

Review: Adding antileukotrienes to inhaled corticosteroids reduces exacerbations in symptomatic chronic asthma

Ducharme F, Hicks G, Kakuma R. Addition of anti-leukotriene agents to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev.* 2002;(1):CD003133 (latest version 25 Oct 2001).

QUESTION

In patients with chronic asthma, how effective and safe is daily antileukotriene (AL) therapy plus inhaled corticosteroids (ICS) compared with ICS alone?

DATA SOURCES

Studies were identified by searching 4 electronic databases up to September 2001; scanning the reference lists of articles and reviews; reviewing meeting abstracts (1998 to 2000); and contacting the international headquarters of AL manufacturers.

STUDY SELECTION

Studies were selected if they were randomized controlled trials evaluating the effectiveness of AL for ≥ 1 month in patients with asthma who were ≥ 2 years of age.

DATA EXTRACTION

Data were extracted independently by 2 reviewers on study quality, patient characteristics, intervention type and duration, and main outcome measures.

MAIN RESULTS

13 trials (12 in adults and 1 in children) were included. Combining data from 2 of the 6 trials in symptomatic patients and after 4 to 16 weeks of treatment showed that the addition of higher-than-licensed AL doses to ICS

reduced the risk for exacerbations requiring systemic corticosteroids (Table). The addition of higher-than-licensed doses also led to an improvement in FEV₁ (weighted mean difference [WMD] 0.10 L, 95% CI 0.01 to 0.20), peak expiratory flow rate (WMD 27.2 L/min, CI 18.6 to 35.8), asthma symptom scores (standardized mean difference [SMD] -0.46, CI -0.25 to -0.66), and mean use of β_2 -agonists (SMD -0.43 puffs/d, CI -0.22 to -0.63). The groups did not differ for any other outcomes. The addition of licensed doses led to nonstatistically significant reductions in the risk for exacerbations requiring systemic steroids (relative risk reduction 39%, CI -5% to 64%).

2 trials that compared ICS plus AL at higher-than-licensed doses with double-dose ICS in symptomatic patients showed no differences between groups for the number of exacerbations requiring systemic steroids or for any other outcome. 4 trials that com-

pared AL (at licensed doses) plus ICS with the same dose of ICS in well-controlled patients showed no difference in reduction in ICS dose after 12 to 20 weeks and no difference in the lowest tolerated dose of ICS.

CONCLUSIONS

In patients with chronic asthma who are symptomatic while receiving moderate-to-high doses of inhaled beclomethasone, the addition of 2 to 4 times the licensed dose of antileukotriene (AL) agents reduces the rate of exacerbations that require systemic corticosteroids. Insufficient evidence exists that AL confers benefit over doubling the dose of corticosteroids or that it has an inhaled corticosteroid-sparing effect.

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Antileukotriene (AL) agents (higher-than-licensed dose) plus inhaled corticosteroids (ICS) vs ICS alone for symptomatic chronic asthma at 4 to 16 weeks*

Outcome	AL + ICS	ICS	RRR (95% CI)	NNT (CI)
Exacerbations	2%	7%	66% (12 to 87)	22 (12 to 125)

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

AL agents provide the first new treatment option for some time in asthma. ALs might be helpful as alternatives to ICS in patients starting regular treatment and as an addition to ICS.

The review by Ducharme and colleagues deals with the latter, when control is inadequate with ICS or as a method of reducing the ICS dose. The reported results are disappointing. In short-term studies, exacerbations were reduced and control was slightly improved with the addition of AL, but some doses were greater than current licenses allow. No difference existed between adding AL to ICS and doubling the dose of ICS, although steroids have been found to have a rather flat dose response, and the introduction of AL did not allow for a reduction in ICS dose in these studies.

2 large studies (1, 2) have examined the effects of adding long-acting inhaled β_2 -agonists (LABAs) at the same point and have shown that LABAs add to the benefits of ICS and are more effective than doubling the steroid dose. LABAs also reduce exacerbations (1). In the studies reviewed by Ducharme and colleagues, patients were not taking LABAs. The clinical implications would seem to be that LABAs should be the first option for patients who are not well controlled with ICS or who require high doses for control. AL might be considered after assessing the response in each patient.

The use of AL as a first prophylactic agent has been assessed in a Cochrane review (3). AL agents were inferior to ICS for effects on lung function, symptoms, and quality of life, although again they were not statistically different for exacerbations.

New drugs for asthma must contend with the facts that ICSs are very effective in asthma and have few side effects at usual doses. AL agents, at the higher doses seen in this review, were found to affect lung function tests, but they are generally safe drugs in asthma. Their effectiveness is limited, however, and indications for their use have not been broadened by this review.

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References

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