

Tiotropium reduced exacerbations and health resource use in COPD

Brusasco V, Hodder R, Miravittles M, et al. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax*. 2003;58:399-404.

QUESTION

In patients with chronic obstructive pulmonary disease (COPD), is tiotropium more effective than salmeterol or placebo in reducing exacerbations and health resource use?

DESIGN

2 randomized (unclear allocation concealment*), blinded (clinicians and patients),* placebo-controlled trials with 6-month follow-up.

SETTING

18 countries.

PATIENTS

1207 patients ≥ 40 years of age (mean age 64 y, 76% men) who had stable airway obstruction ($FEV_1 \leq 65\%$ of predicted normal and $\leq 70\%$ of forced vital capacity) and a smoking history > 10 pack-years. Exclusion criteria included history of asthma and supplemental oxygen use. Follow-up was 80%.

INTERVENTION

Patients were allocated to tiotropium, 18 μg once daily via HandiHaler, plus twice-daily metered-dose inhaler placebo ($n = 402$); salmeterol, 50 μg twice daily, plus HandiHaler placebo ($n = 405$); or combination placebo ($n = 400$) for 6 months. Oral steroid bursts and theophylline were permitted.

MAIN OUTCOME MEASURES

Exacerbations, health resource use, lung function, and health-related quality of life

(HRQL) assessed by the St. George's Respiratory Questionnaire (SGRQ).

MAIN RESULTS

A greater delay in time to first COPD exacerbation occurred with tiotropium than with placebo ($P \leq 0.01$). Tiotropium, salmeterol, and placebo groups did not differ for proportion of patients with ≥ 1 exacerbation during follow-up (32%, 35%, and 39%, respectively, $P > 0.05$). Patients who received tiotropium had fewer COPD exacerbations and exacerbation-days per patient-year than patients who received placebo (Table). Fewer hospital admissions for any cause occurred in the tiotropium group than the placebo group (0.43 vs 0.86, $P < 0.05$). The mean number of admissions in the salmeterol group (0.65) did not differ from those of the tiotropium or placebo groups. SGRQ scores improved in the tiotropium, salmeterol, and placebo group by a mean of 4.2, 2.8, and

1.5 units, respectively (tiotropium vs placebo, $P < 0.01$). The mean improvement in trough FEV_1 for tiotropium and salmeterol was 0.12 L and 0.09 L, respectively ($P < 0.01$ for both compared with placebo, $P < 0.05$ for tiotropium compared with salmeterol) on the last day of the study.

CONCLUSIONS

In patients with chronic obstructive pulmonary disease, tiotropium reduced exacerbations, resource use, and improved health-related quality of life more than placebo. Salmeterol showed no effect on outcomes.

Source of funding: Boehringer Ingelheim Pharmaceuticals.

For correspondence: Dr. V. Brusasco, Università di Genova, Genova, Italy. E-mail brusasco@dism.unige.it. ■

*See Glossary.

Tiotropium, salmeterol, and placebo for chronic obstructive pulmonary disease (COPD) at 6 months

Outcomes	Comparisons	Event rates	P value
Number of COPD exacerbations per patient-y	Tiotropium vs placebo	1.07 vs 1.49	0.025
	Salmeterol vs placebo	1.23 vs 1.49	0.296
	Tiotropium vs salmeterol	1.07 vs 1.23	0.222
Number of exacerbation days per patient-y	Tiotropium vs placebo	17.2 vs 25.0	0.025
	Salmeterol vs placebo	24.1 vs 25.0	0.330
	Tiotropium vs salmeterol	17.2 vs 24.1	0.215

COMMENTARY

Brusasco and colleagues focused on 3 (exacerbations, HRQL, and dyspnea) of the 4 important clinical outcomes (the fourth is exercise capacity) in evaluating pharmacotherapy for COPD. The requirement to stop inhaled anticholinergic therapy and long-acting β -agonists before enrollment probably contributed to withdrawals (similar or lower than those of other 6- to 12-mo trials) and shows the challenges of long-term trials in symptomatic and impaired patients.

The delayed time to first exacerbation and the fewer number of COPD exacerbations observed with tiotropium can be expected to have a major effect on reducing hospitalizations and overall health care costs.

Although both tiotropium and salmeterol improved HRQL and dyspnea, neither agent achieved the minimal important difference (MID) established for the SGRQ compared with placebo. However, proportion analyses (proportion of patients achieving the MID) showed favorable results for tiotropium. Compared with placebo, salmeterol was efficacious in some randomized controlled trials, but this and other trials failed to show a consistent benefit (1, 2). Although

methodological issues exist about the measurement and interpretation of the MID (3, 4), a therapeutic trial of tiotropium or salmeterol is appropriate in individual patients with symptomatic COPD.

Donald A. Mahler, MD
Dartmouth-Hitchcock Medical Center
Lebanon, New Hampshire, USA

References

- Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest*. 1999;115:957-65.
- Appleton S, Poole P, Smith B, Veale A, Bara A. Long-acting beta2-agonists for chronic obstructive pulmonary disease patients with poorly reversible airflow limitation. *Cochrane Database Syst Rev*. 2002;(3):CD001104.
- Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Curr Opin Rheumatol*. 2002;14:109-14.
- Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc*. 2002;77:371-83.