The "Towards a Revolution in COPD Health" study

Comparing treatment strategies

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Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356(8):775-89.

Research question

Does treatment with salmeterol and fluticasone propionate combination (SFPC) reduce all-cause mortality compared with placebo (PL) in patients with chronic obstructive pulmonary disease (COPD)?

Type of article and design

Prospective, randomized, double-blind trial, in which outcomes for patients taking 50µg of salmeterol plus 500µg of fluticasone propionate (the SFPC regimen) twice daily (administered with single inhalers) were compared with outcomes for patients taking PL, 50µg of salmeterol alone, or 500µg of fluticasone propionate (FP) alone, twice daily, for a period of 3 years. All-cause mortality was the primary outcome variable for the comparison between SFPC and PL.

Relevance to family physicians

Chronic obstructive pulmonary disease affects about 4% of Canadian adults, and it is estimated that morbidity and mortality from COPD will continue to increase during the next 15 years, particularly among aging women.[1] With the exception of smoking cessation programs for patients with early-stage disease,[2] lung-volume reduction surgery for selected patients with emphysema,[3] and home oxygen therapy for chronically hypoxic patients,[4] no treatment has been shown to reduce mortality.

Retrospective data[5] suggest that inhaled corticosteroids (ICSs) reduce mortality among patients with COPD and that this benefit can be enhanced with the addition of a long-acting β_2-agonist (LABA).[6] Surprisingly, ICSs have little or no effect on the rate of lung function decline in COPD. Current guidelines suggest that ICSs are overused in patients with COPD.[1] At present, it is not clear how different treatment strategies—including the ICS and LABA combination—influence long-term COPD management and mortality.

Overview of study outcomes

The study involved patients (n=6112, 75% male) who were current or former smokers with at least a 10-pack-year history, who had diagnoses of COPD, and who had mean values of postbronchodilator forced expiratory volume in 1 second (FEV_1) of approximately 44% of predicted value. After a 2-week run-in period, patients were randomized to the SFPC, salmeterol, FP, or PL regimens, all taken in the morning and in the evening for 3 years. Study medications were administered as dry powders using inhalers. Before the run-in period, ICS and LABA therapies were discontinued but patients were allowed to continue using other medications for COPD. An independent safety and efficacy data-monitoring committee performed safety measures every 6 months. Two interim efficacy analyses were performed, the first after 358 deaths had occurred and the second after a total of 680 deaths had occurred. Assuming a 17% mortality rate in the PL group at 3 years, it was estimated that 1570 patients would be needed for each study group to detect a reduction in mortality of 4.3% in the SFPC group compared with the PL group, at the 2-sided α level of .05 with a power of 90%. Difference in time to death from any cause between the SFPC and PL groups was analyzed with the use of the log-rank test (with stratification according to smoking status) and expressed as a hazard ratio. A Cox proportional hazard model was used as a supportive secondary analysis.

Results

Vital statistics were known for all the 6112 patients included in the efficacy analysis at 3 years. Deaths from any cause at 3 years were at 12.6%, 15.2%, 13.5%, and 16% in the SFPC, PL, salmeterol, and FP groups, respectively. There was a 2.6% absolute risk reduction of death in the SFPC group compared with the PL group and a hazard ratio of 0.825 (95% confidence ratio, 0.681 to 1.002; $P=.052$). Mortality rates for salmeterol alone and FP alone did not differ significantly from that of PL ($P=.18$ and $P=.53$, respectively). The risk of death in the SFPC group did not differ significantly from that in the salmeterol group ($P=.48$). Patients in the SFPC group were less likely to die than those receiving FP alone ($P<.007$). Annual admission rates were 17% lower in the SFPC and salmeterol groups compared with the PL group ($P\leq.03$ for both). The SFPC, salmeterol, and FP groups reduced the annual rate of exacerbations compared with the PL group. There were no differences in the incidence of ocular or bone side effects in any of the groups. Of interest, the probability of having pneumonia reported as an adverse event was higher among patients receiving therapy that contained FP (19.6% in the SFPC group

and 18.3% in the FP group) than in the PL group (12.3%) ($P<.001$ for comparisons between SFPC or FP and PL). Cumulative incidences of discontinuation of study drugs at 3 years were 33.7%, 38.1%, 36.4%, and 43.5% in the SFPC, FP, salmeterol, and PL groups, respectively.

Analysis of methodology

This landmark study compared various treatment strategies with PL with all-cause mortality as the primary outcome variable. Given the need for 2 interim analyses to evaluate efficacy and safety between SFPC and PL, the *P* value for the primary comparison between SFPC and PL was adjusted upward to maintain an overall significance level of .05. Given the trial design and the nature of the primary outcome variable, the use of a log-rank test, with stratification according to smoking status, seems appropriate.

As current treatment guidelines recommend the use of long-acting bronchodilators as first-line maintenance therapy in COPD when symptoms are persistent, it could be argued that the comparison of SFPC with PL among patients who require (at minimum) regular maintenance therapy would be less clinically relevant than a comparison between SFPC and an LABA such as salmeterol.

Application to clinical practice

This study suggests that treatment with SFPC, salmeterol, or FP does not significantly improve all-cause mortality compared with PL. The finding of high discontinuation rates among all the active treatment groups underscores the reality that many patients with COPD do not appear to respond favourably to currently available therapies, making it very difficult for family physicians to identify which patients are likely to benefit from long-term therapy. The finding that there were no differences between SFPC and salmeterol for all-cause mortality and severe exacerbations requiring hospitalizations suggests that treatment with salmeterol is also effective; however, end points such as exacerbations requiring systemic corticosteroids, lung function, and quality of life respond more favourably to SFPC than the other groups studied. It is not clear why the probability of having pneumonia reported as an adverse event was high among patients receiving therapy that contained FP, but this observation has been confirmed by another recent study[7] involving patients using SFPC. These findings require further study. The fact that 75% of patients studied were men also limits application of these findings to women with COPD.

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Competing interests

Dr D'Urzo *has received research and consulting fees from the following companies: Novartis, AstraZeneca, Methapharma, and Schering-Plough.*

BOTTOM LINE

- Treatment with salmeterol and fluticasone propionate combination does not significantly reduce mortality compared with placebo or salmeterol.
- There were no differences between salmeterol and the salmeterol and fluticasone propionate combination in all-cause mortality and severe exacerbations requiring hospitalization.
- Therapy that contains fluticasone propionate is associated with high probability of pneumonia.
- The high discontinuation rate of all the treatments makes it difficult to generalize the findings of this study to COPD patients in real-world practice.
- The results of this study do not justify changes in guideline recommendations for COPD management.

POINTS SAILLANTS

- Le traitement combinant du salmétérol et du propionate de fluticasone ne réduit pas la mortalité de manière significative en comparaison du placebo ou du salmétérol seul.
- Il n'y avait pas de différence entre le salmétérol et la combinaison de salmétérol et de propionate de fluticasone en ce qui a trait la mortalité toutes causes confondues et aux exacerbations graves exigeant l'hospitalisation.
- Les thérapies à base de propionate de fluticasone sont associées à une forte probabilité de pneumonie.
- Le taux élevé de discontinuation de tous les traitements rend difficile la généralisation des constatations de cette étude aux patients atteints de BPCO dans la pratique réelle.
- Les résultats de cette étude ne justifient pas de changer les recommandations des lignes directrices pour la prise en charge de la BPCO.

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