

Formoterol in addition to tiotropium improved airflow obstruction in chronic obstructive pulmonary disease

van Noord JA, Aumann JL, Janssens E, et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest*. 2006;129:509-17.

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

QUESTION

In patients with chronic obstructive pulmonary disease (COPD), does the addition of inhaled formoterol, once or twice daily, to inhaled tiotropium improve efficacy?

METHODS

Design: Randomized, placebo-controlled, crossover trial.

Allocation: Unclear allocation concealment.*

Blinding: Blinded (outcome assessors).*

Follow-up period: 2 weeks for each treatment.

Setting: 3 hospitals in The Netherlands and Belgium.

Patients: 95 patients ≥ 40 years of age (mean 64 y, 76% men) who were current or former smokers and had COPD, stable airways obstruction with $FEV_1 \leq 60\%$ of predicted value, and an FEV_1 -FVC ratio $< 70\%$. Exclusion criteria included asthma, allergic rhinitis, other serious disease, recent cardiac disease, current receipt of oxygen, and recent respiratory infection.

Intervention: All patients had 2 weeks of pre-treatment with tiotropium inhalation powder, 18 μg once daily, then received 3 treatments for 2 weeks each, in random order without washout: tiotropium plus placebo morning and evening; tiotropium plus formoterol inhalation powder, 12 μg , in the morning and placebo in the evening; and tiotropium plus formoterol morning and evening. The appearance of the placebo differed from that of formoterol; thus, the patient was not blinded. Salbutamol was provided as rescue medication as needed.

Outcomes: Average, peak, and trough response (difference from baseline) in FEV_1 , FVC, and inspiratory capacity (IC) in the last 24 hours of each treatment period; and use of rescue medication.

Patient follow-up: 96%.

MAIN RESULTS

Tiotropium plus formoterol once or twice daily improved 24-hour average and peak response in FEV_1 , FVC, and IC compared with tiotropium alone (Table). Tiotropium plus formoterol twice daily also improved trough response in FEV_1 compared with tiotropium alone, and 24-hour average and trough response in FEV_1 compared with tiotropium plus formoterol once daily (Table). Average response in FEV_1 and FVC in the second half of the 24-hour period

was greater with tiotropium plus formoterol twice daily than with the other 2 treatments. Rescue medication was used less with formoterol. Adverse events did not differ among groups.

CONCLUSION

In patients with chronic obstructive pulmonary disease, the addition of inhaled formoterol, once or twice daily, to inhaled tiotropium improved lung function.

Source of funding: Boehringer Ingelheim.

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*See Glossary.

Tiotropium alone or with formoterol once or twice daily for chronic obstructive pulmonary disease at 2 weeks†

Outcomes	Value	Mean response (change from baseline)		
		Tiotropium	Tiotropium + formoterol once daily	Tiotropium + formoterol twice daily
FEV_1 (L)	24-h average	0.08	0.16‡	0.20‡§
	Peak	0.23	0.38‡	0.39‡
	Trough	0.13	0.13	0.18‡§
FVC (L)	24-h average	0.28	0.40‡	0.43‡
	Peak	0.59	0.79‡	0.78‡
	Trough	0.37	0.34	0.39
IC (L)	24-h average	0.12	0.20‡	0.22‡
	Peak	0.39	0.53‡	0.55‡
	Trough	0.17	0.17	0.19

†IC = inspiratory capacity. Baseline values were 1.05 L for FEV_1 , 2.57 L for FVC, and 2.18 L for IC.

‡ $P < 0.05$ vs tiotropium.

§ $P < 0.05$ vs tiotropium + formoterol once daily.

COMMENTARY

Several randomized controlled trials have shown that monotherapy with long-acting acetylcholinesterase inhibitors has a positive effect on health-related quality of life, exacerbations, and dyspnea in patients with COPD (1). Additional therapy with long-acting β -agonists (LABAs) may further improve patient-important consequences because of the different mechanism of action.

Van Noord and colleagues showed that combination therapy under controlled experimental conditions improved average daily pulmonary function. While elegant in the 24-hour measurement of pulmonary function, including IC, this fairly small study in a selected group of patients with COPD has several features that require attention. First, the improvements in pulmonary function measures were small and their importance to patients is not known. Second, patient-important, long-term outcomes were not studied. Third, the size of the study

precluded addressing moderately frequent adverse outcomes. Fourth, safety issues about LABAs have been raised because of increased rates of hospitalization and death (2, 3). Thus, before dual therapy is adopted, larger randomized trials addressing patient-important outcomes are needed. At present, safety concerns should limit its use.

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References

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