Review: Antileukotriene agents at licensed doses plus inhaled corticosteroids do not reduce asthma exacerbations more than inhaled corticosteroids alone


Questions
In patients with chronic asthma, does adding antileukotriene (AL) agents to inhaled corticosteroids (ICSs) reduce exacerbations and improve asthma control more than ICSs alone? Do ALs allow a reduction in ICS dose?

Methods
Data sources: Cochrane Airways Group Asthma trials register, Cochrane Central Register of Controlled Trials, references of relevant articles, pharmaceutical companies manufacturing ALs and ICSs, and abstracts of the American Thoracic Society and European Respiratory Society Meetings (1998 to 2003).

Study selection and assessment: Randomized controlled trials (RCTs) comparing ALs plus ICSs with the same dose of ICSs, double the dose of ICSs, or a tapered dose of ICSs in patients with recurrent or chronic asthma who were ≥ 2 years of age. Study quality was assessed using the Jadad 5-point scale.

Outcomes: Exacerbations and change from baseline dose of ICSs required to maintain control, and change from baseline in asthma control measures. Trials were grouped for licensed dose and higher-than-licensed dose of ALs.

Main results
27 RCTs met the inclusion criteria, 25 in adults and 2 in children. 16 RCTs contributed data that could be meta-analyzed. At licensed doses, ALs plus ICSs did not reduce the rate of exacerbations requiring systemic steroids more than ICSs at the same or double the dose (Table). ALs showed a modest improvement compared with the same dose of ICSs for change from baseline in morning PEFR (4 RCTs, weighted mean difference [WMD] 7.65 L/min [95% CI 3.55 to 11.75]) and β2-agonist use (4 RCTs, standardized mean difference [SMD] –0.15 [CI –0.24 to –0.05]). Groups did not differ for change in FEV1 or symptom scores. At higher-than-licensed doses, ALs plus ICSs reduced exacerbations (Table) and use of rescue β-agonists (SMD –0.43 [CI –0.22 to –0.63]) and improved FEV1 (WMD 0.10 L [CI 0.01 to 0.20]) and PEFR (WMD 27.2 L/min [CI 18.6 to 35.8]) more than the same dose of ICSs. ALs plus ICSs did not differ from ICSs alone at double the dose for asthma-control measures or exacerbations, but the results did not meet criteria for equivalence. In patients with well-controlled asthma at baseline, the addition of ALs did not affect the percentage change from baseline in the ICS dose required to maintain control (4 RCTs, WMD –3% [95% CI –7 to 2]).

Conclusions
In patients with chronic asthma, adding antileukotriene (AL) agents at licensed doses to inhaled corticosteroids does not reduce exacerbations and only modestly improves asthma control. At higher-than-licensed doses, ALs reduce exacerbations.

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For correspondence: Dr. F Ducharme, McGill University Health Centre, Montreal, Quebec, Canada. E-mail Francine.ducharme@muhc.mcgill.ca.

Antileukotriene (AL) agents plus inhaled corticosteroids (ICs) vs ICSs alone to reduce exacerbations requiring systemic steroids in chronic asthma

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Dose of ALs</th>
<th>Number of trials (number of patients)</th>
<th>Treatment duration</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALs + ICSs vs ICS (same dose)</td>
<td>Licensed</td>
<td>4 (988)</td>
<td>4 to 16 wk</td>
<td>36% (–7 to 62)</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Higher-than-licensed</td>
<td>2 (451)</td>
<td>6 wk</td>
<td>66% (12 to 87)</td>
<td>22 (17 to 117)</td>
</tr>
<tr>
<td>ALs + ICSs vs ICS (double dose)</td>
<td>Licensed</td>
<td>2 (1179)</td>
<td>12 to 13 wk</td>
<td>8% (–51 to 44)</td>
<td>Not significant</td>
</tr>
<tr>
<td></td>
<td>Higher-than-licensed</td>
<td>2 (816)</td>
<td>12 to 13 wk</td>
<td>5% (–2 to 45)</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary. A fixed-effects model was used.

Commentary
In 2002, a commentary on the Cochrane review of ALs in patients with asthma taking ICSs concluded that the role of ALs was limited (1). 2 years later the authors have updated their analyses and the number of studies has doubled, but the conclusions have changed little.

The addition of ALs to ICSs reduced exacerbations significantly only when AL doses were higher than the current licensed range. Higher doses are associated with an increased likelihood of abnormal results of liver function tests. At licensed doses, there was a small effect on peak flow. There may be a steroid-sparing effect because asthma control was slightly better on a reduced ICS dose when ALs were taken. However, the estimate is that the maximum effect would be less than the equivalent of 300 μg of beclomethasone per day. The comparisons of AL addition with doubling the dose of ICSs did not come close to the criteria to establish equivalence between ALs and increased ICSs.

Unfortunately, many of the trials of ALs are of poor quality. Most of the steroid-sparing trials did not have an adequate run-in period to reduce ICSs to a minimum effective dose before the active part of the trial. Without this run-in, large reductions in ICS dose are likely even in patients on placebo. None of the studies was really of adequate duration to monitor exacerbations and side effects; the longest of the 27 included studies was just 20 weeks.

In most asthma guidelines, long-acting β-agonists have been recommended as the next step if asthma is not controlled by low-dose ICSs (2). However, each patient must be considered individually when choosing a treatment. A recent study (3) has suggested that ALs may improve quality of life and protect against exacerbations as effectively as long-acting β2 agonists. But this updated review on ALs does not change the conclusions of 2 years ago (1), indicating a limited role for ALs.

P. John Rees, MD, FRCP
Guy’s, King’s & St Thomas’ School of Medicine
London, England, UK

References