Chronic obstructive pulmonary disease: the evidence for use of tiotropium

Tiotropium is the first long-acting anticholinergic bronchodilator for the treatment of chronic obstructive pulmonary disease. There is now evidence that it improves key clinical outcomes. Doctors need to decide how this evidence base should influence clinical practice.

Chronic obstructive pulmonary disease (COPD) is a progressive destructive pathology primarily caused by cigarette smoking. It is currently estimated that almost 1 million people in the UK have been diagnosed with COPD, with an equivalent number undiagnosed (Soriano et al, 2000). Worldwide approximately 1 million people die each year as a direct result of COPD and its complications (Ezzati and Lopez, 2003). Many more patients suffer disability, reduced quality of life and social isolation.

Clinically, COPD is characterized by airflow obstruction, which is not fully reversible. The absence of significant reversibility (in contrast to asthma) has led, in the past, to a rather nihilistic approach to its management.

The guideline on the management of COPD from the National Institute for Clinical Excellence (NICE, 2004) identifies aims of treatment as controlling symptoms, improving exercise tolerance and decreasing exacerbation frequency. This reflects a philosophical shift in clinical practice away from defining success by changes in lung function to outcomes that are important to patients. Underlying this change is a better understanding of how abnormal respiratory dynamics contribute to symptoms and an accumulation of evidence from randomized trials that inhaled therapy can have a significant impact on important clinical outcomes.

Short-acting bronchodilators in COPD

Airflow obstruction in COPD is secondary to both airway and parenchymal pathology. Within the airways, lumenal narrowing results from both inflammatory changes (Barnes, 2000) and bronchoconstriction mediated by increased cholinergic tone (Gross et al, 1989).

Inhaled short-acting bronchodilators (salbutamol and ipratropium) are the drugs of first choice to reduce breathlessness in patients with stable COPD. Management guidelines avoid choosing between these agents (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2004; NICE, 2004; PRODIGY, 2004) but inhaled short-acting beta-2 agonists are more widely used. Beta-2 agonists cause bronchodilatation by stimulating beta-adrenergic receptors on bronchial smooth muscle, whereas anticholinergic agents increase airways patency by blocking muscarinic receptors on airways smooth muscle, reducing cholinergic tone; they also decrease mucus secretion, although the clinical importance of this is uncertain.

Salbutamol has a faster onset of action than ipratropium (5 minutes *vs* 15 minutes) and is therefore preferred for use as a rescue bronchodilator; however, its duration of action is shorter. Short-acting beta-2 agonists have been shown to increase forced expiratory volume in 1 second (FEV_1), reduce breathlessness and improve disease-related aspects of quality of life; short-acting anticholinergic agents (i.e. ipratropium) have also been shown to increase FEV_1 but there are conflicting data on their effects on clinical outcomes (NICE, 2004). COPD is a progressive disease so most patients will inevitably require more intensive bronchodilator therapy sooner or later. Beta-2 agonists and anticholinergic agents have complementary modes of action and, in the short term, regular administration of salbutamol with ipratropium improves lung function (as measured by FEV_1) by about one-quarter compared with monotherapy (Kerstjens et al, 2004). However, there is a lack of evidence that symptoms are also improved (Bone et al, 1994) and if there is no clinical improvement after a 4-week trial combination therapy should be discontinued.

Tiotropium: a long-acting anticholinergic bronchodilator

Tiotropium is a recently developed long-acting anticholinergic bronchodilator. It has both a greater affinity for and a slower rate of dissociation from muscarinic receptors than ipratropium (Haddad et al, 1994). Tiotropium also displays selectivity in receptor subtype blockade, with more specific inhibition at the M3 muscarinic receptor. Low activity at the M2 (feedback) receptor reduces paradoxical increased acetylcholine release, as is observed with ipratropium. This explains the long duration of action of tiotropium, which lasts at least 24 hours with a single daily dose regimen (Celli et al, 2003).

Early studies in COPD patients demonstrated the ability of the compound to improve spirometry (FEV_1, and forced vital capacity (FVC)) up to 20–25% of baseline over a brief course of treatment (Maesen et al, 1995).

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In comparisons with ipratropium, reduced requirements for rescue medications such as salbutamol were identified in addition to improved spirometry (van Noord et al, 2000). Littner et al (2000) demonstrated a dose-related increase in FEV_1 that increased over time. Steady state was reached within 1 week of therapy with a 2–3-week washout period. A similar study from Casaburi et al (2000) reproduced these findings with sustained improvements in peak expiratory flow rate (PEFR), FEV_1 and FVC observed at 150 days.

Patient-focussed outcomes

Treatment targets that are important to patients with COPD include a reduction in breathlessness (with improved exercise tolerance), fewer exacerbations (and associated admissions) and improved quality of life.

In clinical trials, change in dyspnoea severity has been measured by the Transition Dyspnoea Index (TDI), and quality of life either by the generic Short Form-36 (SF-36) or the disease-specific St George's Respiratory Questionnaire (SGRQ) in which a clinically meaningful difference is conventionally defined as 4 units.

Tiotropium 18 µg once daily has been compared with placebo (Casaburi et al, 2002) and ipratropium 40 µg four times daily (Vincken et al, 2002) over 1 year and with salmeterol 50 µg twice daily over 6 months (Brusasco et al, 2003). These large studies (n = 921, 535 and 1207 respectively) included patients with a mean FEV_1 predicted of 38–42%, indicating moderately severe COPD. Rescue treatment with inhaled salbutamol and stable treatment with theophylline and inhaled or oral steroids were permitted by Casaburi et al (2002) and Vincken et al (2002) but concurrent medication was not reported by Brusasco et al (2003).

Breathlessness

Compared with placebo, tiotropium significantly reduced dyspnoea scores (*Figure 1*) and symptom scores (Casaburi et al, 2002). Defining response as a clinically meaningful change in TDI (score ≥1.0), the response rate at various time points through the study was 42–47% with tiotropium and 29–34% with placebo (P<0.01). Tiotropium also significantly improved breathlessness compared with ipratropium over 1 year, with response rates of 31% and 18% respectively (P=0.004) (Vincken et al, 2002). Tiotropium and salmeterol similarly improved TDI score over 6 months with response rates of 43% and 41% respectively (30% with placebo) (Brusasco et al, 2003).

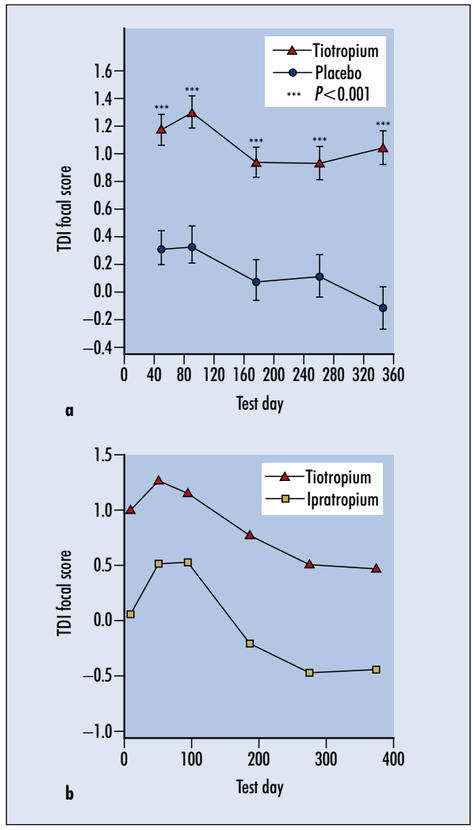
Patients taking tiotropium reported less use of rescue salbutamol compared with placebo (3.2 *vs* 4.1 doses/day, P<0.01) (Casaburi et al, 2002) and, for 40 of the 52 weeks, ipratropium (four fewer inhalations per week, P<0.05) (Vincken et al, 2002). Salbutamol use was not reported by Brusasco et al (2003) but in a subgroup of this study tiotropium and salmeterol were associated with reductions of approximately 1.4 doses per day compared with placebo (Donohue et al, 2002).

Exacerbations

Acute exacerbations significantly impair quality of life in patients with COPD: in one 2-year study of 336 patients with moderately severe COPD, 1015 exacerbations were recorded and 31% of patients were admitted to hospital at least once (Miravitlles et al, 2004). It is also reported that exacerbations may contribute to the long-term decline in lung function (Donaldson et al, 2002).

In a report of two identical studies of COPD patients (FEV_1 <65% predicted) tiotropium reduced the frequency of exacerbation (0.76 *vs* 0.95 events per patient-year with placebo, P<0.05) and the proportion of patients who experience an exacerbation (36 *vs* 42%, P<0.05) (Casaburi et al, 2002). In this study, tiotropium almost halved hospital admissions for exacerbation (0.086 *vs* 0.161 events per patient-year, P=0.019; 5.5 *vs* 9.4% of patients admitted, P<0.05) and patients spent significantly fewer days in hospital (0.6 *vs* 1.2 days per patient-year, P=0.023).

Figure 1. Effect of treatment with tiotropium 18 µg/day (a) vs placebo or (b) vs ipratropium on breathlessness in patients with moderately severe chronic obstructive pulmonary disease. Mean transitional dyspnoea index (TDI) over the course of a year. From Casaburi et al (2002), Vinken et al (2002).



Tiotropium similarly reduced exacerbations compared with ipratropium (0.73 *vs* 0.96 events per year, P=0.006; 35% *vs* 46% of patients affected, P=0.014) but there were no significant differences in hospitalization for exacerbation or the proportion of patients admitted (Vincken et al, 2002). There were no differences between tiotropium and salmeterol in exacerbation rates or hospital admissions (*Figure 2*), although the mean duration of hospital stay (all cause admissions) was shorter by more than 1 day with tiotropium (2.38 *vs* 3.46 days, P<0.05) (Brusasco et al, 2003).

A cost analysis of ipratropium and tiotropium demonstrated reduced comparative hospital admissions (46%), hospital days (42%) and unscheduled visits to healthcare providers (36%), which offset increased treatment costs (180 Euros/patient/yr) for tiotropium (Oostenbrink et al, 2004).

A Cochrane review of nine randomized trials involving a total of 6584 patients concluded that tiotropium reduces the odds of exacerbation (odds ratio (OR) = 0.74) and related admissions (OR = 0.64) compared with placebo or ipratropium (Barr et al, 2005). Assuming an annual risk of 45% for exacerbations and 10% for admission, the number needed to treat (NNT) for tiotropium compared with placebo or ipratropium is 14 to prevent one exacerbation and 30 to prevent one admission.

Quality of life

Tiotropium significantly improved SGRQ scores in every domain compared with placebo (Casaburi et al, 2002) and the proportion of patients with a clinically meaningful improvement in score was significantly greater with tiotropium (49% *vs* 30%, P<0.05). These changes were reflected in significant improvements in the physical domains of the SF-36. Similarly, mean SGRQ score was significantly improved compared with ipratropium (P=0.004), with more patients achieving a clinically meaningful change (at 1 year 52% *vs* 35%, P=0.001) (*Figure 3*) (Vincken et al, 2002). There were few differences between the groups in SF-36 scores. Tiotropium and salmeterol achieved similar improvements in SGRQ score, with response rates of

Figure 2. The effect of 6 months' treatment with tiotropium or salmeterol on exacerbations. From Brusasco et al (2003).

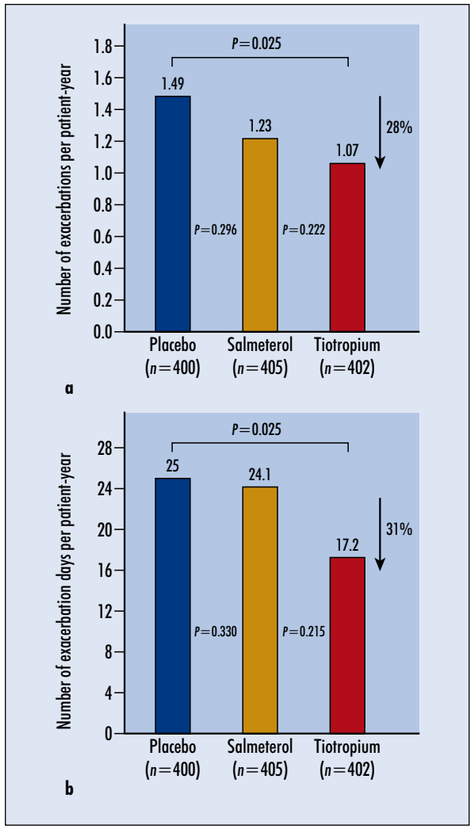
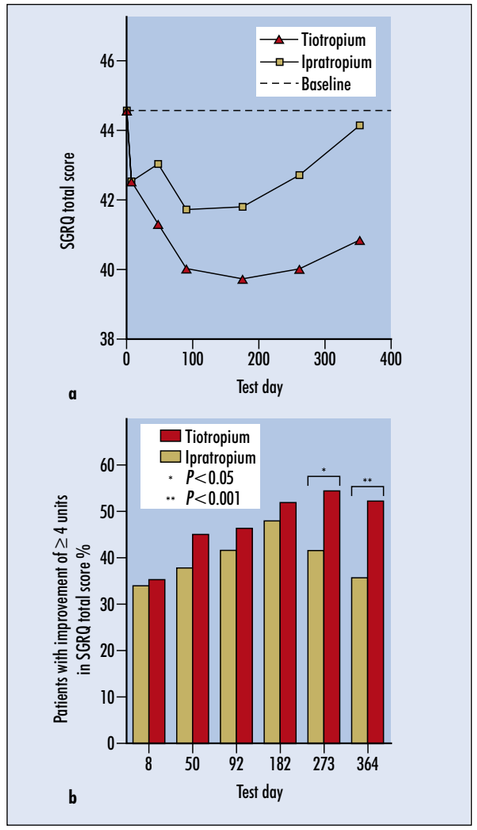


Figure 3. The effect of 1 year's treatment with tiotropium or ipratropium on quality of life (St George's Respiratory Questionnaire (SGRQ) score). From Vincken et al (2002).



48.9% and 43.2% respectively compared with 39.3% with placebo (Brusasco et al, 2003).

Exercise tolerance

Casaburi et al (2005) assessed walking endurance time (at a predetermined 80% maximum speed) for 5 weeks before, during and for 12 weeks after an 8-week pulmonary rehabilitation (PR) programme. Mean endurance time difference (tiotropium minus placebo) before PR, at the end of PR and 12 weeks after PR were 1.65 min (P=0.183), 5.35 min (P=0.025) and 6.6 min (P=0.018) respectively. It is hypothesized that the improvement in ventilatory mechanics with tiotropium permitted enhanced training benefits from PR.

Physiological change and symptoms

FEV_1 is the principal index defining severity in COPD. Traditionally change in FEV_1 has also been the yardstick by which therapeutic interventions have been assessed. In recent years, however, it has been recognized that other ('patient focussed') indices, such as those discussed above, may respond to treatment that does not produce a significant change in FEV_1. Poor understanding of the reason for the weak correlation between FEV_1 and these important clinical measures has probably delayed their acceptance as valid outcomes.

Studies have improved our understanding of the relationship between physiological change in response to therapy and clinical effect.

In health at the end of a normal tidal expiration (functional residual capacity, FRC) (*Figure 4*), the tendency for the lungs to contract down and for the chest wall to spring out are in balance. No effort is required to maintain this lung volume. Tidal breathing from FRC is akin to gently stretching a slack spring and therefore requires little effort. At high lung volume the lungs are in a stretched state – the 'spring' is under great tension. Tidal breathing at high lung volume therefore requires significant effort and the work of breathing can be considerable.

Airway narrowing in COPD leads to hyperinflation of the lungs. This is a natural and unconscious attempt to obviate airway resistance. By breathing at a higher lung volume the airways are 'stretched open' by their parenchymal attachments which act as 'guy ropes' linking them to the chest wall. Airway resistance is reduced, but at the cost of an increased work of breathing.

In exercise, oxygen demand is increased and respiration is stimulated. Airway narrowing in COPD limits expiratory flow, which would tend to prevent the required increase in ventilation. To reduce airway resistance and allow greater flow, breathing occurs at yet higher lung volumes. This progressive inflation during exercise is know as 'dynamic hyperinflation' and leads to further increases in the work of breathing. The phenomenon substantially contributes to the sensation of breathlessness and ultimately limits exercise tolerance.

Measures of expiratory flow rate (e.g. FEV_1) correlate poorly with changes in exercise endurance and patients' ratings of breathlessness. The best correlates are changes in lung volume and, in particular, inspiratory capacity, a measure of lung hyperinflation (O'Donnell et al, 1999) (*Figure 4*).

The effect of treatment with tiotropium on lung hyperinflation at rest has been assessed in severe COPD (FEV_1 = 43% predicted) (Celli et al, 2003). Spirometry showed that, as expected, tiotropium significantly increased FEV_1 and FVC compared with placebo. It also significantly increased inspiratory capacity (*Figure 5*) and reduced thoracic gas volume (*Figure 6*), showing that tiotropium reduced static hyperinflation.

Tiotropium also reduces dynamic hyperinflation which, as the main factor limiting exercise capacity, is more relevant to patient-focused treatment. In a 6-week trial in moderately severe COPD (FEV_1 = 44% predicted), those taking tiotropium experienced significantly less dyspnoea at a constant level of exercise and could exercise for significantly longer before the onset of intolerable dyspnoea compared with patients taking placebo (O'Donnell et al, 2004a). During exercise, tiotropium significantly increased tidal volume and inspiratory capacity, and reduced both total and end expiratory lung volumes compared with placebo (*Figure 7*). The increase in inspiratory capacity correlated significantly with the increase in exercise time and a reduction in the intensity of dyspnoea during exercise.

Long-acting inhaled beta-2 agonists have also been shown to reduce dynamic hyperinflation and dyspnoea during exercise (O'Donnell et al, 2004b) but these effects have not been compared with those of tiotropium in published comparative studies.

Disease progression

COPD is a progressive disease. The only intervention which has been shown, unequivocally, to slow the rate of decline in FEV_1 is smoking cessation. In the lung health study patients with mild to moderate COPD who continued to smoke had an average rate of decline in FEV_1 of 62 ml/year (Anthonisen et al, 1994). Both cross-sectional and longitudinal studies suggest that the rate of decline in lung function after smoking cessation is similar to that in lifelong non-smokers. (Fletcher, 1976; Peat et al, 1990; Anthonisen et al, 1994; Ferguson et al, 2000; Scanlon et al, 2000).

Two major international, multicentre studies failed to demonstrate an improvement in rate of decline in FEV_1 from inhaled corticosteroids (Pauwels et al, 1999; Burge et al, 2000).

A beneficial effect on rate of progression of COPD remains the 'holy grail' for pharmaceutical interventions.

Figure 4. a. Lung volume parameters (right) compared with typical spirometer output (left). b. Lung volumes in healthy people and patients with chronic obstructive pulmonary disease (COPD). FRC = functional residual capacity; IC = inspiratory capacity; TLC = total lung capacity; VC = vital capacity. From Ferguson (2004).

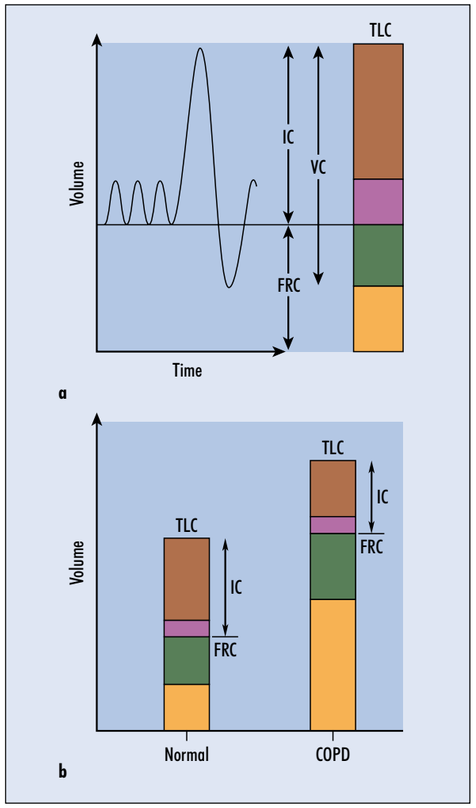


Figure 5. Effect of 4 weeks' treatment with tiotropium on inspiratory capacity (IC) at rest. From Celli et al (2003).

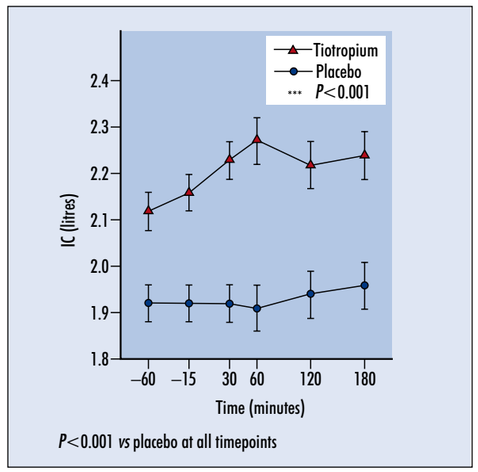


Figure 6. Changes in thoracic gas volume (TGV) (at rest) after 4 weeks' treatment with tiotropium or placebo. Respective agent inhaled at time zero. From Celli et al (2003).

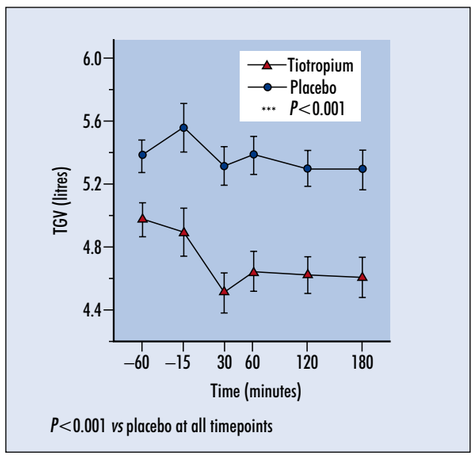
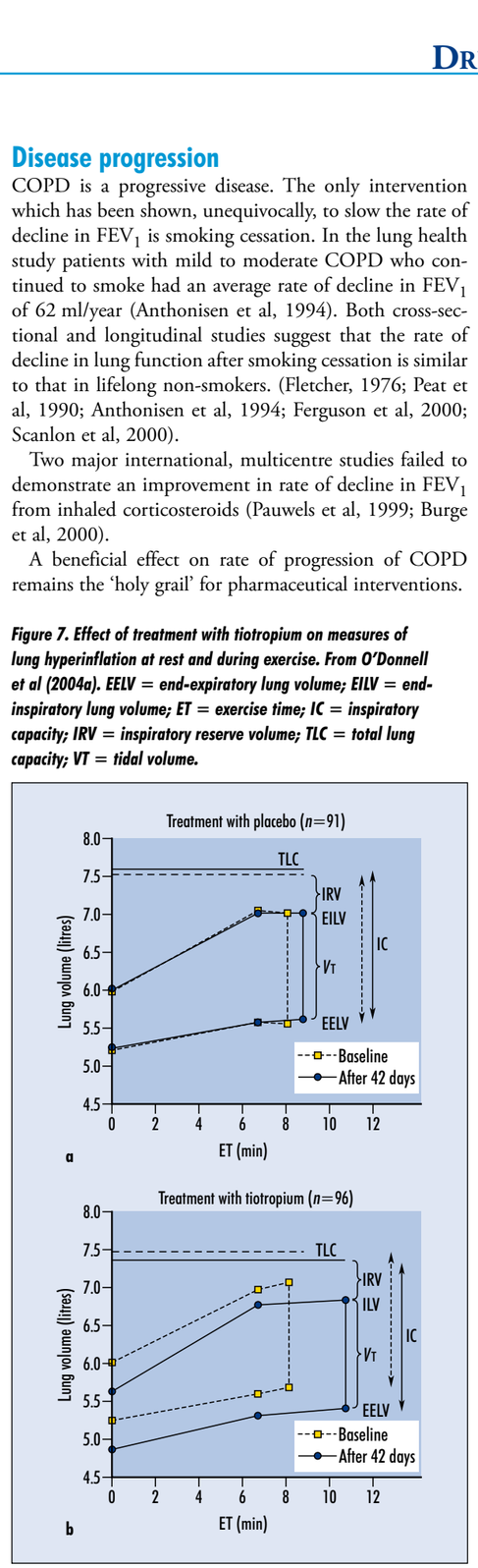


Figure 7. Effect of treatment with tiotropium on measures of lung hyperinflation at rest and during exercise. From O'Donnell et al (2004a). EELV = end-expiratory lung volume; EILV = end-inspiratory lung volume; ET = exercise time; IC = inspiratory capacity; IRV = inspiratory reserve volume; TLC = total lung capacity; VT = tidal volume.



Meta-analysis

A Cochrane review (Barr et al, 2005) identified two 12-month trials with data on decline in FEV_1 from 'steady state' (taken to be day 8 of study) to end of study. One study compared tiotropium to placebo (Casaburi et al, 2002; although this included unpublished data) and the other comparing tiotropium to ipratropium (Vincken et al, 2002). Decline in trough FEV_1 from steady state was 30 ml less with tiotropium than with placebo or ipratropium over 1 year. The Cochrane authors concluded that tiotropium 'may have slowed decline in FEV_1'.

Some caution needs to be exercised in the interpretation of these data. The results for decline in mean and peak FEV_1 were variable with no statistically significant benefit in the tiotropium arms. This raises the possibility that the observed benefit seen in trough FEV_1 may not have been the result of a change in underlying pathophysiology. A cumulative effect from continued administration of tiotropium could also explain this result if tiotropium had a functional half-life measured in days (such that steady state would not be achieved by day 8). It is perhaps noteworthy that rates of decline in FEV_1 from day 50 to end of study were not statistically different between the treatment limbs (Anzueto et al, 2004).

Although these data are promising, additional long-term studies are required to evaluate the effect on rate of decline of FEV_1.

Adverse effects

In studies where they are reported, the overall rate of adverse effects associated with tiotropium was similar to that with placebo. Tiotropium was consistently associated with a higher frequency of dry mouth: 16% *vs* 2.7% with placebo (Casaburi et al, 2002), 12.1% *vs* 6.1% with ipratropium (Vincken et al, 2002), and 8.2% *vs* 1.7% with salmeterol *vs* 2.3% with placebo (Brusasco et al, 2003). The incidence of serious adverse events and events leading to discontinuation of treatment were similar.

KEY POINTS

- Success in the treatment of chronic obstructive pulmonary disease (COPD) should now be measured by patient-focussed outcomes rather than change in spirometry.
- Tiotropium reduces exacerbations and improves dyspnoea, exercise tolerance and quality of life in COPD compared with placebo or ipratropium.
- Dynamic hyperinflation is reduced by tiotropium; this improvement in ventilatory mechanics appears to permit enhanced training benefits from pulmonary rehabilitation.
- Tiotropium may slow the rate of progression of COPD; an outcome not demonstrated for any other pharmaceutical intervention.
- Further studies are needed to determine the effect on mortality, and the efficacy of combined treatment with tiotropium and a long-acting beta-2 agonist or an inhaled steroid.
- Tiotropium should be the first choice maintenance therapy in COPD patients who remain symptomatic despite short-acting bronchodilators.

Tiotropium *vs* long-acting beta 2 agonists

Long-acting inhaled bronchodilators, a beta-2 agonist (salmeterol, formoterol) or an anticholinergic (tiotropium) are recommended for patients who are symptomatic despite treatment with short-acting agents, and for those who experience two or more exacerbations per year (NICE, 2004). They appear to have additional benefits over combination therapy and they offer a more convenient once- or twice-daily dosing regimen.

In meta-analysis tiotropium and beta-2 agonists produce similar results for exacerbation rates, quality of life and symptom scores (Barr et al, 2005). However, tiotropium increased FEV_1 and FVC by more than long-acting beta-2 agonists and may also slow the decline in FEV_1.

In a 6-month study by Donohue et al (2002) reductions in early gains in dyspnoea scores were observed for salmeterol, suggesting tolerance or tachyphylaxis may develop within even short treatment periods. This phenomenon has not been reported for anticholinergic agents.

Combining tiotropium with other interventions

As noted above, tiotropium was evaluated in patients who were permitted to continue using inhaled or oral steroids, or theophylline (Casaburi et al, 2002; Vincken et al, 2002). However, no subgroup analysis to determine the impact on treatment efficacy was reported.

A systematic review has suggested that combining a long-acting beta-2 agonist with an inhaled steroid will produce a relative risk (RR) of exacerbation of 0.70 compared with placebo; for lone agents tiotropium has a RR=0.74, long-acting beta-2 agonists have a RR=0.79, and inhaled steroids have a RR=0.76, (Sin et al, 2003).

The effectiveness of PR is enhanced during treatment with tiotropium compared with placebo as discussed above (Casaburi et al, 2005).

Conclusions

Tiotropium has been shown to be effective and well tolerated as maintenance treatment for patients with moderate and severe COPD using endpoints that matter to patients. Further studies are needed to determine its effects on mortality, and the efficacy of combined treatment with a long-acting beta-2 agonist.

Further comparative studies are probably required to clarify the relative merits of tiotropium and long-acting beta-2 agonists although on current evidence tiotropium provides superior bronchodilatation over 24 hours and may slow the rate of decline in FEV_1 over time. Salmeterol also appears to demonstrate tachyphylaxis (Donohue et al, 2003).

The risks and benefits of combined treatment with tiotropium and inhaled steroids needs further study. There is also a need to compare the long-term cost effectiveness of these agents.

Nevertheless, the available evidence now supports the use of tiotropium as maintenance therapy in patients with moderately severe COPD who remain symptomatic despite treatment with a short-acting bronchodilator or who have frequent exacerbations. **BJHM**

Conflict of interest: Dr Burns has previously received travel grants to attend national and international scientific meetings from GlaxoSmithKline, AstraZeneca, 3M and Boehringer Ingelheim. He has also received support for educational meetings from GlaxoSmithKline, AstraZeneca, 3M, Boehringer Ingelheim, Schering-Plough, Altana Pharma, MSD and Pfizer. He has sat on advisory panels for GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim and Pfizer. Dr Bianchi has previously received two travel grants from GlaxoSmithKline to attend the American Thoracic Society Annual Scientific meeting.

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