=64; mild asthmatic children with exercise-induced bronchoconstriction (EIB) | LTRA (Montelukast) (n=40) vs. placebo (n=24) | • Asthma symptom score: LTRA>placebo (p<0.01)  
• FEV1: LTRA>placebo (p<0.01)  
• Time to recovery: LTRA>placebo (P=0.26) | LTRAs may be useful for the long term management of asthmatic children with EIB |
| William et al., 2006; US; manufacturer-funded | N=455; patients with chronic asthma and seasonal aeroallergen sensitivity | LTRA (Montelukast) (n=225) vs. placebo (n=230) | • Daytime asthma symptom score: LTRA>placebo (p<0.001)  
• β-agonist use: LTRA>placebo (p=0.003)  
• Nighttime symptoms: LTRA>placebo (p<0.001)  
• Peak expiratory flow rates: LTRA>placebo(p<0.001) | LTRAs provided significant asthma control during the allergy season |
| The American Lung Association Asthma Clinical Research Centers, 2007; US; funded jointly by manufacturer and the association | N=489; patients with poorly controlled asthma | LTRA (Montelukast) (n=164) vs. placebo (n=164) vs. Low-dose theophylline (n=161) | • EPAC: LTRA = placebo ; low-dose theophylline >placebo  
• Post-bronchodilator FEV1: LTRA >placebo (p=0.13); low-dose theophylline >placebo (p=0.005)  
• Nausea in the first 4 wk: more common with theophylline  
• Asthma symptoms: LTRA = placebo; low-dose theophylline =placebo  
• Quality of life: LTRA = placebo; low-dose theophylline =placebo | Neither LTRA nor theophylline lowered the EPAC rate despite improved lung function. For patients with not using inhaled corticosteroids, theophylline is probably worth considering compared to montelukast or placebo |
| David et al., 2006; US; manufacturer-funded | N=51; adult asthma patients with EIB | LTRA (Montelukast) (n=25) vs. placebo (n=26) | • Onset of protection against EIB: quicker with LTRA (p<=0.001)  
• Duration of protection against EIB: longer with LTRA (p<=0.001)  
• Patients required post-exercise β-agonist rescue at 2 hours after treatment: fewer with LTRA (p=0.03) | LTRA provided significant protection against EIB |
**Health Technology Inquiry Service (HTIS)**

<table>
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<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
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| C.R. Jenkins et al., 2005<sup>11</sup>, Australia; funded by the Cooperative Research Centre for Asthma | N=58; patients aged 16-75 years with mild to moderate asthma | LTRA (montlukast) (n=29) vs. LABA (eformoterol) (n=29) vs. ICS (fluticasone) (n=53) | • Symptom/reliever use: LABA > ICS > LTRA  
• Lung function: ICS > LABA > LTRA  
• Patient-centre factor: LABA = ICS > LTRA |
| Hans et al., 2005<sup>12</sup>, Denmark; manufacturer-funded | N=549; children aged 2 to 5 years with a history of intermittent asthma symptoms | LTRA (Montelukast) (n=278) vs. placebo (n=271) | • Rate of asthma exacerbations: LTRA < placebo  
• The median time to first exacerbation: LTRA < placebo (p=0.024)  
• The rate of inhaled corticosteroid courses: LTRA < placebo (p=0.027) |
| Janet et al., 2005<sup>14</sup>, US; manufacturer-funded | N=256; children aged 6-24 months with asthma | LTRA (Montelukast) (n=175) vs. placebo (n=81) | • Adverse experiences: LTRA = placebo  
• No significant difference between groups in other outcomes |
| Robert et al., 2005<sup>18</sup>, US; manufacturer-funded | N=400; patients aged 15-85 years with mild persistent asthma | LTRA (Montelukast) (n=189) vs. ICS (inhaled fluticasone) (n=191) | • Mean percentage of rescue-free days: LTRA = ICS in the treatment period; LTRA < ICS in the open-label period  
• Asthma symptoms: LTRA = ICS in the double blind period; LTRA < ICS in the open-label period  
• Quality of life: LTRA = ICS  
• Symptom-free days: LTRA = ICS (p=0.003)  
• Lung function: LTRA < ICS |
| L. Jayaram et al., 2005<sup>19</sup>, Brazil and Canada; partially funded by manufacturer | N=50; adults with symptomatic steroid naïve asthma and sputum eosinophilia of >=3.5% | LTRA (Montelukast) (n=19) vs. ICS (low dose fluticasone) (n=18) vs. placebo (n=13) | • Reduction in sputum eosinophils: LTRA < ICS (p=0.04)  
• Improvement in FEV₁: LTRA < ICS (p=0.02) |

In asthma treatment, traditional end-points do not fully capture patient-centered benefits, and the relationship between end-points differs with medication class.

LTRA effectively reduced asthma exacerbations in 2- to 5-year-old patients with intermittent asthma over 12 months of treatment and was generally well tolerated.

LTRA was well tolerated but its favorable improvement in efficacy endpoints was not statistically significant.

LTAR and ICS have the similar effectiveness over the short term but ICS controlled asthma better during the prolonged open-label treatment. For patients with decreased lung function and greater albuterol use at baseline, ICS seemed more favorable.

LTAR is not as effective as low dose ICS in reducing or maintaining an anti-inflammatory effect in steroid naïve eosinophilic asthma.
Robert et al., 2005; US; funded by the National Heart, Lung, and Blood Institute

N=144; children aged 6 to 17 years with mild-to-moderate persistent asthma

LTRA (montelukast) (n=73 in the period 1 and n=68 in the period 2) vs. ICS (fluticasone propionate) (n=71 in the period 1 and n=68 in the period 2)

- Clinical outcomes: LTRA<ICS (p<0.05)
- Pulmonary responses: LTRA<ICS (p<0.05)
- Improvement in inflammatory biomarkers: LTRA<ICS (p=0.0028)

The more favorable clinical, pulmonary, and inflammatory responses to an ICS than to an LTRA

Iwona et al., 2005; Poland; unclear fund source

N=51; children aged 6-18 years with newly diagnosed asthma and sensitive to house-dust mites

LTRA (Montelukast) (n=17) vs. Medium dose ICS (budesonide) (n=16) vs. high dose ICS (budesonide) (n=18)

- Levels of total and specific IgE: improved in LTRA group and high dose ICS group, no effect in medium dose ICS group
- Improvement in clinical score and FEV₁: significance in medium dose of ICS (p=0.002) and high dose of ICS (p=0.001) as well as LTRA (p=0.002).
- No difference between all groups in terms of changes of all clinical parameters after treatment

Only high doses of ICS and LTRA decreased the serum IgE levels. Perhaps long-term treatment with montelukast will be beneficial

Nancy et al., 2005; US; manufacturer-funded

N=342; children aged 6-12 years with persistent asthma

LTRA (Montelukast) (n=170) vs. ICS (fluticasone propionate) (n=172)

- Mean percent change of FEV₁: ICS>LTRA (p=0.002)
- Improvement in morning PEF: ICS>LTRA (p=0.004)
- Improvement in evening PEF: ICS>LTRA (p=0.02)
- Percent rescue-free days: ICS>LTRA (p=0.002)
- Reduction night time symptom score: ICS>LTRA (p<0.001)
- Reduction mean total symptom score: ICS>LTRA (p=0.018)
- Reduction in night time albuterol use: ICS>LTRA (p=0.001)
- Withdrawal frequency: LTRA>ICS
- Eman end point to baseline 12-hour urinary cortisol excretion ratios: similar among two groups

LTRA was less effective than ICS in improving pulmonary function, asthma symptoms, and rescue albuterol use. They had similar safety profiles. Parent and physician reported satisfaction ratings were higher with ICS than with LTRA.
LTRA for Asthma

M. Luz Garcia Garcia et al., 2005[^1]; Multiple countries; manufacturer-funded

- N=994; children aged 6-14 years with mild persistent asthma
- LTRA (Montelukast) (n=494) vs. ICS (Fluticasone) (n=499)
  - Percentage of asthma rescue-free days: LTRA=ICS
  - The proportion of patients requiring systemic corticosteroids: LTRA>ICS
  - Asthma attack: LTRA>ICS
  - Tolerance: both well tolerated
  - Percentage of predicated FEV₁: LTRA<ICS (p=0.004)
  - Days with β-receptor agonist use: LTRA>ICS (p=0.003)
  - Quality of life: LTRA<ICS (p=0.036)

LTRA was proved to be not inferior to ICS in asthma RFDs, but with more asthma attacks and required more systemic corticosteroids.

Homer et al., 2005[^2]; US, funded by the National Institutes of Health

- N=225; asthma patients aged 18 to 65 years
- LTRA (zafirlukast) +placebo inhaler (n=76) vs. ICS (budesonide) + placebo tablets (n=73) vs. placebo tablets +placebo inhaler (called as intermittent treatment) (n=76)
  - PEF: similar among three groups (p=0.9)
  - Rate of asthma exacerbations: similar among groups (p=0.24)
  - ICS > other two groups in FEV₁ (p=0.005), bronchial reactivity (p<0.001), the percentage of eosinophils in sputum (p=0.007), exhaled nitric oxide level (p=0.006), scores for asthma control (p<0.001), the number of symptom-free days (p=0.03)
  - Quality of life: no difference significant (p=0.18)
  - All outcomes: no difference between LTRA group and intermittent treatment group

It may be possible to treat mild persistent asthma with short, intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen. Further studies are required to determine whether this novel approach to treatment should be recommended.

R.H. Green et al., 2006[^3]; UK, funded by Asthma UK

- N=49; patients aged 18-75 years with asthma and being treated with the equivalent of <=400 μg/day beclomethasone dipropionate.
- LTRA (Montelukast)+low dose ICS (budesonide) (n=43) vs. LABA (formeterol) + low dose ICS (budesonide) (n=40) vs. placebo+ low dose ICS (budesonide) (n=41) vs high dose ICS (budesonide) (n=42)
  - The change in sputum eosinophil count in terms of reduction degree: LTRA +ICS = placebo +ICS, LABA+ICS < placebo+ICS < high-dose ICS
  - The change in methacholine airway responsiveness: no difference between groups
  - Symptom scores: vary most among high dose ICS

Treatment given in addition to low dose ICS results in modest benefits. LABA and high dose budesonide have contrasting effects on eosinophilic airway inflammation.
### LTRA for Asthma

<table>
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<th>Study</th>
<th>Population Description</th>
<th>Interventions</th>
<th>Findings</th>
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| Koray et al., 2005<sup>29</sup>; Turkey, funding source (NA) | N=51; children aged 2-5 years with mild to moderate acute asthma | LTRA (Montelukast) + asthma reliever (inhaled salbutamol) (n=25) vs. placebo + asthma reliever (inhaled salbutamol) (n=26) | - Morning PEFR: vary most among high dose ICS  
- FEV <sub>1</sub>: vary most among high dose ICS  
- LTRA+salbutamol< placebo+salbutamol in pulmonary index scores (p=0.01), respiratory rate (p=0.01), oral steroid need (p=0.22)  
- Hospitalization rates: no difference between two groups |
| Gokul et al., 2006<sup>28</sup>; India, funding source (NA) | N=71; children with moderate persistent asthma | LTRA (Montelukast) + low does ICS(budesonide) (n=34) vs. high does (budesonide) (n=37) | - FEV <sub>1</sub>: no difference between two groups  
- PEFR: no difference  
- Asthma symptom score: no difference  
- Frequency of exacerbations: LTRA+ICS< ICS (p<0.01) |
| Christine et al., 2006<sup>17</sup>; US, funded by grants from the National Heart, Lung and Blood Institute | N=285; children aged 6-14 years with mild to moderate persistent asthma on the basis of symptoms, and with FEV <sub>1</sub> >=80% predicted and methacholine FEV <sub>1</sub>, PC<sub>20</sub> <=12.5 mg/mL | LTRA (Montelukast) (n=95) vs. ICS (Fluticasone) (n=96) vs. ICS(Fluticasone)+LABA (Salmeterol) (n=94) | - percent of asthma control days: ICS monotherapy = the combination  
- ICS>the combination in terms of clinical-measured FEV <sub>1</sub>/forced vital capacity (p=0.015), maximum bronchodilator response (p=0.009), exhaled nitric oxide (p<0.001), and PC<sub>20</sub> (p=<0.001)  
- Asthma control days and other control outcomes: ICS better than LTRA (p=0.004)  
- Growth: no difference among groups |
| Aaron et al., 2007<sup>30</sup>; US; funded jointly by the National Heart, Lung and Blood Institute | N=192; patients aged 12 to 65 year with moderate asthma | LTRA (Montelukast) +LABA (Salmeterol) (n=98) vs. ICS (beclomethasone) + LABA (Salmeterol) (n=92) | - Protection against asthma treatment failures: LTRA+LABA< ICS+LABA (p=0.0008)  
- Lung function: LTRA+LABA< ICS+LABA (p=0.011)  
- Asthma control score: LTRA+LABA< ICS+LABA (p=0.038)  
- Patients with moderate asthma should not substitute the combination of an LTRA and an LABA for the combination of inhaled corticosteroid and an LABA. |

LTAR had the potential to provide additive clinical benefit when administered concomitantly with short-acting β<sub>2</sub>–agonist bronchodilators as the initial treatment.

The overall control of asthma with the combination of LTRA and ICS is inferior to that with high dose of ICS alone.

ICS monotherapy and the combination with LABA achieved greater improvements in asthma control days than LTRA. However, ICS monotherapy was superior to the combination group in achieving other dimensions of asthma control. Growth was similar in all groups.
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<th>Study</th>
<th>Design</th>
<th>Objective</th>
<th>Results</th>
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| Tomoko et al., 2005<sup>27</sup>; Japan; funding source (NA) | N=67; adult asthmatic patients LTRA (Pranlukast)+ICS (n=33) vs. Theophylline +ICS (n=34) | LTRA+LABA< ICS+LABA                                                      | - Markers of inflammation and airway reactivity: LTRA+LABA< ICS+LABA  
- Symptom score: LTRA+ICS = Theo.+ICS  
- Use of rescue $\beta_2$–agonist: LTRA+ICS = Theo.+ICS  
- Daily PEF variability: LTRA+ICS = Theo.+ICS  
- Morning and evening PEF improvement: LTRA+ICS = Theo.+ICS  

The addition of either LTRA or sustained released Theo does not improve asthma-related symptoms but significantly and equally increase PEF. |
| A.R.Shah, et al., 2006<sup>26</sup>; India; funding source (NA) | N=90; asthma patient aged 18 to 60 years LTRA (Montelukast)+ICS (budesonide) (n=30) vs. Theophylline +ICS (n=30) vs. ICS (n=30) | LTRA+ICS > the other two groups (p=0.001)  
PEFR: LTRA+ICS > the other two groups (p=0.01) | - Improvement in FEV<sub>1</sub>: LTRA+ICS > the other two groups (p=0.001)  
- PEFR: LTRA+ICS > the other two groups (p=0.01)  

Addition of montelukast to budesonide is safe and results in greater improvement in pulmonary function test parameters than high-dose budesonide treatment or addition of theophylline. |
| Kondo et al., 2006<sup>25</sup>, funding source (NA)<sup>2</sup> | 6- to 14-year asthmatic children LTRA (monelukast) +ICS vs. Theophylline +ICS | LTRA+ICS > Theophylline +ICS (at week 2, p=0.041; at week 4, p=0.012)  
Improvement in evening PEF at week 4: LTRA+ICS > Theophylline +ICS (p=0.027)  
Incidences of clinical and laboratory adverse experiences: no significant difference | - Improvement in morning PEF: LTRA+ICS > Theophylline +ICS (at week 2, p=0.041; at week 4, p=0.012)  
- Improvement in evening PEF at week 4: LTRA+ICS > Theophylline +ICS (p=0.027)  
- Incidences of clinical and laboratory adverse experiences: no significant difference  

LTRA added to low dose ICS is an effective and safe option for the treatment of asthma in children. |

**Note:** 1. LTRA = leukotriene receptor antagonists, ICS=inhaled corticosteroids, LABA=long acting $\beta_2$ - agonists, FEV<sub>1</sub>=forced expiratory volume in 1 second, EPAC= episodes of poor asthma control, PEFR= peak expiratory flow rate, PEF= peak expiratory flow, EIB= exercise-induced bronchoconstriction  
2. The information for this trial is based on its abstract. Its full text is not available during the time of this report preparation.