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Which bronchodilator in COPD?

There have been few developments in the pharmacotherapy of chronic obstructive pulmonary disease (COPD) that have been so eagerly awaited as that of a long acting anticholinergic compound. For the first time there was a treatment available which was designed with COPD specifically in mind. This was not an asthma treatment that had been tried in COPD with more hope than expectation. Tiotropium has now been available in Europe for 5 years and in the US for 3. Has this drug lived up to the expectations with which it was greeted?

In this edition of the *International Journal of COPD* we publish two papers which review the data for the efficacy of Tiotropium and compare its effects with long acting beta-agonists. The analysis of Rice and colleagues (2007) clearly demonstrates that Tiotropium is an effective bronchodilator in COPD patients. Peak and trough forced expiratory volume in one second (FEV_1) measurements were significantly increased and these changes were sustained throughout the study periods (up to 1 year). Exacerbations of COPD are of great importance to patients, medical staff and medical funding bodies. The finding of a reduction in exacerbation rate and hospital admissions is thus of significance.

Hodder and colleagues (2007) compare in a post-hoc analysis the efficacy of tiotropium and salmeterol in patients who may or may not be taking inhaled corticosteroids in two studies over a six month period. The findings do not help us understand the role of inhaled steroids in COPD but do demonstrate that both salmeterol and tiotropium are effective notwithstanding the steroid status of the subjects. The patients taking steroids were found to have worse lung function and breathlessness at enrolment. The reduced responses to therapy, particularly the exacerbation rate, may reflect this. However it was clear that a physician's decision to place a patient on inhaled steroids is based on more than a slightly worse FEV_1 or slightly more breathlessness.

There is still a need in such studies to demonstrate clinically meaningful benefit. Lung function changes are straightforward to measure but do they translate into improvements in quality of life and exercise tolerance? The data presented thus far is relatively weak in this area. Moreover there is a question or the generalisability of the data presented. For reasonable reasons patients with significant co morbidities are excluded (especially cardiovascular disease) which is never the case in real life. What effect the inclusion of such patients would have on trial results is uncertain; such patients are more symptomatic, have more exacerbations and thus may decline faster. On the other hand these patients may respond better to an effective therapy.

The other pressing need that these papers demonstrate is that we need an understanding of disease phenotype (Celli and Roger 2006). Of greater clinical significance is that we do not understand the phenotypes of potential responders to pharmacological therapies. Who will respond to anticholinergics, who to beta agonists? Who should receive inhaled corticosteroids? The pragmatic approach is to use both or all in combination in severe disease as each therapy has an entirely different mechanism of action which may be complementary. Each does contribute something to a reduction in exacerbation rate, an improvement in lung function and perhaps an improvement in a patient's life. The recent study by Aaron and colleagues (2007) shows some benefits for combining tiotropium with a long acting beta agonist and an inhaled corticosteroid

in terms of lung function and symptoms, but the study was underpowered to evaluate its primary endpoint of exacerbation rates. Further studies to define properly the benefits of such a combined therapy approach are needed. The results of the now complete UPLIFT study are thus eagerly awaited (Decramer et al 2004).

References

Aaron SD, Vandemheen KL, Fergusson D, et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. 2007. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*, 146:545–55.

Celli BR, Roger S. 2006. Mitchell lecture. Chronic obstructive pulmonary disease phenotypes and their clinical relevance. *Proc Am Thoracic Soc*, 3:461–5.

Decramer M, Celli B, Tashkin DP, et al. 2004. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD*, 1:303–12.

Hodder R, Kesten S, Menjoge S, et al. 2007. Outcomes in COPD patients receiving tiotropium or salmeterol plus treatment with inhaled corticosteroids. *Int J COPD*, 2:157–167.

Rice KL, Kunisaki KM, Niewoehner DE. 2007. Role of tiotropium in the treatment of chronic obstructive pulmonary disease. *Int J COPD*, 2:95–105.