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

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation throughout the airways, parenchyma, and pulmonary vasculature. As the number of inflammatory cells increase in parts of the lung, these cells release substances that can damage the lung or sustain neutrophilic inflammation.[1] As the severity of COPD increases, the number of neutrophils also increases.[2]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] defines COPD as a preventable and treatable disease with extra-pulmonary effects that may contribute to the severity of disease in individual patients. Its pulmonary component is characterized by airflow limitation that is only partially reversible. Based on 2004 data, COPD was the fourth leading cause of death in Canada.[4]

Because COPD is incurable, the goal of treatment is to slow disease progression and to control symptoms. The reduction of therapy in the management of stable COPD is usually not possible, and the deterioration of lung function usually requires the progressive introduction of more pharmacologic and non-pharmacologic treatments in an attempt to halt the deterioration. Three classes of inhaled drugs are prescribed for the treatment of moderate-to-severe COPD: short-acting anticholinergic (SAAC) and long-acting anticholinergic (LAAC) bronchodilators, short-acting beta-agonist (SABA) and long-acting beta-agonist (LABA) bronchodilators, and inhaled corticosteroids (ICS). Both classes of bronchodilators produce smooth muscle relaxation with bronchodilation. They have different mechanisms of action so that they can be used in combination.[5]

Canadian guidelines recommend the use of triple therapy (LAAC plus LABA plus ICS) in two clinical scenarios.[6] In scenario one, patients with moderate-to-severe COPD and infrequent acute disease exacerbations (less than one per year, on average, for two consecutive years) have persistent disability despite the use of dual therapy with a LAAC plus a LABA. In scenario two, patients with moderate-to-severe COPD have persistent symptoms and a history of exacerbations (one or more per year, on average, for two consecutive years). The level of evidence on these recommendations is stronger for scenario two than for scenario one.[6]

Pharmacotherapy plays a role in the management of COPD. The anticipated increase in the use of triple therapy, based on Canadian guidelines,[6] may have an impact on publicly funded drug programs. Although some jurisdictional drug programs do not restrict the coverage of some of the drugs, several do limit the coverage. In the jurisdictions with limited coverage, patients with COPD need to meet pre-established criteria for coverage of some of the drugs. A comprehensive health technology assessment evaluating the clinical and cost-effectiveness of triple therapy could help decision-makers make coverage decisions. Based on the health technology assessment 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.

Objective

The aim of the health technology assessment is to evaluate the 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 compared 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.

Results

Clinical Effectiveness

Four randomized clinical trials[7-9] evaluated triple therapy in 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, decreased the number of severe COPD exacerbations that result in hospitalization compared with monotherapy. Triple therapy, dual bronchodilator therapy, and combination therapy produced greater improvements in patients' quality of life compared with monotherapy. Triple therapy and combination therapy produced greater FEV_1 improvements compared with monotherapy. Combination therapy was 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 of exacerbation with triple therapy from Aaron et al.'s study,[10] 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 relative risk (0.38) of exacerbation for triple therapy from Welte et al.'s study[9] 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 relative risk from Welte et al.'s study,[9] triple therapy became dominant (less costly, produced 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.

Limitations

Four randomized controlled trials evaluated triple therapy. Therefore, the data for the economic model's assumptions are limited. The least amount of data was available for comparisons of dual bronchodilator therapy with monotherapy and triple therapy. Therefore, the findings in the economic analysis that dual bronchodilator therapy is extendedly dominated by monotherapy and triple therapy should be interpreted with caution. As is seen in the sensitivity analyses, the results change, sometimes drastically, depending on which study the data assumptions are based on.

The findings cannot be generalized to all patients with moderate-to-severe COPD; they can be generalized only to those with moderate-to-severe COPD who have a history of smoking and exacerbations. As the disease progresses and symptoms become more frequent and debilitating, pharmacotherapy increases. Triple therapy is effective in managing COPD and, therefore, could be used when patients can no longer be managed on dual bronchodilator therapy or combination therapy.

There seemed to be clinical improvement in the exacerbation rate with triple therapy, but not in all patients. This explains the wide 95% confidence intervals for the estimates. The characteristics of patients who will improve on triple therapy remain unanswered. Therefore, future studies could stratify patients by COPD severity, exacerbation severity, and frequency.

The FEV_1 measure, which is a standard outcome in COPD trials, is an excellent measure to track individual patient improvement; but it is unclear if it could be used to determine inter-patient differences. The more reliable functional residual capacity and the inspiratory capacity may be more sensitive measures to use as a standard lung function outcome in clinical trials.[11]

Conclusions

Based on the four publications that evaluated triple therapy, there is insufficient evidence to determine if triple therapy is clinically superior to dual bronchodilator therapy or combination therapy. Evidence to determine whether the use of triple therapy decreases the overall exacerbation rate compared with monotherapy is also inconclusive. The use of triple therapy, however, decreases the number of severe COPD exacerbations resulting 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.

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 QALY. Therefore, triple therapy would be cost-effective if societies' willingness to pay for a QALY is greater than $111,458. The economic findings varied, however, according to the model's assumptions. For example, depending on which LABA plus ICS combination drug the triple therapy costs were based on, the incremental cost per QALY of triple therapy ranged from $63,593 (budesonide plus formoterol) to $133,982 (fluticasone plus salmeterol).

References

1. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med. 2001 Apr;163(5):1256-76.

2. Saetta M. Airway inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999 Nov;160(5 Pt 2):S17-S20.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease [Internet]. Bethesda (MD): National Heart, Lung and Blood Institute; 2008. [cited 2009 Jun 3]. Available from: http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=2003

4. Statistics Canada. Mortality, summary list of causes 2004 [Internet]. Ottawa: Statistics Canada; 2007. [cited 2009 Nov 30]. Available from: http://www.statcan.gc.ca/pub/84f0209x/84f0209x2004000-eng.pdf

5. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk D, Balter M, et al. State of the art compendium: Canadian Thoracic Society recommendations for the management of chronic obstructive pulmonary disease. Can Respir J. 2004 Jul;11 Suppl B:7-59B.

6. O'Donnell DE, Aaron S, Bourbeau J, Hernandez P, Marciniuk DD, Balter M, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can Respir J. 2007;14(Suppl B):5-32B.

7. Fang LZ, Liang X, Zhang JQ, Liu L, Fu WP, Zhao ZH, et al. Combination of inhaled salmeterol/fluticasone and tiotropium in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi. 2008;31(11):811-4.

8. Cazzola M, Ando F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. Pulm Pharmacol Ther. 2007;20(5):556-61.

9. Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in COPD patients. Am J Respir Crit Care Med. 2009 Aug 13;180:741-50.

10. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone- salmeterol

for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007;146(8):545-55.

11. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J. 2008 Feb;31(2):416-69.