Combination of ICSs and LABAs should be used in the management of patients with COPD – The con argument

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The management of patients with symptomatic chronic obstructive pulmonary disease (COPD) has become more clear in the past several years. New medications have been developed and their efficacy has been evaluated using important outcomes in addition to forced expiratory volume in 1 s (FEV_1), such as health-related quality of life (HRQL), frequency of exacerbations and dyspnea scores. I will review five well-designed, randomized, controlled trials that have advanced our knowledge about the use of inhaled corticosteroids (ICSs), long-acting beta₂-agonists (LABAs) and their combination.

The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study (1) compared fluticasone propionate 1000 µg daily with placebo. There was no difference in the rate of decline in FEV_1 . However, in this group of severe (as measured by FEV_1) COPD patients (FEV_1 1.4 L, 50% predicted), the exacerbation rate decreased by 25%. Exacerbations were defined as those requiring antibiotics and/or oral steroids. Patients received 14 days of 0.6 mg/kg prednisolone in the run-in period; responders to this oral steroid trial in terms of FEV_1 did not predict response to ICSs. HRQL declined more rapidly in the placebo group, and the reduced rate of decline in HRQL in the treatment group was attributed to the reduction in exacerbations in the treatment group. A meta-analysis (2) of ICS trials before the ISOLDE study supported the observation of a 30% reduction in exacerbation rate. Two recent observational studies have evaluated the effectiveness of ICSs in reducing mortality and hospital readmission rates in patients with COPD (3,4). Inherent biases in observational studies, particularly immortal time biases, lead to conflicting results regarding the positive effect of ICSs. The prescription of ICSs also must be balanced against the potential side effects. A recent meta-analysis by Lipworth (5) highlighted the potential adverse effects, including adrenal suppression at doses greater than 1500 µg (beclomethasone equivalent), increased risk of subcapsular cataracts, and skin bruising and thinning. Recent studies (6-8) have also pointed to a relationship between ICSs and reduced bone marrow density and increased vertebral fractures. The latter three studies, however, were observational and are hence subject to some bias.

Who in the COPD population benefits from ICSs? They have not been shown to be disease modifying. In themselves, they appear to have little effect on dyspnea relief, there are potential side effects and the old 'saw a trial of oral steroids to look for the so-called steroid responder' argument appears to be invalid. The ISOLDE study did not find that responders to

prednisone in the run-in period predicted response to ICSs; Senderovitz et al (9) studied patients with COPD and found that only two of 40 responded to oral prednisone. The recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommended a one-and-one-half- to three-month trial of ICSs and a reassessment of the FEV_1 at the end of the trial, which should show a 200 mL or 15% increase. There are no data that the present author is aware of that substantiate this approach, but it may be useful in separating out misdiagnosed asthmatic patients. Accordingly, ICSs used alone may indeed benefit patients with recurrent exacerbations (at least three/year), as suggested by the recent Canadian COPD guidelines (10), but their role otherwise in COPD remains unclear.

What about the addition of a LABA to an ICS, ie, combination therapy? I will review the four available papers that evaluate combination therapy compared with either monocomponent therapy or placebo in the treatment of COPD. The first, the Trial of Inhaled Steroids and Long-Acting Beta₂-Agonists (TRISTAN) by Calverley et al (11), evaluated the effect of fluticasone propionate 1000 µg daily in combination with salmeterol 100 µg daily in patients with severe COPD (mean FEV_1 1.3 L). These patients were similar to the ISOLDE study patients in terms of severity of COPD and lack of response to bronchodilators (mean response 4%). These patients differed in that they were selected on the basis of having had at least one exacerbation in each of the previous three years. The primary outcome in this study was FEV_1 , and one of the main secondary outcomes was the exacerbation rate. The ISOLDE study lasted for three years, but the TRISTAN study only lasted for one year. Patients were allowed to continue taking anticholinergics, theophylline and salbutamol, but this was not done in any regimented fashion. Exacerbations were again defined as requiring antibiotics and/or systemic steroids. The combination showed no benefit over fluticasone propionate alone or, indeed, over salmeterol alone in reducing the exacerbation rate. There was a statistically significant benefit of the combination therapy over salmeterol alone in terms of FEV_1 , but this only amounted to 48 mL on average and did not result in any significant benefit in HRQL. In this study, the LABA alone reduced the exacerbation rate to a similar degree as the combination therapy or, indeed, as fluticasone propionate alone.

The second study evaluating combination therapy by Szafranski et al (12) studied a slightly more severe group of

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COPD patients (mean FEV₁ 1 L, 36% predicted). These patients also had a minimal bronchodilator response (on average 5% to 6%) and had had at least one exacerbation in the previous year. Compared with the TRISTAN study (11), the placebo group had 1.9 exacerbations compared with 1.3 exacerbations, which suggests that not only was the FEV₁ lower, but the exacerbation rate was higher in the Szafranski et al (12) study. The duration was again one year, and the patients were allowed only terbutaline as a relieving medication. As in all of these studies, there was a high dropout rate, between 30% and 45%. Exacerbations were defined in a similar fashion. The dose of ICSs was less than in the TRISTAN study – 640 µg daily – and the ICS used was budesonide rather than fluticasone. The LABA was formoterol, at a total daily dose of 18 µg. With this intervention, the combination reduced the exacerbation rate by 24% compared with placebo. However, budesonide alone did not reduce exacerbations significantly. The combination produced an impressive 150 mL improvement in FEV₁, the primary outcome variable, compared with placebo. However, this improvement in FEV₁ was not better than formoterol alone. The increase in FEV₁ was associated with an improvement in HRQL, but this benefit was also obtained with formoterol alone. Accordingly, in this more severe group of COPD patients, ICSs alone did not reduce the exacerbation rate. ICSs did produce a small increase in FEV₁, but this was not translated into improvement in HRQL. Compared with salmeterol alone in the TRISTAN study, the LABA formoterol did not result in a similar reduction in exacerbation rate compared with the combination therapy.

The two remaining studies that evaluated combination therapy include a study by Mahler et al (13) and one by Hanania et al (14). Both of these studies evaluated combination therapy, but in a different population than the TRISTAN (11) and Szafranski et al (12) studies. The patients did have severe COPD (FEV₁ 1.2 L, 40% predicted). However, these patients were selected based on a history of chronic bronchitis and demonstrated, on average, a 20% response to an inhaled bronchodilator. The primary outcomes again included FEV₁. The studies were shorter in duration (six months). Neither study was designed to evaluate exacerbations as a secondary outcome, but HRQL and dyspnea indexes, and the transitional dyspnea index (TDI) were evaluated. The Mahler et al study used total daily doses of 1000 µg fluticasone propionate and 100 µg salmeterol. Salbutamol and theophylline were allowed as relieving medications. In the Mahler et al study, combination therapy produced an impressive improvement in FEV₁ of 231 mL postbronchodilator, which resulted in an improvement in HRQL and the TDI. Compared with salmeterol alone, the FEV₁ only increased by 40 mL. This did not result in an improvement in HRQL, but did result in an improvement in

the TDI of 1.2, which would be considered clinically significant. The Hanania et al study used salmeterol and a total daily dose of 500 µg fluticasone propionate. Again, a marked improvement in FEV₁ (214 mL) with combination therapy compared with placebo was found, and this resulted in an improvement in HRQL and the TDI. When the combination was compared with salmeterol alone, there was a 74 mL benefit of the combination therapy versus salmeterol alone, but this did not result in a corresponding improvement in HRQL or the TDI. These two studies suggest that combination therapy can produce an additional benefit over salmeterol alone in terms of FEV₁, and this does, in some cases, translate into a reduction in the TDI (in the Mahler et al study but not in the Hanania et al study). Accordingly, in patients with severe COPD and a marked reversible component (eg, 20%), combination therapy using a high dose of the ICS fluticasone (1000 µg daily) produced a statistically significant benefit in FEV₁ in one study (40 mL), which resulted in an improved sensation of dyspnea compared with salmeterol alone.

The above studies do show some benefits of combination therapy in specific instances. However, no study has looked at the effects of combination therapy when the patients were on optimal bronchodilation. Patients were allowed varying amounts of different types of relieving medications during the studies. Because there was no routine use of first-line bronchodilators, it is difficult to determine which patients should be offered either monotherapy or combination therapy with ICSs and a LABA. Patients who are frequent exacerbators and have severe COPD may benefit from high dose ICSs, eg, a total daily dose of 1000 µg of fluticasone propionate, in terms of reducing exacerbations. However, salmeterol alone may produce similar reductions in exacerbation rate based on the TRISTAN study. For patients with severe COPD and a large reversible component, combination therapy can impart a significant improvement in FEV₁, which, in the Mahler study, translated into an improvement in sensation of dyspnea (TDI score).

In the end, patients with severe COPD are struggling to breathe, and clearly, their quality of life is affected by severe exacerbations. In my opinion, and as an admitted participant in the recently published CTS COPD guidelines, a stepwise approach to the treatment of COPD as advocated in the guidelines is preferred. When patients remain symptomatic after administration of the available bronchodilators, a trial of combination therapy, eg, adding an ICS, should be considered on a case-by-case basis. The effect of such an intervention should be closely monitored in individual patients to determine any perceived benefits. We await the results of ongoing and future studies to more precisely define the role of combination therapy.

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