

Review: Adding long-acting β_2 -agonists to inhaled corticosteroids reduces asthma exacerbations more than adding antileukotrienes

Ram FS, Cates CJ, Ducharme FM. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst Rev.* 2005;(1):CD003137.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★☆☆ Pulmonology ★★★★★☆☆

QUESTION

In patients with recurrent or persistent asthma, what are the relative benefits of adding long-acting β_2 -agonists (LABAs) or leukotriene-receptor antagonists (LTRAs) to inhaled corticosteroids?

METHODS

Data sources: Cochrane Airways Review Group register (to January 2004) containing searches in MEDLINE, EMBASE/Excerpta Medica, and CINAHL; Cochrane Clinical Trials Register; reference lists of relevant studies and reviews; authors of included studies; pharmaceutical companies manufacturing the study agents; and conference abstracts.

Study selection and assessment: Randomized controlled trials comparing LABAs or LTRAs added to inhaled corticosteroids in patients with recurrent or persistent asthma. Patients were required to be on a stable dose of inhaled corticosteroid during a treatment period ≥ 28 days. The quality of the individual studies was assessed with the Jadad scale. **Outcomes:** Asthma exacerbations requiring systemic corticosteroids. Secondary outcomes included asthma control measures, adverse effects, and withdrawals.

MAIN RESULTS

12 RCTs met the inclusion criteria; 8 RCTs ($n = 5895$, mean age range 35 to 43 y, mean asthma duration 10 to 26 y) had sufficient data to contribute to a meta-analysis. The

overall methodological quality of the trials was high. The LABAs used were salmeterol (7 RCTs) and formoterol (1 RCT). The LTRAs used were zafirlukast (2 RCTs) and montelukast (6 RCTs). The addition of LABAs to inhaled corticosteroids reduced the risk for asthma exacerbations more than did the addition of LTRAs (Table). All asthma-control outcomes favored LABAs (Table). Fewer patients who received LABAs withdrew for any reason (8 RCTs, $n = 5894$) (relative risk 0.84, 95% CI 0.74 to 0.96). Groups did not differ for severe adverse

events (6 RCTs, $n = 5592$) (RR 1.32, CI 0.98 to 1.79).

CONCLUSION

In patients with recurrent or persistent asthma, adding long-acting β_2 -agonists to inhaled corticosteroids is more effective than adding leukotriene-receptor antagonists.

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For correspondence: Dr. F. Ducharme, McGill University Health Centre, Montreal, Québec, Canada. E-mail francine.ducharme@mhuc.mcgill.ca. ■

Long-acting β_2 -agonists (LABAs) vs antileukotriene-receptor antagonists (LTRAs) added to inhaled corticosteroids for inadequately controlled asthma at 4 to 48 weeks*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		LABAs	LTRAs		
≥ 1 exacerbation requiring systemic corticosteroids	6 (5571)	9%	11%	17% (3 to 29)†	38 (23 to 247)
Weighted mean difference (CI)					
Change in morning PEF (L/min)	8 (5383)	15.48 (12.92 to 18.04)†			
Change in evening PEF (L/min)	7 (3672)	11.86 (8.85 to 14.86)†			
Change in FEV ₁ (L)	7 (4445)	0.08 (0.06 to 0.10)†			
Rescue-free d (%)	4 (2371)	9% (4 to 14)‡			
Rescue medication (puffs/d)	6 (4015)	-0.37 (-0.52 to -0.23)‡			
Symptom-free days (%)	4 (2384)	6% (2 to 11)‡			
Night awakenings per wk	4 (4214)	-0.12 (-0.19 to -0.06)†			

*Abbreviations defined in Glossary. All differences favor LABAs.

†A fixed-effects model was used.

‡A random-effects model was used.

COMMENTARY

Patients benefit from the addition of LABAs or LTRAs to inhaled corticosteroids more than from increasing doses of inhaled corticosteroid alone. The review by Ram and colleagues compares the relative merits of each, across 8 studies of high methodological quality.

Adding LABAs showed an 18% relative risk reduction of exacerbations requiring systemic corticosteroids (the primary outcome of interest) compared with adding LTRAs to inhaled corticosteroids. The clinical significance of the relative advantages seen in a range of other outcome measures, such as an 80-mL greater increase in FEV₁, is less certain.

A potential advantage of LTRAs for the longer term is ease of compliance with a once-daily pill. Only 2 RCTs had > 12-week follow-up; therefore, allergy-related seasonal benefits of LTRAs may be underestimated (1). Exercise- and aspirin-induced asthma could not be appraised as a subgroup.

The entry of patients into all 8 RCTs required 12% reversibility to short-acting β -agonists. This selection criterion may have identified a particular group of patients, who may have been undertreated or not

adherent to their medications.

The homogeneity of the results might suggest a lack of diversity among the types of patients studied. The findings might be less generalizable to patients receiving higher doses of inhaled corticosteroids (400 to 565 μg of beclomethasone dipropionate per d or equivalent), children, adults > 65 years of age, persons with mild or severe asthma, and smokers.

These caveats aside, if adult asthma is inadequately controlled on inhaled corticosteroids and particularly if systemic corticosteroid requirements are of concern, the findings of this review favor the addition of LABAs over LTRAs.

*Brian Smith, MD
Queen Elizabeth Hospital
Woodville, South Australia, Australia*

Reference

1. Krawiec ME, Jarjour NN. Leukotriene receptor antagonists. *Seminars in Respiratory and Critical Care Medicine.* 2002;23:399-410.