Review: Corticosteroids plus long-acting β-agonists reduce exacerbations more than long-acting β-agonists alone in COPD

Nannini L, Cates C, Lasserson T, Poole P. **Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2007;(4):CD006829.

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

QUESTION

In patients with stable chronic obstructive pulmonary disease (COPD), how do inhaled corticosteroids (ICSs) combined with long-acting β-agonists (LABAs) compare with LABAs alone?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cochrane Central Register of Controlled Trials, Cochrane Library (issue 1, 2007), Cochrane Airways Group Specialized Register, 4 other databases, reference lists, and conference abstracts.

Study selection and assessment: Randomized, double-blind, controlled trials (RCTs) comparing combination therapy of ICSs plus LABAs with LABAs alone in patients > 45 years of age with stable COPD and no exacerbation for 1 month before study entry, including those with partial reversibility on pulmonary function testing. Studies of patients who had asthma, bronchiectasis, cystic fibrosis, or other lung diseases were excluded. Quality assessment of individual studies was based on the 5-point Jadad scale. 10 RCTs (n = 7598) met the selection criteria: 8 compared fluticasone plus salmeterol with salmeterol alone, and 2 compared budesonide plus formoterol with formoterol. Jadad scores ranged from 3 to 5.

Outcomes: Exacerbations, death, and pneumonia. Secondary outcomes included rescue medication use, quality of life (St. George's Respiratory Questionnaire and Chronic Respiratory Disease Questionnaire), and adverse events.

MAIN RESULTS

Meta-analysis showed that combination therapy reduced exacerbations more than did LABAs alone; groups did not differ for death (Table). Combination therapy improved quality of life but increased pneumonia compared with LABAs alone (Table); groups did not differ for change in rescue medication use. Adverse events associated with fluticasone plus salmeterol included candidiasis and upper respiratory tract infection.

CONCLUSION

Combined inhaled corticosteroids plus long-acting β-agonists reduce exacerbations more than long-acting β-agonists alone in patients with stable chronic obstructive pulmonary disease.

Source of funding: Not stated.

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Combined long-acting β-agonists (LABAs) plus inhaled corticosteroid (ICSs) vs LABAs alone in stable chronic obstructive pulmonary disease*

Outcomes at 8 to 156 weeks	Number of trials (n)	Weighted event rate		RRR (95% CI)	NNT
		LABAs + ICSs	LABAs		
Mortality	6 (6747)	6.4%	7.1%	10% (–7.4 to 26)	Not significant
				RRI (CI)	NNH (CI)
Pneumonia	7 (7173)	9.9%	6.4%	56% (32 to 83)	29 (19 to 50)
				Rate ratio (CI)	
Exacerbations	5 (5696)			0.82 (0.78 to 0.88)	
				Weighted mean difference (CI)	
Change in SGRQ score	4 (4700)			–1.6 (–2.3 to –1.0)†	
Change in CRDQ score	2 (680)			2.8 (0.2 to 5.4)‡	

*CRDQ = Chronic Respiratory Disease Questionnaire; SGRQ = St. George's Respiratory Questionnaire; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from control event rates and odds ratios using a fixed-effects model.
†Lower scores indicate better quality of life.
‡Higher scores indicate better quality of life.

COMMENTARY *(continued from page 48)*

Nannini and colleagues included the Towards a Revolution in COPD Health (TORCH) trial (2) in their assessment of overall efficacy of combination therapy and excluded a study by Mahler (3), in which patients were withdrawn after exacerbation. Wilt and colleagues included the Mahler study in their analysis but excluded the TORCH trial because of their chosen method of reporting exacerbations. Future trials should aim for more consistency in both definition and reporting of results. In the meantime, the meta-analysis by Nannini and colleagues, which used exacerbation rate per group as an endpoint and included results of the TORCH trial, concludes that combination therapy is probably more effective at reducing exacerbations than its monocomponents.

Combination therapy also has marginally greater benefits on quality of life and FEV_1 than its monocomponents. Combination therapy with fluticasone and salmeterol appears to reduce mortality compared with placebo or fluticasone alone, although not compared with salmeterol. As ICSs appear to be associated with increased incidence of pneumonia (although not with hospitalizations or deaths), increased clinician vigilance and patient education about prompt treatment of infections when these drugs are used seem prudent.

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References

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