Review: Tiotropium reduces exacerbations and hospitalizations in COPD and improves quality of life

Barr RG, Bourbeau J, Camargo CA, Ram FS. **Inhaled tiotropium for stable chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2005;(2):CD002876.

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

QUESTION

In patients with stable chronic obstructive pulmonary disease (COPD), is tiotropium more effective than placebo or other bronchodilators for reducing risk for clinical endpoints?

METHODS

Data sources: The Cochrane Airways Review Group Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE/Excerpta Medica, CINAHL, LILACS (to October 2004); hand-searching 20 respiratory journals, conference abstracts, and bibliographies of relevant studies; and contacting authors.

Study selection and assessment: Randomized controlled trials (RCTs) in any language that included patients > 35 years of age with known stable COPD without evidence of an exacerbation for 1 month before study entry, and compared tiotropium with placebo, ipratropium bromide, or long-acting β-agonists (salmeterol or formoterol) for ≥ 1 month. Studies of patients with diseases other than COPD, previous asthma, cystic fibrosis, bronchiectasis, or other lung diseases were excluded. Study quality was assessed using Cochrane criteria for allocation concealment and the 5-point Jadad scale.

Outcomes: Exacerbations (respiratory symptoms lasting ≥ 3 d), hospitalizations for exacerbations, and all-cause mortality. Secondary outcomes included health-related quality of life assessed using the St. George's Respiratory Questionnaire (SGRQ) and the Transitional Dyspnea Index (TDI), change in FEV_1, change in FVC, and adverse events.

MAIN RESULTS

9 RCTs (n = 6584) met the selection criteria. Tiotropium was compared with placebo (8 RCTs), ipratropium (1 RCT), and salmeterol (1 RCT). Permissible co-therapies were β_2-agonists and inhaled corticosteroids. Allocation concealment was uncertain in 7 RCTs and adequate in 2 RCTs. 7 RCTs had a Jadad score of 4 out of 5 (range 3 to 5). Meta-analysis of 8 RCTs showed that tiotropium reduced exacerbations more than placebo (Table). Tiotropium was more effective than ipratropium in 1 RCT (relative risk [RR] 0.77, 95% CI 0.62 to 0.95). 3 pooled RCTs showed that tiotropium reduced hospitalizations more than placebo (Table). All-cause mortality did not differ between tiotropium and placebo (Table), ipratropium (1 RCT, RR 1.51, CI 0.41 to 5.50), or salmeterol (1 RCT, RR 0.17, CI 0.2 to 1.39). Tiotropium improved mean scores on the SGRQ (weighted mean difference [WMD] −3.27, CI −4.50 to −2.04) and the TDI (RR 1.53, CI 1.33 to 1.77) and increased FEV_1 (WMD 204 mL, CI 185 to 223) and FVC (WMD 387 mL, CI 343 to 431) more than placebo. Dry mouth was a frequent adverse effect in the tiotropium group (Table).

CONCLUSION

In patients with stable chronic obstructive pulmonary disease, tiotropium reduces exacerbations and hospitalizations, and improves health-related quality of life.

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Tiotropium vs placebo for chronic obstructive pulmonary disease at mean 6.3 months*

Outcomes	Number of trials (*n*)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Tiotropium	Placebo		
Exacerbations	8 (5644)	26%	31%	18% (10 to 25)	20 (13 to 34)
Hospitalizations	3 (3552)	5.4%	8.4%	33% (14 to 47)	34 (25 to 100
All-cause mortality	2 (1723)	0.6%	1.6%	50% (–24 to 80)	Not significant
				RRI (CI)	NNH (CI)
Dry mouth	3 (1791)	11%	2%	381% (109 to 672)	12 (7 to 34)

*Abbreviations defined in Glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

The well-executed meta-analysis by Barr and colleagues documents compelling evidence for the efficacy of tiotropium in COPD. Tiotropium has shown beneficial effects for most outcomes that clinicians and patients with COPD consider important. Notable exceptions include mortality and decline in lung function over time. However, no other medications have yet been proven to alter these outcomes, either.

Evidence exists to support a preference for tiotropium over ipratropium, an older, short-acting inhaled anticholinergic that has been the mainstay of COPD therapy for years. Barr and colleagues identified 1 long-term RCT comparing the 2 drugs. This study had the highest methodological validity of any tiotropium study and showed benefits over ipratropium that were both clinically and statistically significant. The greater efficacy of tiotropium is biologically plausible because it has been shown to be more potent, selective, and longer-lasting than ipratropium (1). Furthermore, because ipratropium must be given 4 times/d, compliance with once-daily tiotropium is easier for patients. Finally, unlike tiotropium, no ipratropium studies have documented benefits for clinical outcomes, including exacerbations.

The major disadvantage of tiotropium is cost (up to 7 times more expensive than ipratropium). However, tiotropium is cost-effective in moderate-to-severe COPD (2). This would support the use of tiotropium over ipratropium in such patients.

Whether further benefits can be achieved with tiotropium in combination with long-acting β-agonists and inhaled corticosteroids is the subject of a current, ongoing RCT. Other unanswered questions include whether a role exists for tiotropium in milder COPD and its role in inpatient management of COPD exacerbations.

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References

1. **Barnes PJ.** Chest. 2000;117:63S-6S.
2. **Oostenbrink JB, Rutten-van Mölken MP, Al MJ, Van Noord JA, Vincken W.** Eur Respir J. 2004;23:241-9.