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Triple Therapy for Moderate-to-Severe Chronic Obstructive Pulmonary Disease

EXECUTIVE SUMMARY

The Issue

Pharmacotherapy plays a role in the management of chronic obstructive pulmonary disease (COPD). The classes of drugs that are used to treat COPD and exacerbations are short-acting anticholinergic (SAAC), long-acting anticholinergic (LAAC), short-acting beta-agonist, and long-acting beta-agonist (LABA) bronchodilators and inhaled corticosteroids (ICS). Because their mechanisms of action differ, these drugs can be used in combination. The anticipated increase in the use of triple therapy, based on Canadian guidelines, will probably have an impact on publicly funded drug programs in Canada. Although some jurisdictional drug programs do not restrict the coverage of some of the drugs that are used in the management of COPD, others do so. A comprehensive health technology assessment (HTA) evaluating the clinical and cost-effectiveness of triple therapy could help decision-makers to make coverage decisions. Based on the HTA conclusions, criteria for coverage of these drugs in the management of COPD could be established. Furthermore, the pre-existing criteria for coverage or the limited-use formulary status of these drugs could be revised.

Objectives

The aim of this HTA was to evaluate the comparative clinical effectiveness, cost-effectiveness, and health services impact (impact on the number of patients using triple therapy and the associated budget impact of triple therapy: LAAC plus LABA plus ICS) in the treatment of moderate-to-severe COPD with dual bronchodilator therapy (LAAC plus LABA, SAAC [regular use] plus LABA), combination therapy (LABA plus ICS), or monotherapy (LAAC).

Methods

Systematic literature searches were undertaken to identify relevant clinical and economic evaluations of triple therapy in the management of COPD. One additional search was conducted to identify the latest North American guidelines on the use of triple therapy. A second additional search was conducted to identify the latest meta-analyses evaluating dual bronchodilator therapy or combination therapy compared with monotherapy in the treatment of COPD.

Clinical Effectiveness

Four randomized clinical trials evaluated triple therapy. The enrolled patients were adults with moderate-to-severe COPD. One trial also included patients with very severe COPD, based on the forced expiratory volume in the first second of expiration (FEV_1) of less than 30% of the

predicted FEV_1. The trials had heterogeneous populations and varying methodological issues. Pre-bronchodilator FEV_1 values for inclusion of patients across the studies varied from 25% to 70% of predicted FEV_1 and the FEV_1/FVC (forced vital capacity) ratio was less than 0.7. All the statistical analyses in these trials involved a comparison of triple therapy (LAAC plus LABA plus ICS) with monotherapy (LAAC). The drug that was used in monotherapy was tiotropium in all studies. Two triple therapy regimens were evaluated: tiotropium (LAAC) plus the combination inhaler fluticasone plus salmeterol (LABA plus ICS) and tiotropium (LAAC) plus the combination inhaler budesonide plus formoterol (LABA plus ICS). Three trials included dual bronchodilator therapy or combination therapy arms, but there were no statistical comparisons between these arms and the triple therapy arms.

There was insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination therapy. There was also inconclusive evidence to determine whether the use of triple therapy decreased the overall exacerbation rate compared with monotherapy. The use of triple therapy, however, decreases the number of severe COPD exacerbations that result in hospitalization compared with monotherapy. Triple therapy, dual bronchodilator therapy, and combination therapy produce greater improvements in patients' quality of life compared with monotherapy. Triple therapy and combination therapy produce greater FEV_1 improvements compared with monotherapy. Combination therapy is also associated with an increased risk of pneumonia compared with monotherapy.

Economic Analysis

A cost-utility analysis, using a Markov model and taken from the publicly funded health care system perspective was conducted. In the base-case analysis, the starting cohort was 65-year old patients (66% males) with severe-to-moderate COPD. This reflected the population characteristics in the main triple therapy trials. The comparators were monotherapy (tiotropium), dual bronchodilator therapy (tiotropium plus LABA), and triple therapy (tiotropium plus LABA plus ICS). The time horizon was initially set for five years.

In the base-case primary economic analysis, using the relative risk (RR) of exacerbation with triple therapy from Aaron et al.'s study, the incremental cost-utility ratio of triple therapy (tiotropium plus fluticasone plus salmeterol) compared with monotherapy (tiotropium) was estimated to be $111,458 per quality-adjusted life-year (QALY). The estimated cost-effectiveness of triple therapy was affected by the cost of the LABA plus ICS combination that was used in the model. If the cost of fluticasone plus salmeterol was used, the cost per QALY of triple therapy became $133,982. If the cost of budesonide plus formoterol was used, the cost per QALY of triple therapy became $63,593. The drug costs were offset by lower exacerbation costs compared with monotherapy. The economic findings varied according to the model's assumptions. For example, if the RR (0.38) of exacerbation for triple therapy from Welte et al.'s study was used in the model, the incremental cost per QALY became $15,555. If the cost of budesonide plus formoterol was assumed in the model with the exacerbation RR from Welte et

al.'s study, triple therapy became dominant (less costly, produces more QALYs) compared with monotherapy.

Health Services Impact

Using provincial and private-payer drug cost data, the expenditures on triple therapy were calculated. Expenditures have risen steadily since 2004-2005. The 2008-2009 expenditures on COPD medications were estimated to be $92,485,163. Using the annualized increase in public spending from 2004 to 2009, the expenditures on triple therapy in 2011-2012 were calculated to be $199,883,022.

Conclusions

There was insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination (LABA plus ICS) therapy. More studies comparing these therapies are needed. The use of triple therapy decreases the number of COPD hospitalizations, improves lung function, and improves the quality of life of patients with moderate-to-severe COPD, compared with tiotropium alone.

In the base-case primary economic analysis, the incremental cost-utility ratio of triple therapy (tiotropium plus LABA plus ICS) compared with monotherapy (tiotropium) was estimated to be $111,458 per quality-adjusted life-year. The cost per QALY of triple therapy varied, however, depending on the source of efficacy data and the assumed cost of the LABA plus ICS. Using the base-case analysis, triple therapy would be cost-effective if societies' willingness to pay for a QALY is greater than $111,458. Otherwise monotherapy would be the cost-effective treatment.