Using tiotropium in the treatment of COPD

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Tiotropium is currently the long acting bronchodilator of choice for the treatment of stable COPD.

What is tiotropium?

Tiotropium (Spiriva) is a long acting, anticholinergic agent that is administered by inhalation. It provides sustained bronchodilation due to its prolonged occupancy of muscarinic M_3 receptors in the airways, which causes smooth muscle relaxation. This allows the convenience of once daily dosing. (Tiotropium has equal efficacy for M_1 to M_5 receptors; bronchodilation is chiefly a local effect.)

In whom is it used?

Tiotropium is indicated for the long term maintenance treatment of patients with COPD and should be considered in every patient with symptomatic COPD.

Establishing the diagnosis

Before prescribing the medication, the diagnosis of COPD should be confirmed by a clinical history consistent with the diagnosis and spirometry showing a reduced FEV_1 and FEV_1/FVC without significant bronchodilator reversibility.

A typical history will reveal exertional dyspnoea, which is often slowly progressive over time, in a current or ex-smoker who has accrued at least a 10-pack year history (one pack year = 20 cigarettes per day for one year). Additional symptoms include intermittent cough, wheeze and sputum production, particularly in association with respiratory tract infections.

Spirometry should be performed before and after bronchodilator therapy. Post-bronchodilator spirometry should reveal an FEV_1 of less than 80% of predicted and an FEV_1/FVC ratio of less than 70%.

Asthma should be excluded by the history and an absence of significant, acute bronchodilator reversibility. For instance, post-bronchodilator values of FEV_1 greater than 80% of predicted and FEV_1/FVC ratio greater than 70% are not consistent with significant COPD. Tiotropium is not indicated in, nor should be prescribed for, asthma because conventional asthma therapies offer superior treatment.

What are the benefits?

In clinical trials of patients with COPD, tiotropium has been compared with placebo, the shorter acting anticholinergic ipratropium and the long acting β-agonist salmeterol.

Compared with patients using placebo over a 12-month period, those using tiotropium had clinically relevant and statistically significant improvements in FEV_1, dyspnoea and quality of life, and reduced frequencies of exacerbations and COPD hospitalisations.[1] Compared with using ipratropium over a 12-month period, tiotropium use to significantly greater improvements in FEV_1, dyspnoea and quality of life, fewer COPD exacerbations and increased time to both first exacerbation and first COPD hospitalisation.[2]

In a six-month randomised trial, salmeterol, placebo and tiotropium were compared.[3] Only patients allocated tiotropium achieved clinically and statistically significant improvements in dyspnoea, quality of life and time to first COPD exacerbation. Patients using tiotropium also experienced significantly fewer exacerbations and all-cause hospitalisations, as well as superior bronchodilation, compared with salmeterol and placebo.

How is tiotropium used?

One capsule, which contains 18 µg of tiotropium, is administered daily by inhalation using the HandiHaler device. Patients with mild COPD (FEV_1 60 to 80% predicted) should be instructed to use short acting β-agonists when required, while those with moderate COPD (FEV_1 40 to 59%) and severe COPD (FEV_1 below 40%) may need to use short acting β-agonists regularly.

Inhaled corticosteroids may be considered and co-prescribed in patients with severe COPD and frequent exacerbations because in this setting, inhaled corticosteroids may reduce the frequency of exacerbations.[4,5] Currently, there is no published trial evidence supporting the use of tiotropium in combination with long acting β-agonists.

Ipratropium should be discontinued when tiotropium is prescribed.

What are the side effects?

Subjects should be forewarned about the most common side effect associated with tiotropium use: xerostomia (dry mouth). This occurs in up to 16% of patients but leads to discontinuation of therapy in less than 1%. Other reported significant side effects include angioedema, hypersensitivity reactions, paradoxical bronchospasm, tachycardia and urinary retention, but these occur in less than 1% of patients using the medication.

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Table. Medical Research Council dyspnoea scale*

Grade	Degree of dyspnoea
Grade 1	Breathless only with strenuous exercise
Grade 2	Short of breath when hurrying or walking up a slight hill
Grade 3	Walks slower than most people of the same age because of breathlessness or stops for breath when walking at own pace on the level
Grade 4	Stops for breath after walking about 100 metres or a few minutes on the level
Grade 5	Too breathless to leave the house, or breathless when dressing

*Adapted from Fletcher CM, Elmes PC, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. BMJ 1959; 2: 257–266.

How is progress monitored?

Clinical progress can be monitored by assessing:

- changes in dyspnoea
- general wellbeing (as a measure of quality of life)
- exacerbation frequency
- the need for short acting reliever medications
- lung function tests (however, clinical improvement may occur in the absence of improved lung function test results).

Changes in dyspnoea may be assessed using a modified Medical Research Council (MRC) dyspnoea scale, outlined in the Table, or by monitoring improvement in a relevant physical activity.

Failure to improve should prompt inquiry about compliance with treatment and correct use of the HandiHaler as well as review of the diagnosis and a search for unrecognised or inadequately treated comorbidities. Specialist referral may be needed.

Important precautions and interactions

Tiotropium is not an acute reliever medication. Short acting β-agonists remain the drug of choice to relieve acute symptoms in patients with COPD. Tiotropium should not be co-prescribed with ipratropium. Being an anticholinergic agent, tiotropium should be used with caution in patients with narrow angle glaucoma, prostatic hyperplasia and bladder neck obstruction.

Other important aspects of treating COPD

The use of tiotropium is only one element in the overall treatment of COPD. Other essential elements of management include:[6]

- optimising function by referring for pulmonary rehabilitation, where available
- identifying and managing comorbidities such as sleep apnoea, ischaemic heart disease, congestive heart failure and depression
- preventing further deterioration by assisting with smoking cessation and vaccinating against influenza and pneumococcal infection
- developing support networks and self-management plans
- managing exacerbations with appropriate antibiotics, short courses of oral corticosteroids and hospital referral when needed.

Conclusion

Tiotropium is a novel, long acting anticholinergic agent indicated in patients with symptomatic COPD. It is more effective than the short acting anticholinergic ipratropium and the long acting β-agonist salmeterol and is generally very well tolerated. Tiotropium is, therefore, currently the long acting bronchodilator of choice in the treatment of patients with stable COPD. It is not indicated for patients with asthma – highlighting the importance of differentiating COPD from asthma, on the basis of history and spirometry. MT

References

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DECLARATION OF INTEREST: Dr Rice-McDonald sits on a Medical Advisory Board for Boehringer Ingelheim.