Inhaled triple therapy in chronic obstructive pulmonary disease

In the TRIBUTE study,[1] Alberto Papi and colleagues (March 17, p 1076) reported a small but significant reduction of the exacerbation rate with the addition of an inhaled corticosteroid to dual long-acting bronchodilation in patients with chronic obstructive pulmonary disease and severe or very severe airway obstruction with at least one exacerbation in the previous year. Data derived from the ISOLDE study[2] showed that abruptly stopping treatment with inhaled corticosteroid was associated with an increased risk of exacerbation in about 25% of patients, with a median delay of 20 days. This result contrasts with data showing that progressive weaning of inhaled corticosteroid is not associated with an increased rate of exacerbation in patients treated with dual bronchodilation, at least in those with blood eosinophils below 2% of total white blood cell count.[3,4]

The run-in period of the TRIBUTE study was only 2 weeks and was associated with an abrupt weaning of inhaled corticosteroid in about two thirds of patients.[1] Accordingly, whether the difference in exacerbation rate between the two study groups was due to the weaning of inhaled corticosteroid at study entry in patients allocated to dual bronchodilation is not clear. This hypothesis fits with the rapid divergence (within 4 weeks of entry in the randomisation phase) of the two groups and the later parallel course when looking at the chance of having an exacerbation (figure 3 of the Article appendix). An analysis of the primary endpoint within subgroups defined according to inhaled corticosteroid treatment before entering the study would therefore be welcome.

See Online for appendix

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1 Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; **391:** 1076–84.
2 Jarad NA, Wedzicha JA, Burge PS, Calverley PM. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. *Respir Med* 1999; **93:** 161–66.
3 Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; **371:** 1285–94.
4 Watz H, Tetzlaff K, Wouters EFM, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; **4:** 390–98.

Alberto Papi and colleagues[1] reported that in 1532 patients with a history of exacerbation, triple therapy significantly reduced the exacerbation rate by 15% compared to double bronchodilation, without changing the individual patient risk of having at least one exacerbation. This statistical significance should be interpreted cautiously. Considering the relatively large difference in exacerbation rate and the large number of patients, a p value of 0·043 could be explained by differences in the distribution of exacerbations per patient.

Szafranski and colleagues[2] reported that adding budesonide to formoterol in 409 patients with chronic obstructive pulmonary disease resulted in a 23% lower exacerbation rate (p<0·043) than in patients treated with formoterol only. From the detailed analysis of the exacerbations distribution, this difference was related to just three patients treated with formoterol who had more than ten exacerbations per year and who might have benefited from steroid treatment (appendix).

The authors of the TRIBUTE study should provide such detailed exacerbations distribution to be truly transparent in the interpretation of the results. A few or even a single patient with very frequent exacerbations might be sufficient to induce such a statistically significant difference between groups.

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1 Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; **391:** 1076–84.
2 Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003; **21:** 74–81.

Single-inhaler triple therapy has been proposed for patients with symptomatic, frequently exacerbating chronic obstructive pulmonary disease (COPD), with the main aim of reducing eosinophilic-driven exacerbations by the inhaled corticosteroid moiety.[1] Findings from the TRIBUTE study[2] showed a 15% overall reduction in exacerbations and no difference in pneumonia risk when comparing a triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium to a dual combination of indacaterol plus glycopyrronium in COPD. The IMPACT trial[3] showed a 25% overall reduction in exacerbations comparing fluticasone furoate, vilanterol, and umeclidinium versus vilanterol plus umeclidinium in COPD in conjunction with a 53% increased pneumonia risk. Unsurprisingly, the same pneumonia signal was seen with fluticasone furoate and vilanterol.