



Issue 35
July 2002

Issues in Emerging Health Technologies

Tiotropium: A Potential Replacement for Ipratropium in Patients with COPD

Summary

- ✓ **Inhaled tiotropium provides a sustained bronchodilator effect over a 24-hour period in patients with chronic obstructive pulmonary disease (COPD).**
- ✓ **There is some evidence that tiotropium 18 µg once daily is more efficacious than ipratropium bromide 40 µg four times daily, for patients with COPD, as measured by improvements in lung function, dyspnea disease-specific quality of life and reductions in hospitalization due to COPD.**
- ✓ **Dry mouth is a more frequent problem with tiotropium than with ipratropium bromide.**

The Technology

Tiotropium (Spiriva; Ba679BR) is a new long-acting anticholinergic bronchodilator, delivered via inhalation. It is structurally related to ipratropium bromide.¹ Unlike ipratropium bromide with its duration of action of six to eight hours, tiotropium has at least a 24-hour duration of action. Tiotropium produces its bronchodilation effect by binding to M₃ and M₁ muscarinic receptors in bronchial smooth muscle.¹ In vitro studies have shown the drug dissociates from M₃ and M₁ receptors 100 times more slowly than ipratropium bromide. Tiotropium was developed by Boehringer Ingelheim². Boehringer Ingelheim and Pfizer have agreed to jointly market this drug.³

Regulatory Status

As of June 2002, tiotropium had not received marketing approval in Canada. Boehringer Ingelheim has submitted a New Drug Application

to the Therapeutic Product Directorate in Canada (Carole Bradley-Kennedy, Boehringer Ingelheim, Burlington (ON): personal communication, 2002 April 30) and the Food and Drug Administration in the US⁴, seeking approval for the treatment of COPD. At present, tiotropium has been approved in the Netherlands, New Zealand, the Philippines, Slovakia and Mexico for maintenance treatment of patients with COPD. Boehringer Ingelheim has also successfully completed the European Mutual Recognition Procedure.⁵

Patient Group

COPD refers to a spectrum of respiratory diseases that is characterized by chronic cough, increased sputum production (bronchitis), shortness of breath (dyspnea), airflow limitation and impaired gas exchange (emphysema).⁶ According to 1998-1999 statistics, the prevalence of bronchitis and emphysema in individuals 45-64 years of age and those ≥ 65 years was 2.4% and 5.8%, respectively.⁷ COPD imposes a high burden of illness on the Canadian health care system.⁸ In 1997, the average length of stay in hospital for a patient with COPD was 10.5 days.⁹ In 1998, COPD accounted for 5,398 deaths among men and 3,643 among women; 4% of all deaths in Canada.

Current Practice

According to the Canadian Thoracic Society guidelines for the treatment of COPD, the first line of treatment for regularly symptomatic patients is the combination of ipratropium bromide, at two to four doses three to four times daily, plus a short-acting β₂-agonist on an as-needed basis.¹⁰ If patients are using substantial amounts of short acting β₂-agonist on an as-needed basis or if symptoms are greater at night or in the early morning, a twice daily long-acting

β_2 -agonist (salmeterol or formoterol) may be useful. Long acting β_2 -agonists (salmeterol or formoterol) are not recommended for rescue treatment. For regularly symptomatic patients, the more recently published Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines are less prescriptive, suggesting β_2 -agonists, anticholinergics, or methylxanthines, depending on "the availability of the medication and individual response in terms of symptom relief and side effects".¹¹

Administration and Cost

The dose of tiotropium used in different clinical studies is 18 μg once daily by inhalation.¹²⁻¹⁵ The drug is delivered via a dry-powder inhaler system. The cost information is not yet available since the drug has not been introduced to the North American market.

Rate of Technology Diffusion

Evidence suggesting the superior effectiveness of tiotropium compared to ipratropium bromide, the interpretation and dissemination of guidelines by the Canadian Respiratory Review Panel, and the co-marketing agreement with Pfizer raising expectations of a 20% sales growth worldwide in 2002¹⁶, will likely influence the selection of tiotropium as first-line therapy in managing stable COPD.

According to data obtained from IMS Health, estimated prescriptions made in a doctor's office for salmeterol and formoterol for COPD from 1996 to 2001 increased 1,150% and 1,975%, respectively. Ipratropium was prescribed for COPD in a doctor's office an estimated 260,000 times in 2001. If we include combination preparations (ipratropium/salbutamol) this number increases to 635,000 and represents 25% of all the drugs used for COPD. Taken together, tiotropium could see rapid uptake and a high rate of diffusion in Canada.

Concurrent Developments

Anticholinergics drugs are considered first line therapy for COPD.^{1,10} At this stage, tiotropium is the only new anticholinergic being explored for

COPD treatment.¹⁷ Recently, the long-acting β_2 -agonists salmeterol and formoterol were approved for the treatment of COPD in Canada. Other novel drugs in the pipeline for the treatment of COPD include the selective phosphodiesterase-4 inhibitors Cilomilast and Roflumilast.¹⁷

The Evidence

Tiotropium versus placebo: In a dose-finding 4-week double blind, randomized, placebo controlled trial (n=35), different doses of tiotropium [4.5 (n=34), 9 (n=33), 18 (n=33) and 36 μg (n=34) OD] were tested in 169 COPD patients.¹⁸ Patients were allowed to take salbutamol on an as-needed basis, plus theophylline, inhaled steroids and/or oral steroids (at a dose of 10 mg/day prednisolone or equivalent) during the trial. All doses of tiotropium significantly improved trough FEV₁ [i.e. forced expiratory volume in 1 second (FEV₁) measured 20 to 24 hours after the previous dose and just before the next dose of tiotropium], peak FEV₁, 6-hour post-dose average FEV₁, forced vital capacity (FVC), and in peak expiratory flow rate (PEFR). Improvement in different outcome measures was not dose-dependent. The mean difference (MD) with 95% confidence interval (95% CI) in trough FEV₁ levels between tiotropium 18 μg OD (the dose used in the majority of trials) and placebo was 150 ml (95% CI 37; 263). Overall, the safety profile of tiotropium was similar to that of placebo. The number of dropouts in the different treatment groups was seven (data on individual groups were not reported).

One study reported the combined results of two identical one-year, double blind, randomized controlled trials, comparing the efficacy of tiotropium 18 μg once daily (n=550), and placebo (n=371).¹⁴ Patients were allowed to take a short acting β_2 -agonist on an as-needed basis, stable doses of theophylline, inhaled glucocorticoids and/or the equivalent of 10 mg/day oral prednisone throughout the study period. Improvement in trough FEV₁ with tiotropium over placebo at different time points was between 120 ml (95% CI 100; 140) and 150 ml (95% CI 110; 190). Other outcome measures improved with tiotropium compared with placebo, such as clinically meaningful improvement in dyspnea (transition

dyspnea scores ≥ 1) [OR 1.41, 95% CI 1.07; 1.85], clinically meaningful improvement (at least 4 unit improvement) in quality of life as assessed by St. George's Respiratory Questionnaire (OR 2.26, 95% CI 1.71; 2.98), and reduction in incidence of hospitalization due to COPD exacerbation [OR: 0.55, 95% CI 0.33; 0.92]. However, the number of patients experiencing at least one COPD exacerbation was not significantly different between the two groups [OR 0.78, 95% CI 0.59; 1.02]. Incidences of dry mouth were more common in the tiotropium group compared to placebo group (OR: 6.88, 95% CI 3.52; 13.41). The numbers of deaths (seven in each group) and incidence of serious adverse events [tiotropium group 99 (18%) versus placebo group 78 (21%)] were not significantly different between the two groups. The definition of serious adverse event is not provided in the report.

Tiotropium versus ipratropium: One study presented the combined results of two identical one-year, multi-centred, randomized, double blind trials comparing the efficacy and safety of tiotropium 18 μg once daily (n=356) and ipratropium bromide 40 μg QID (n=179).¹⁵ Patients were allowed to take salbutamol on an as-needed basis, theophylline, inhaled steroids and/or oral steroid (10 mg/day prednisolone or equivalent) during the trial. Tiotropium, compared to ipratropium, significantly improved (change from day 1 baseline) trough FEV₁ (120 ml versus -30 ml; p<0.001) and trough FVC (320 ml versus 110 ml; p<0.05). The number of patients with one or more COPD exacerbations was lower in the tiotropium group, as compared to the ipratropium group (OR: 0.64, 95% CI 0.44; 0.92). More patients in the tiotropium group (compared to the ipratropium group) showed clinically meaningful improvement (transition dyspnea index scores ≥ 1) in dyspnea (OR 2.05 95% CI 1.32; 3.20) and clinically meaningful improvement (at least 4 unit improvement) in quality of life as assessed by the St. George's Respiratory Questionnaire (OR 1.92 95% CI 1.38; 2.89). The incidence of dry mouth was more common in the tiotropium group compared to the ipratropium group (12.1% versus 6.1%; p=0.03). The number of deaths [tiotropium 9/356 (2.5%) versus ipratropium 3/179 (1.7%)] and incidence of serious adverse events leading to discontinuation of therapy

[tiotropium 36/356 (10.1%) versus ipratropium 23/179 (12.8%)] were not significantly different between the two groups.

Tiotropium versus salmeterol: Two conference abstracts reported the results of one six-month study comparing the efficacy of tiotropium 18 μg OD (n=209), salmeterol 50 μg BID (n=213) and placebo (n=201).^{12,13} Tiotropium was superior to salmeterol in improving lung function (change from baseline) as measured by trough FEV₁ (MD: 52 ml 95% CI 13; 91), trough FVC (MD: 110 ml 95% CI 32; 188), FEV₁ average (0-12 hr) (MD: 77ml 95% CI 34; 120) and FEV₁ peak (0-3 hr) (MD: 83 ml 95% CI 38; 128).¹³ Both tiotropium and salmeterol compared to placebo produced clinically meaningful improvements (number of patients with transition dyspnea index scores ≥ 1) in dyspnea. (Tiotropium versus placebo OR: 2.08, 95% CI 1.37; 3.17; salmeterol versus placebo OR: 1.56, 95% CI 1.02; 2.38).¹²

Implementation Issues

Tiotropium has the potential to replace ipratropium bromide as the recommended first line therapy for long-term management of COPD because of its more convenient dosing schedule and demonstrated efficacy compared to ipratropium. It is known that patients are more likely to comply with once-daily regimens than with multiple dose regimens.¹⁹ However the long-term safety profile is not known and adverse events such as dry mouth may not always make it the best choice for individual patients.

At this stage, therefore, it is not clear whether this advantage will lead to overall cost savings for the health care system; this issue will be clear once the Canadian price of tiotropium is available.

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ISSN 1488-6324 (online)

ISSN 1488-6316 (print)

Publications Agreement Number 40026386