COPD Update

Our COPD programme ran in April 2005 and in this article we provide further information and relevant updates from the literature.

Key messages

- Bronchodilators are beneficial even if there is no evidence of airway reversibility. There is evidence that they reduce air trapping (Price, 2005).
- Long acting bronchodilators (tiotropium or long acting beta-2 agonists – LABA) may improve symptom control when patients continue to have symptoms or deteriorate despite the use of short acting bronchodilators. With respect to improvements in health outcomes, no consistent differences have been identified between LABA (salmeterol or eformoterol) and tiotropium. Tiotropium may be better tolerated than a LABA. If a long acting bronchodilator is indicated a LABA would only be considered if the patient is unable to tolerate or does not respond to tiotropium.
- Inhaled corticosteroids (ICS) do not slow the rate of decline in lung function associated with COPD but they do slow the rate of exacerbations compared with placebo.
- ICS may reduce all cause mortality in COPD but there is currently insufficient evidence to change the recommended criteria for their use.
- Patients should be encouraged to exercise as it is likely to reduce the risk of hospital admission and mortality in patients with COPD.
- COPD patients who are still smoking should be offered help to stop at every opportunity.

Tiotropium is an effective option

Trials indicate that tiotropium has beneficial effects compared to ipratropium and placebo but there are no clear differences when compared with LABA. Tiotropium is an effective option in the stepwise treatment of moderate to severe COPD. It is currently funded for severe COPD.

A recent meta-analysis supports the results of earlier trials that tiotropium is more effective than placebo in reducing the rate of exacerbations and hospital admissions (Rodrigo, 2006). For exacerbations the NNT of about 21 to prevent one exacerbation was similar for shorter trials (6 weeks or less) to longer trials (6 months or more). In the three longer studies tiotropium also reduced hospital admissions compared to placebo (NNT 20).

In an update of the previous Cochrane review the authors systematically reviewed high quality trials of greater than 12 weeks duration that compared tiotropium to placebo, ipratropium or LABA (Barr, 2006). Nine trials (a total of over 8000 patients) met the inclusion criteria.

Compared to placebo or ipratropium, tiotropium significantly reduced COPD exacerbations (NNT 13 to prevent one exacerbation) and related hospitalisation (NNT 38 to prevent one hospitalisation) but not pulmonary or all cause mortality. There were no statistically significant differences between tiotropium and LABA. Similar patterns were observed for symptom and quality of life scales. Tiotropium also gave greater increases in FEV1 and FVC from baseline to 6 – 12 months than with placebo, ipratropium or LABA.

These trials indicate that tiotropium has beneficial effects compared to ipratropium and placebo and that there are no clear differences in these measures when compared with LABA. On the other hand improved compliance in practice with once daily tiotropium may lead to better outcomes than ipratropium four times daily. As shown with ipratropium, significant systemic anticholinergic effects such as dry mouth can be experienced by patients on tiotropium (Barr, 2006).

Tiotropium is an effective option in the stepwise treatment of moderate to severe COPD. Further trials are required to investigate the effectiveness of tiotropium in mild and very severe COPD as trials to date have only included those with moderate to severe disease.

Table 1. Tiotropium (Spiriva) Special Authority for Subsidy

Initial application only from a general practitioner or relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:

All of the following:

1. To be used for the long-term maintenance treatment of bronchospasm and dyspnoea associated with COPD; and
2. In addition to standard treatment, the patient has trialed a dose of at least 40 mcg ipratropium q.i.d for one month; and
3. The patient's breathlessness ≥ grade 4 according to the Medical Research Council (UK) dyspnoea scale. Grade must be stated on the application; and
4. FEV1 < 40% of predicted (actual result and predicted value to be stated on form); and
5. Either:
   - 5.1 Patient is not a smoker; or
   - 5.2 Patient is a smoker and been offered smoking cessation counselling; and
6. The patient has been offered annual influenza immunisation.

(Source: Pharmaceutical Schedule; Pharmac)

Medical Research Council dyspnoea scale for grading the degree of a patient's breathlessness

1. Not troubled by breathlessness except on strenuous exercise.
2. Short of breath when hurrying or walking up a slight hill.
3. Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace.
4. Stops for breath after about 100 m or after a few minutes on the level.
5. Too breathless to leave the house, or breathless when dressing or undressing.

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Long acting beta-2 agonists

There is no evidence that LABA are any more effective or better tolerated than tiotropium in COPD. LABA are recommended as monotherapy in some international COPD guidelines but the safety of their use without an ICS is unknown.

LABA such as salmeterol and formoterol are long acting bronchodilators prescribed extensively overseas for COPD but comparisons with tiotropium have not demonstrated any differences in clinical effectiveness or health outcomes. A recent systematic review from Canada analysed 33 RCTs (duration up to one year) of patients with mild to severe COPD (Shukla, 2006). LABA reduced exacerbations and hospitalisations compared with placebo but no consistent differences in outcomes were observed when compared with tiotropium or ipratropium. There was also some evidence that salmeterol is not as well tolerated as tiotropium but significant anticholinergic effects can occur with the latter.

Further comparisons with tiotropium are required especially with respect to effects on change in FEV1 and mortality (MeRec, 2006). LABA are not currently recommended in New Zealand for the treatment of COPD and the only current justification for their use would be in patients who are unable to tolerate or do not respond to tiotropium.

In asthma, the SMART trial indicated the potential hazards from LABA monotherapy and emphasised the importance of their use along with an ICS (Anderson, 2005). In COPD, LABA are recommended as monotherapy in some international guidelines but the safety of their use without an ICS is unknown (Reid, 2006).

Inhaled corticosteroids

ICS may reduce exacerbation rates and improve quality of life in people with frequent exacerbations but are unlikely to have any long-term clinically significant effects on the rate of decline in lung function in people with COPD.

The debate on the value, rationale and place in therapy of inhaled corticosteroids in treatment of COPD continues. Randomised controlled trials have shown that ICS are unlikely to have any long-term clinically significant effects on the rate of decline in lung function in people with COPD. However, ICS may reduce exacerbation rates and improve quality of life in people with frequent exacerbations (MeRec, 2006). A recent pooled analysis has explored the unknown effect of ICS on all cause mortality in patients with COPD (Sin, 2005). Overall ICS reduced all cause mortality by 25% (HR 0.73, 0.55 – 0.96) compared with placebo. This looks encouraging but several of the trials included in the analysis had important differences in design, inclusion criteria and patient follow up. The authors also suggested that further trials are required to see if survival benefits persist beyond 2 - 3 years. The effect of ICS on mortality in COPD remains inconclusive and the clearest indication for their use remains the reduction of exacerbations. A trial of ICS is recommended in patients with an FEV1 of less than or equal to 50% of predicted who have had two or more exacerbations requiring treatment with oral corticosteroids or antibiotics in a 12 month period. They could also be trialled in patients with moderate to severe COPD with monitoring of objective measures of response. If there is no response they should be discontinued (bpac^{nz}, 2005).

Exercise is beneficial

The importance of maintaining a tolerable level of exercise has been illustrated in a recent population study from Denmark (Garcia-Aymerich, 2006). People were followed for up to 20 years and those who self reported some degree of physical activity over those reporting low activity (basically sedentary) had a lower risk of both hospital admissions and mortality. Whilst there are methodological problems with such observational studies it does provide some evidence that patients with COPD should be encouraged to maintain or increase their levels of regular physical activity.

Should an anticholinergic be the bronchodilator of choice in patients with COPD?

A recent systematic review (Salpeter, 2006) in COPD patients has suggested that an anticholinergic drug (ipratropium or tiotropium) should be the bronchodilator of choice in patients with COPD as beta-2 agonists may be associated with worsening of disease control. Unfortunately in the analysis of this trial the investigators did not differentiate between long and short acting bronchodilators which makes it difficult to identify and quantify any specific risks associated with LABA or short acting beta-2 agonists compared with an anticholinergic. At the moment, in the treatment of COPD there is no compelling evidence to justify the choice of one short acting or long acting bronchodilator over another but the debate is fuelled to continue.

References

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