EDITORIAL

Uplifting times for COPD

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Knowing how to translate the results of clinical trials into routine patient management is often difficult, since patients entered into trials are not usually typical of patients seen in routine practice – often because the severity of their disease is different, or because people with co-morbidities are excluded. Moreover, patients in clinical trials are often not allowed to take other medications which would normally be prescribed outside the setting of a clinical trial.

How then should we interpret the results of the UPLIFT study – the latest of a series of trials looking at the long term effects of inhaled therapy in patients with COPD? The study differs from many earlier trials, in that patients with a wide range of FEV₁ impairment were included and patients were allowed to take their usual medication. This has important implications for the interpretation of the results and their translation into clinical practice.

UPLIFT was a four-year randomised double-blind placebo-controlled study which examined the effects of tiotropium.¹ The double-blind treatment period of 1440 days was followed by a 30-day period during which all patients received ipratropium. Tiotropium had no effect on the rate of decline of either pre- or post-bronchodilator FEV₁, which were the co-primary endpoints. There were, however, significant effects on the absolute values of FEV₁ and FVC – which were maintained over four years – as well as reductions in exacerbation and hospitalisation rates, and improvements in health status in patients treated with tiotropium.

The authors made every effort to ensure that vital status data was available on all patients up to four years, and they examined effects on mortality using intention to treat analyses covering both the 1440-day randomisation period and the whole 1470-day study period. The 1440-day mortality was significantly reduced (relative risk (RR) 0.87 (95% CI 0.76-0.99) $p=0.034$) and there was a non-significant trend to reduced mortality when the 30-day follow up period was also included (RR 0.89 (95% CI 0.79-1.02) $p=0.09$). The significance of the deaths that occurred during the 30-day follow-up period, when tiotropium had been stopped, is not clear.

Reducing the rate of decline of FEV₁ has been considered the acid test of disease modification, and the UPLIFT study was established to determine whether tiotropium could affect this outcome – as had been suggested by a post-hoc analysis of data from 12-month studies.² The authors set themselves a difficult task, particularly as all patients were allowed to take other respiratory medication, including long-acting beta-agonists (LABA) and inhaled steroids (ICS), throughout the duration of the study. Overall, 72% of patients were on LABAs and 74% were taking ICS. The rate of decline in post-bronchodilator FEV₁ ($\pm$ SE) seen in the control group was similar to the rates of decline in patients treated with salmeterol, fluticasone, or the salmeterol/fluticasone (SFC) combination in the TORCH study (42 ± 1 ml/y, UPLIFT controls; 42.3 ± 3.1 ml/y, salmeterol; 42.3 ± 3.1 ml/y, fluticasone; 39.0 ± 3.0 ml/y, SFC).³ These rates are all lower than the rates of decline reported in earlier studies (e.g. 59.0 ± 4.4 ml/y in patients in the placebo arm of the ISOLDE study⁴) and in patients in the placebo arm of the TORCH study (55.3 ± 3.2 ml/y). This suggests that pharmacotherapy can slow the rate of decline in FEV₁ but that a ceiling effect is seen.

Throughout the UPLIFT study the response of patients to bronchodilators was measured. Following maximal short-acting bronchodilator therapy with 80 mcg ipratropium and 400mcg salbutamol, 53% of the patients showed an increase of 200ml or more in their FEV₁, despite a mean baseline FEV₁ of only 1100ml.⁵ These results,

together with the absolute increases in FEV₁ and FVC seen with tiotropium, should finally put to rest the idea that COPD is an irreversible disease and that a bronchodilator response confirms a diagnosis of asthma.

Unlike many earlier studies, UPLIFT included a large proportion of patients with mild airflow obstruction as defined in the NICE guideline⁶ (equivalent to GOLD stage II⁷): 40% of the patients had an FEV₁ over 50% predicted. This has important implications for clinical practice, since many patients with mild airflow obstruction experience significant symptoms and yet are not prescribed long-acting bronchodilator therapy despite guideline recommendations.⁸ The additional benefits of tiotropium on reducing exacerbation and hospitalisation rates and improving health status give further reasons for treating symptomatic patients whether their FEV₁ is above or below 50% predicted. Again, it is important to remember that these benefits were seen even though the majority of patients were taking LABAs or ICS or both. We cannot use these data to assess whether tiotropium is more or less effective than LABAs, ICS, or an ICS/LABA combination, since the use of ICS and LABA was not randomised.

The information on adverse events that occurred during the study is particularly timely, as a recently published meta-analysis of the safety of anticholinergic therapy in COPD suggested that both tiotropium and ipratropium were associated with an increased risk of cardiac morbidity and mortality.⁹ This meta-analysis has limitations, particularly the fact that there was double-counting of some patients and that only one-third of the patients randomised to receive ipratropium in the trial which contributed 70% of the weight of the analysis actually took the drug regularly.¹⁰ The UPLIFT data clearly show a reduction in the incidence of myocardial infarction in patients treated with tiotropium (RR 0.71 (95% CI 0.52-0.99)). There was also no evidence that stroke or pneumonia were more common in patients receiving tiotropium.

So what do these and other trial results mean for the management of patients with COPD in primary and secondary care? A large number of patients with COPD experience regular symptoms, particularly breathlessness and exercise limitation. They worry about exacerbations, have impaired health status, and are likely to die of COPD or a related co-morbidity. Many of these patients are currently only prescribed intermittent short-acting bronchodilators. The TORCH study has shown that LABAs and LABA/ICS combination inhalers produce a sustained improvement in lung function and health status, and a sustained reduction in the risk of an exacerbation over a three-year period in patients with an FEV₁ < 60% predicted.¹¹ The UPLIFT data now show that tiotropium produces similar benefits in patients with a post-bronchodilator FEV₁ < 70% predicted and that these benefits are present even if patients are taking LABA or ICS. The data do not allow us to state categorically which order the drugs should be given in, but I believe that taken together they show that patients with an FEV₁ greater than 50% predicted can derive important benefits from triple therapy with tiotropium, LABA and

ICS, as has been reported in earlier shorter studies.¹² Furthermore, the data suggest that therapy is associated with a reduction in mortality and that tiotropium and LABAs¹³ are safe in patients with COPD.

Long-term cost effectiveness data for combinations of these drugs is still not available and this will be important for future discussions of when they should or should not be used. In the meantime we must embrace the data from studies like UPLIFT and offer patients the most effective inhaled therapy currently available to help them live with this disabling and depressing condition.

Conflict of interest declaration

Dr Halpin was the Principal Investigator in the UK for the UPLIFT study. He has received sponsorship to attend international meetings, and honoraria for lecturing, attending advisory boards and preparing educational materials, from AstraZeneca, GlaxoSmithKline, Pfizer and Boehringer Ingelheim. His department has received research funding from AstraZeneca.

References

1. Tashkin D, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; **359**:1543-54.
2. Anzueto A, Tashkin D, Menjoge S, Kesten S. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. *Pulm Pharmacol Ther* 2005; **18**(2):75-81.
3. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008; **178**(4):332-8.
4. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; **320**(7245):1297-303.
5. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008; **31**(4):742-50.
6. National Institute for Clinical Excellence (NICE). Chronic obstructive pulmonary disease. National clinical guideline for management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; **59** (Suppl 1):1-232.
7. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; **176**(6):532-55.
8. Ramsey SD. Suboptimal medical therapy in COPD: exploring the causes and consequences. *Chest* 2000; **117**(2 Suppl):335-7S.
9. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA* 2008; **300**(12):1439-50.
10. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; **166**(3):333-9.
11. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; **356**(8):775-89.
12. Aaron SD, Vandemheen KL, Fergusson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; **146**(8):545-55.
13. Rodrigo GJ, Nannini LJ, Rodriguez-Roisin R. Safety of long-acting beta-agonists in stable COPD: a systematic review. *Chest* 2008; **133**(5):1079-87.