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Tiotropium; more knowledge leads to more questions

This issue of the *International Journal of COPD* has 3 original research papers that study the effects of tiotropium. These papers are very different, addressing the effect of tiotropium on the small airways (Incorvaia et al 2008), the benefit of additional tiotropium treatment during a pulmonary rehabilitation programme (Kesten et al 2008), and the effect of tiotropium when prescribed to patients already taking theophylline (Kawayama et al 2008). Each paper offers new information about the effects of tiotropium, but also leads us towards further questions that need answering.

Incorvaia and colleagues (2007) had previously shown that tiotropium has greater effects than oxitropium on FEF25-75, a measurement of small airway function. In the current issue, this observation is further extended as treatment with tiotropium for 3 months was found to improve FEF25-75 in patients with frequent exacerbations (>2 exacerbations per year) (Incorvaia et al 2008). Interestingly, FEF25-75 before treatment with tiotropium was significantly lower in patients with frequent exacerbations compared to those with <2 exacerbations per year. This suggests that frequent exacerbations are associated with small airway dysfunction that can be improved by tiotropium. The limitations of the study are a small sample size, and the statistics used only evaluated changes within a group, not between frequent and infrequent exacerbators.

There is other data recently published that also shows the benefit of tiotropium on small airway function (Borrill et al 2008). The physiological benefits of improved small airway function include improved lung mechanics by reducing hyperinflation, thus reducing symptoms (Matlais et al 2005). Less clear is the question of whether improved small airway function can actually reduce exacerbation rates. Tiotropium is known to reduce exacerbation rates (Brusasco et al 2003), but this effect does not seem to be mediated by a change in the profile of inflammatory cells in the airways (Powrie et al 2007). So how does tiotropium reduce exacerbations? Mucus hypersecretion is known to be a risk factor for exacerbations (Seemungal et al 1998; Foreman at al 2007), and perhaps tiotropium by its anticholinergic action alters alters mucus production or mucus clearance by improving small airway function. These are important questions that need answering.

Casaburi and colleagues (2005) had previously shown that tiotropium in combination with pulmonary rehabilitation improved pulmonary function and exercise endurance compared to rehabilitation alone. A subgroup analysis is presented in this issue focusing on the group of patients who also completed a self reported exercise participation questionnaire (Kesten et al 2008). There were significant increases in activity duration in the tiotropium but not the placebo group, although between group differences were not significant. This was a subset analysis that was not statistically powered, and so must be considered as exploratory data. The well validated measurements of health status and breathlessness (St Georges Respiratory Questionnaire and Dyspnoea Index, respectively) did show a benefit for tiotropium over placebo. Overall, the extra benefits of tiotropium therapy during a pulmonary rehabilitation programme are clear. This leads us to the question of optimising medical therapy during rehabilitation to achieve maximum benefits. "Combination therapy" in COPD is often thought of as involving drug treatments. However, a good combination therapy also appears to be tiotropium plus rehabilitation.

Kawayama and colleagues (2008) studied the effect of add on therapy with tiotropium in patients already taking theophylline. Meta-analysis show that theophylline has beneficial therapeutic effects in COPD (Molfino and Zhang 2006). Consequently, theophylline is widely prescribed in Japan, so adding tiotropium to theophylline is common practice. There were improvements in lung function and symptoms with tiotropium, but the study suffers from not having a tiotropium alone (without theophylline) treatment arm. Cazzola and Gabriella Matera (2007) showed that adding theophylline to tiotropium plus formoterol had no effect, although in a different study there was some benefit when theophylline was added to salmeterol (Zuwallack et al 2001). The merits of theophylline combination therapy with long acting bronchodilators remains unclear, and perhaps the best prospect for combination therapy involving theophylline is with corticosteroids, as theophylline may enhance corticosteroid effects (Cosio et al 2004).

The future of COPD therapy for patients with more severe disease appears to be combination therapy approaches. The most promising combinations that include tiotropium appear to be "triple therapy" with a long-acting beta agonist and inhaled corticosteroid, which improves pulmonary function and symptoms more than the individual components (Aaron et al 2007; Cazzola et al 2007; Singh et al 2008). The long term benefits of such a "triple therapy" approach needs to be evaluated in properly powered studies of exacerbation rates. Maybe we should consider "quadruple therapy", if we add in pulmonary rehabilitation.

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