Treatment of chronic obstructive pulmonary disease: Combination or component therapy?

Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al, for the TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449-56.

Background: Chronic obstructive pulmonary disease (COPD) is a progressive disorder marked by frequent exacerbations, impaired health status and substantial economic costs. Long-acting β_2-agonists improve lung function and health status and alleviate symptoms in patients with COPD, and inhaled corticosteroids decrease the frequency of exacerbations and reduce the rate of decline in health status.[1,2]

Question: Is combined therapy with salmeterol (a β_2-agonist) and fluticasone (an inhaled corticosteroid) for COPD better than either drug used alone?

Methods: This randomized, double-blind, placebo-controlled trial recruited 1465 outpatients with COPD in 25 countries. Inclusion criteria were a baseline, pre-bronchodilator forced expiratory volume in 1 second (FEV_1) 25%–70% of that predicted, an increase in post-bronchodilator FEV_1 less than 10% of that predicted and a pre-bronchodilator ratio of FEV_1 to forced vital capacity (FVC) of 70% or less. Participants also had a history of at least 10 cigarette pack-years of smoking, chronic bronchitis, at least 1 acute COPD exacerbation per year in the previous 3 years, and at least 1 COPD exacerbation in the year before trial entry. Exclusion criteria were the presence of respiratory disorders other than COPD, the need for regular oxygen therapy or the use of systemic corticosteroid therapy, high-dose inhaled steroid therapy or antibiotic therapy in the 4 weeks before enrolment.

Patients were randomly assigned to receive salmeterol alone (50 μg twice daily), fluticasone alone (500 μg twice daily), a combination of salmeterol and fluticasone (50 and 500 μg, respectively, twice daily) or placebo. The primary end point was the FEV_1 after 12 months of treatment. Secondary end points included other lung function measurements, use of relief medication, respiratory symptoms, COPD exacerbations, health status (defined using a validated questionnaire) and adverse events. Analyses were performed according to the intention-to-treat principle.

Results: The mean age of the participants was 63 years, 27% were women, and 51% were current smokers. The mean pre-treatment FEV_1 was 45% of that predicted. Significantly fewer patients withdrew from the fluticasone (29%) and combination (25%) groups than from the placebo (39%) and salmeterol (32%) groups.

There was a significantly greater improvement in pre-bronchodilator FEV_1 at 12 months in the combination group (10% increase) than in the other groups (2% increase in the salmeterol and fluticasone groups, and 3% decrease in the placebo group). Improvement was evident by week 2 and was sustained throughout treatment; similar trends were noted for other lung function measures. All 3 active treatments significantly reduced the incidence of COPD exacerbations (by 19%–25%) compared with placebo, with no significant differences between the treatment groups. Combination therapy significantly reduced symptoms of dyspnea and use of rescue medication, as compared with the other 3 groups. Only patients in the combination group had a significant improvement in health status by week 52. Rates of adverse events were similar between the groups, except for oropharyngeal candidiasis, which was more frequent in the fluticasone (7%) and combination (8%) groups than in the salmeterol or placebo (2% in each) groups.

Commentary: COPD is a leading cause of morbidity and mortality worldwide and imposes a considerable burden on patients, health care services and society.[3] Goals of therapy are to control symptoms, prevent exacerbations and improve lung function and health status. This well-conducted randomized controlled study has persuasively demonstrated that it is possible to achieve all of these aims with the combination of a long-acting β_2-agonist and inhaled corticosteroid, therapies that individually have shown efficacy for this disease.[1,2] Combination therapy improved FEV_1, other lung function measures and daily respiratory symptoms to a greater extent than either drug alone and was the only treatment that improved health status. Benefit was apparent very early and was sustained over the course of the trial.

The strengths of the TRISTAN trial include its negligible loss to follow-up (2%), a longer duration than most previous COPD trials and the fact that individual therapies were compared with both combination therapy and placebo. There were several limitations, however. Notably, the trial recruited a select group of patients with COPD, and the results may not be generalizable to patients with extremely advanced or mild forms of the disorder. Also, it was not possible to demonstrate a difference in the rate of exacerbations between the component groups and the combination group, a problem that may have been due to the unexpectedly low number of exacerbations in the trial.

Practice implications: Previous guidelines for the management of COPD have emphasized a stepwise treatment approach: bronchodilators are introduced early for all patients with COPD, and inhaled corticosteroids are added only for those with severe disease (FEV_1

less than 50% of predicted), repeated exacerbations and a documented spirometric response to inhaled steroids.[4] The TRISTAN study widens the indications for inhaled corticosteroids to patients with frequent exacerbations and moderate to severe disease, largely irrespective of FEV_1, and probably will obviate the need to demonstrate steroid responsiveness a priori. Therefore, the combination of a long-acting β_2-agonist and an inhaled corticosteroid should be considered for patients with moderate to severe COPD who have frequent exacerbations of their disease.

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