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New options for bronchodilator treatment in COPD

P M A Calverley

Although the definition of chronic obstructive pulmonary disease (COPD) is now more elaborate than in the past,¹ the presence of persistent airflow obstruction is still a cardinal feature of this illness, and improved lung emptying, usually expressed as an increase in forced expiratory volume in 1 s (FEV₁), is a key goal of chronic disease management. This can be achieved in several ways, ranging from lung volume reduction surgery² to anti-inflammatory treatments such as inhaled corticosteroids or phosphodiesterase type IV (PDE IV) inhibition^{3,4} even on a background of existing inhaled bronchodilators.⁵ However, for most patients, inhaled bronchodilator drugs remain the cornerstone of drug treatment for this disease. Historically, shorter acting bronchodilators, and especially the antimuscarinic agent ipratropium, were the mainstay of treatment. Although these drugs were initially recommended for use twice or three times per day, later data based on the time course of FEV₁ change showed that their effects only lasted for 4–6 h at best. Combining β -agonists with antimuscarinic drugs increased the peak values for FEV₁ change without greatly changing this limited period of activity.⁶ The development of long-acting inhaled β -agonists, such as salmeterol⁷ and formoterol,⁸

showed that it was possible to improve lung function and health status, although their effects on exacerbation frequency were less impressive.^{9,10} When the first truly 24 h bronchodilator drug, the antimuscarinic agent tiotropium, became available, it soon became obvious that this drug could produce significant improvements in morning FEV₁¹¹ together with better health status and fewer exacerbations than had proved possible with regular ipratropium treatment,¹² findings shown to occur on a background of multiple other treatments in the recent UPLIFT trial.¹³ Previous randomised direct comparisons between tiotropium and salmeterol suggested that lung function tended to be better with tiotropium treatment, with non-significant differences in health status and exacerbations tending to favour the antimuscarinic drug.¹⁴ Whether these differences represent an important clinical effect or, specifically, a more favourable response resulting from blockade of muscarinic receptors remained unclear, particularly since the duration of action of the drugs was quite different.

Recently, the first once-daily inhaled β -agonist indacaterol has been tested in healthy subjects, patients with asthma and subjects with COPD. Dose-ranging trials have been reported in patients with COPD which showed benefits at some doses comparable with those seen in a tiotropium comparator group.¹⁵ In this issue of *Thorax* (see page 473), Dahl and colleagues (the same first author who reported the early beneficial effects or

formoterol 8 years ago) present the results of a large randomised prospective double-blind placebo-controlled study that compares two doses of indacaterol (300 and 600 mg) given once daily with formoterol 12 μ g twice daily and placebo in 1732 stable patients with COPD.¹⁶ The primary outcome was the change in trough FEV₁—that is, the value before the morning dose of medication, which was 170 ml greater than placebo when indacaterol was given and 100 ml greater than formoterol at 12 weeks into the study. Both these comparisons were statistically significant and were supported by significant improvements in other prespecified pulmonary function outcomes in favour of indacaterol. These changes were maintained throughout the study and were independent of concomitant medication including inhaled corticosteroids. Clinically, the patients receiving the inhaled β -agonists fared better, with more of them completing the 1 year trial. All three β -agonist regimes were associated with better clinical outcomes such as reductions in the exacerbation rate, the total St Georges Respiratory Questionnaire (SGRQ) score and in reported dyspnoea relative to placebo-treated patients. Numerically, greater improvements in SGRQ and dyspnoea scores (but not exacerbation rate) were observed when compared with formoterol. However, these differences in clinical outcomes were not statistically significant when directly compared. Overall, there were no worrying safety concerns with the new drug and no excess episodes of tachycardia or evidence of ECG changes in the indacaterol-treated patients. However, tremor was reported slightly more often in patients receiving the higher dose of indacaterol, whilst transient cough after using the inhaled treatment was an issue in almost 1 in 5 of indacaterol-treated participants. Although

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a consistent finding, it did it seem to impact their health status adversely.

Inevitably this well conducted trial will raise some further questions. The patients included here were less severe, as judged by their postbronchodilator lung function, than in other recent COPD studies (mean FEV₁ 52% predicted here). They appeared to have a greater degree of reversibility than reported in other COPD trials, although the absolute lung function changes are difficult to calculate from the data given and are unlikely to be as great as the numbers based on a percentage change from baseline would suggest.¹⁷ Over half of the patients were using inhaled corticosteroid during the trial and it would be interesting to know whether some of the clinical outcomes, such as the improvement in breathlessness or the exacerbation frequency, showed any interaction between this background treatment and the new drugs. Certainly, the exacerbation rate was lower than in other studies, perhaps reflecting the selection criteria or the use of concomitant medication. Similar problems have been seen when the effects of combination of treatments with monotherapy with long-acting β -agonists on these clinical outcomes have been compared in similar 1 year studies.¹⁸ However, the data showing superiority of indacaterol to formoterol in terms of lung function are very convincing. Direct comparisons between indacaterol and long-acting antimuscarinic agents such as tiotropium will be awaited with interest and should resolve the long-standing question of whether drugs targeted to block or stimulate specific pathways moderating airway smooth muscle function do produce different responses in patients with COPD. Likewise it will be

important to establish whether there are advantages in combining once-daily β -agonists with once-daily inhaled corticosteroids, which can also have clinical effects in COPD,¹⁹ when compared with existing twice-daily regimes. For now we can be assured that long-acting inhaled β -agonists have arrived, are effective and offer the prospect of simpler treatment for our patients.

Competing interests I have advised and led clinical trials of bronchodilator therapy for several companies including GSK, Boehringer Ingelheim and AstraZeneca. I have advised Noartis, the study sponsors, on study design and serve on a data safety monitoring board for another trial they are running in COPD.

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Respiratory disease in 2010: looking to the past will prepare us for the future

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Hanging on the wall in my office are two obituaries, one of Dr Charles Fletcher who died in 1995¹ and the other of Dr Benjamin Burrows who died in 2002.² Their pictures look over the desk where I do a great deal of my work and provide

inspiration and, through their collective body of work, guidance. I would like to think that the work that I do continues in a very small way the work that these giants in our field started. Dr Fletcher was responsible for, among other accomplishments, defining the natural history of chronic obstructive pulmonary disease in his landmark study of British men.^{3–5} Dr Burrows founded the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD)⁶ that has added greatly to our knowledge of respiratory disease. Drs Fletcher and Burrows trained and mentored many of our current leaders in respiratory health and coauthored several publications.^{7–8} An ongoing legacy