Critical Appraisal

New therapy for managing moderate to severe chronic obstructive pulmonary disease

Andrew Chou MD Anthony D’Urzo MD MSc CCFP FCFP


Clinical question
What is the effect of rofumilast on lung function in patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are already being treated with salmeterol or tiotropium?

Type of article and design
The study encompassed 2 randomized double-blind multicentre trials in an outpatient setting. One trial (M2-127), consisting of salmeterol (long-acting β₂-agonist [LABA]) plus rofumilast (selective phosphodiesterase 4 inhibitor), was conducted in 135 centres in 10 countries. The other trial (M2-128), consisting of tiotropium (long-acting anticholinergic antagonist) plus roflumilast, was conducted in 85 centres in 7 countries. The studies recruited patients with moderate to severe COPD defined using spirometry.

Inclusion criteria were age older than 40 years; a 10-pack-year history of smoking, either as a current or former smoker (1 year or longer smoking cessation); postbronchodilator forced expiratory volume in 1 second (FEV₁) of 40% to 70% of the predicted value; a postbronchodilator FEV₁/FVC ratio of 0.7 or less; partial reversibility with 400 µg albuterol (increase in FEV₁ of ≤ 12% or 200 mL); and stable disease. Initially, patients in both studies were involved in a 4-week run-in period during which they received placebo tablets once daily in the morning. Patients, but not investigators, were blinded to the assigned treatment group during the run-in period only. Using daily diary cards, patients recorded their use of short-acting bronchodilators, as well as their cough and sputum production. Patients were then randomly assigned to rofumilast (500 µg once daily) or placebo for the subsequent 24 weeks if they took at least 80% of their prescribed placebo tablets during the 4-week run-in period without evidence of moderate to severe COPD exacerbation.

Patients were assessed every 4 weeks for the first 12 weeks, and then every 6 weeks until week 24. At each visit, prebronchodilator and postbronchodilator spirometric measurements were carried out. Additionally, body weight, exacerbation events, adherence to treatment medication, daily diary record completeness, and use of short-acting β₂-agonists were recorded. Finally, the Shortness of Breath Questionnaire (SOBQ) and investigator-administered transition dyspnea index (TDI) were completed.

Relevance to family medicine
Chronic obstructive pulmonary disease, which affects at least 700 000 Canadians, is a commonly encountered, yet underdiagnosed, respiratory illness. Beyond education, smoking cessation, and vaccination programs, pharmacotherapy is used for long-term symptom management. Current Canadian guidelines recommend the use of long-acting bronchodilators (long-acting anticholinergics or LABAs) for management of persistent symptoms with a short-acting β₂-agonist used as a reliever.¹ The use of inhaled corticosteroid (ICS) monotherapy in COPD continues to be controversial; the landmark TORCH (Towards a Revolution in COPD Health) trial² revealed that the combination of an ICS (fluticasone) and a LABA³ (salmeterol) was associated with a reduction in mortality that almost achieved statistical significance. However, the use of ICSs alone was associated with a significant increase in the risk of pneumonia in a COPD population with little influence on mortality (P<.001).² Despite the currently available pharmacotherapeutic agents, many patients with COPD continue to experience regular symptoms. This underscores the need to develop additional therapies. In November 2010, rofumilast was approved by Health Canada for use as “add-on therapy to bronchodilator treatment, for the maintenance treatment of severe COPD associated with chronic bronchitis (patients with a history of cough and sputum) in adult patients with a history of frequent exacerbations.”³

Outcomes
In the M2-127 trial (salmeterol plus rofumilast [S+R]), 1221 patients were recruited, with 286 patients withdrawing during screening or not meeting entry criteria. Of the remaining 935 patients, 467 were assigned to the rofumilast group, and 468 were assigned to the placebo group. In the treatment arm, 107 patients discontinued rofumilast. In the control arm, 82 patients discontinued the placebo. In the M2-128
trial (tiotropium plus roflumilast [T+R]), 910 patients were recruited, with 166 patients withdrawing during screening or not meeting entry criteria. Of the remaining 744 patients, 372 were randomly assigned to the roflumilast group and 372 were assigned to the placebo group. In the treatment arm, 62 discontinued roflumilast. In the control arm, 39 discontinued the placebo. Data for efficacy were evaluated with intention-to-treat analysis for patients given at least 1 dose of study medication.

Compared with baseline, the treatment arms in both trials demonstrated an improvement in FEV₁ compared with the control arms. In the S+R arm, the mean change in prebronchodilator FEV₁ was 39 mL compared with -10 mL in the salmeterol and placebo (S+P) arm (difference of 49 mL, \( P < .0001 \)). In the T+R group, the mean change in prebronchodilator FEV₁ was 65 mL, compared with -16 mL in the tiotropium and placebo (T+P) arm (difference of 80 mL, \( P < .0001 \)). Similarly, the treatment arms of both groups demonstrated improvements in postbronchodilator FEV₁: 68 mL for S+R and 8 mL for S+P (difference of 60 mL, \( P = .0001 \)); 74 mL for T+R and -7 mL for T+P (difference of 81 mL, \( P = .0001 \)). Both groups also demonstrated improvements in postbronchodilator FVC: 67 mL for S+R and 10 mL for S+P (difference of 57 mL, \( P = .0028 \)); 27 mL for T+R and -74 mL for T+P (difference of 101, \( P = .0004 \)). There was no statistically significant change in prebronchodilator FVC. Both the exacerbation rates and the time to first exacerbation were not significantly different between the roflumilast and control groups, a finding which might be related to a lack of study power. However, an exception was that the proportion of patients with exacerbations rated as moderate or severe was slightly less in the S+R group compared with placebo (11% vs 18%, respectively; \( P = .0015 \)). Patient-reported outcomes (ie, TDI and SOBQ scores) were significantly improved \((P < .05) \) in the T+R trial compared with placebo. The patient-reported outcomes in the S+R trial were not statistically different from placebo.

The mean compliance was similar in all groups and ranged between 94% and 97%; however, treatment discontinuation was higher among patients treated with roflumilast. The most frequent adverse events in both studies were COPD related, reported by 16% of patients with limited acute bronchodilator reversibility, it is possible that the benefits of salmeterol and tiotropium might be underestimated. Further, the fact that COPD patients exhibit bronchodilator reversibility might limit the extent to which the findings reported in these trials can be applied to other COPD populations. It is relevant to note that two-thirds of the population in the 2 studies had moderate COPD, and one-third suffered from severe COPD. Rofumilast trials lasting longer than 1 year would provide evidence relating to sustained effect. Furthermore, while the instruments used to capture patient-reported outcomes have been validated in the clinical trial setting, similar data captured in the real-world setting are lacking. The study was funded by the sponsor Nycomed. The authors had full access to the data and

### Overview of study outcomes

The primary end point was the mean change in prebronchodilator FEV₁ from baseline to each visit after randomization during the treatment period. Additional secondary end points included the mean rate of COPD exacerbations, the use of rescue medication, and the mean change in the investigator-administered TDI and in the SOBQ scores from baseline to each visit after randomization. In both trials, patients in the treatment and control groups were comparable in terms of demographic characteristics and COPD status. Trial profiles in the studies provide a detailed breakdown of the number of patients who completed the study, as well as the reasons for discontinuing medication. However, the study does not specify reasons why patients requested discontinuation of the medication. Further, the study does not go into any detail regarding adverse event severity and whether the adverse events were verified by physicians or solely based on patient report.

### Analysis of methodology

Both the studies were double-blind, placebo-controlled trials. Both the studies were adequately powered for the primary end point. On the basis of reasonable assumptions, the power was 97% for the M2-127 study and 91% for the M2-128 study. The primary end point data were analyzed by repeated-measures analysis of covariance, and a sensitivity analysis confirmed the robustness of the results for the primary end point with respect to the effect of differential dropouts and missing data. Given that patients were screened for limited acute bronchodilator reversibility, it is possible that the benefits of salmeterol and tiotropium might be underestimated. Further, the fact that most COPD patients exhibit bronchodilator reversibility might limit the extent to which the findings reported in these trials can be applied to other COPD populations. It is relevant to note that two-thirds of the population in the 2 studies had moderate COPD, and one-third suffered from severe COPD. Rofumilast trials lasting longer than 1 year would provide evidence relating to sustained effect. Furthermore, while the instruments used to capture patient-reported outcomes have been validated in the clinical trial setting, similar data captured in the real-world setting are lacking. The study was funded by the sponsor Nycomed. The authors had full access to the data and
Critical Appraisal

were responsible for the decision to publish the report. The sponsor did not place any restrictions on statements made by the investigators in the paper.

Application to clinical practice

The results of these 2 trials suggest that roflumilast provides benefit for COPD patients already using regular maintenance therapy with long-acting bronchodilators. This provides an important alternative therapeutic strategy for physicians and patients. Given the reported adverse events associated with roflumilast use, physicians will have to regularly monitor risk and benefit issues. It appears that the adverse events associated with roflumilast treatment constitute a disadvantage that could force some patients to discontinue this drug. At the present time, the role of roflumilast in combination with ICSs remains unclear. Studies that directly compare roflumilast with ICSs are lacking. Further, prospective studies comparing the addition of roflumilast to combination ICSs plus LABAs with ICSs or LABAs alone are needed. Roflumilast is not recommended as monotherapy. Since Health Canada approved roflumilast, there have been no unexpected adverse events reported.

Dr Chou is a family medicine resident at the University of Toronto in Ontario. Dr D’Urzo is Associate Professor in the Department of Family and Community Medicine at the University of Toronto.

Competing interests

Dr D’Urzo has received research, consulting, and lecturing fees from GlaxoSmithKline, Sepracor, Schering-Plough, Altana, Methapharma, AstraZeneca, ONO Pharmaceutical, Merck Canada, Forest Laboratories, Novartis, Boehringer Ingelheim Ltd, Pfizer Canada, SkyPharma, and KOS Pharmaceuticals.

References


BOTTOM LINE

- While roflumilast offers statistically significant improvement in lung function in patients with moderate to severe chronic obstructive pulmonary disease already using maintenance therapy with long-acting bronchodilators (P < .001), the clinical significance of this improvement is less clear.

- Roflumilast is an important new therapeutic option for the management of moderate to severe chronic obstructive pulmonary disease, but more studies are required to better understand its positioning in management guidelines, including its role as add-on therapy to the new long-acting β-agonist indacaterol.

- In the trials, treatment discontinuation was higher among patients receiving roflumilast. Mean weight loss with roflumilast was 2 kg.

POINTS SAILLANTS

- Le roflumilast procure une amélioration statistiquement significative de la fonction pulmonaire chez les patients souffrant d’une bronchopneumopathie chronique obstructive de modérée à grave qui utilisent déjà une thérapie de maintien au moyen de bronchodilatateurs à longue durée d’action (P < .001), mais la signification clinique de cette amélioration est moins évidente.

- Le roflumilast est une importante nouvelle option thérapeutique pour la prise en charge de la bronchopneumopathie chronique obstructive, mais il faut davantage d’études pour mieux comprendre son positionnement dans les guides de pratique clinique, y compris son rôle comme thérapie adjuvante au nouveau indacaterol bêta-2-agoniste à longue durée d’action.

- Durant les études, la cessation du traitement était plus fréquente chez les patients qui prenaient du roflumilast. La perte moyenne de poids avec le roflumilast était de 2 kg.