# Roflumilast: clinical benefit in patients suffering from COPD

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## Abstract

*Background and aims:* Chronic obstructive pulmonary disease (COPD) is associated with substantial morbidity and mortality and is characterised by persistent airway inflammation, which leads to impaired airway function, quality of life and intermittent exacerbations. In spite of recent advances in the treatment of COPD, new treatment options for COPD are clearly necessary.

The oral phosphodiesterase-4 (PDE4) inhibitor roflumilast represents a new class of drugs that has shown efficacy and acceptable tolerability in preclinical and short-term clinical studies in patients with COPD.

*Methods and results:* The available long-term clinical studies reviewed here suggest that the clinical efficacy of roflumilast is likely because of the suppression of airway inflammation and not through bronchodilation. Furthermore, the clinical studies have shown a modest improvement in airway function, including $FEV_1$, and a reduction in frequency and severity of COPD exacerbations, as well as a positive effect on several patient-reported outcomes. The clinical benefit of roflumilast appears to be greatest in patients with more symptomatic and severe disease who experience exacerbations. The most common adverse effects are gastrointestinal events, primarily diarrhoea, nauseas and weight loss.

*Conclusion:* Roflumilast is beneficial for maintenance treatment of patients with severe and symptomatic COPD and with a history of frequent acute exacerbations as an add-on to treatment with long-acting bronchodilators. It may have a role as an alternative to inhaled corticosteroids in more symptomatic COPD patients with frequent exacerbations, although direct comparisons are currently lacking.

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COPD – exacerbations – lung function – roflumilast

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## Introduction

Although drug treatment for chronic obstructive pulmonary disease (COPD) improves lung function and quality of life, and reduce symptoms and exacerbations, most patients remain symptomatic (1–3). Furthermore, disease modification remains a largely unmet goal of pharmacotherapy for COPD (4, 5). New therapies for COPD are therefore required.

Phosphodiesterase-4 (PDE4) inhibition provides a novel approach to the treatment of COPD. The second-generation PDE4 inhibitor roflumilast has been shown to reduce airway inflammation in COPD (6) and may offer a new possibility for maintenance treatment of COPD.

This short review will focus on the clinical benefit of roflumilast in patients with moderate to very severe COPD.

## Clinical findings with roflumilast

Roflumilast has undergone wide-scale clinical investigation in patients with moderate to very severe COPD, and the majority of the available efficacy and safety data arises from large prospective, randomised, double-blind, placebo-controlled studies.

Rabe *et al.* (7) enrolled 1411 patients with moderate to severe COPD (mean post-bronchodilator $FEV_1$, 50% of predicted) and a documented absence of bronchodilator reversibility in a 24-week study. Subjects were randomised to receive roflumilast 250 or 500 μg, or matching placebo, orally, once daily. The two co-primary outcome measures were changed from baseline in post-bronchodilator $FEV_1$ and in the St George's Respiratory Questionnaire (SGRQ), and exacerbation rate defined by additional bronchodilator use was among the secondary end points. A total of 82% of the subjects completed the study, and withdrawals were slightly higher in the two active treatment arms. At the 24-week end point, a significant improvement from baseline values were observed in post-bronchodilator $FEV_1$ in both active treatment arms, the increase over placebo on post-bronchodilator $FEV_1$ being 74 and 97 mL in the roflumilast 250 and 500 μg groups, respectively ($P < 0.0001$). A comparable improvement was observed in pre-bronchodilator $FEV_1$ and forced vital capacity (FVC). The changes from baseline in SGRQ were statistically significant, being −3.4 and −3.5 units for 250 and 500 μg of roflumilast, respectively ($P < 0.0001$), but compared with placebo, neither of these improvements were statistically significant. Fewer subjects in both active treatment arms experienced an acute exacerbation of COPD (AECOPD), the mean number of AECOPDs being 1.13, 1.03 and 0.75 per patient per year in the groups receiving placebo, 250 and 500 μg of roflumilast, respectively. The reduction in exacerbation rate was statistically significant compared with placebo for both active treatment groups ($P = 0.003$); the greatest effect was observed in the 500-μg roflumilast group (34% reduction in AECOPDs).

Calverley *et al.* (8) recruited 1513 patients with severe COPD (mean post-bronchodilator $FEV_1$, 41% of predicted) and a documented absence of bronchodilator reversibility in a 1-year study. Inhaled corticosteroids and short-acting anticholinergics were allowed at a constant daily dose, if used before study entry; all patients used short-acting $\beta_2$-agonist as rescue medication, whereas other COPD medications were stopped before the run-in period. Enrolled subjects were randomised to roflumilast 500 μg once daily or matching placebo. The primary efficacy variables were the change from baseline to end point in post-bronchodilator $FEV_1$ and the number of moderate or severe exacerbation per patient per year. The main secondary variable was the change from baseline in SGRQ total score. Over 70% of the randomised subjects completed the study, and the number of dropouts was higher in the active treatment arm. The post-bronchodilator $FEV_1$ increased by 39 mL with roflumilast compared with placebo by 52 weeks ($P = 0.001$). No significant difference in overall rate of moderate to severe exacerbations was found between roflumilast- and placebo-treated patients, the mean number of exacerbations defined by the use of antibiotics and/or corticosteroids being 0.86 and 0.92 per patient per year, respectively. However, a retrospective analysis revealed that the exacerbation rate in patients in GOLD stage IV was 36% lower in patients treated with roflumilast than in those treated with placebo (1.01 vs 1.59 exacerbations/patient/year, respectively; $P = 0.024$). The SGRQ total score deteriorated similarly in both treatment arms (−1.7 and −2.0 units, respectively), but the retrospective analysis by GOLD stage showed that subjects with very severe disease (GOLD stage IV) improved with roflumilast by 2.97 units compared with placebo ($P = 0.086$).

To further expand on the findings related to exacerbations in patients with severe COPD, an identical pair of studies was performed and reported in a single publication by Calverley *et al.* (9). The enrolled patients had severe COPD (mean post-bronchodilator $FEV_1$, 36% of predicted), chronic cough and sputum production, and at least one COPD exacerbation within the previous year, findings predictive of a higher exacerbation rate in post hoc analysis of the earlier studies. Long-acting bronchodilators were allowed, but inhaled corticosteroids were withheld throughout the study period. Patients were assigned to treatment, stratified according to smoking status and treatment with long-acting $\beta_2$-agonists, with oral roflumilast 500 μg once daily ($n = 1537$) or placebo ($n = 1554$) for 52 weeks. The co-primary end points were change in pre-bronchodilator $FEV_1$ and the rate of moderate to severe exacerbations. The secondary outcome variables included post-bronchodilator $FEV_1$ and transition dyspnoea index (TDI) focal score. In both studies, patient withdrawal was similar in the roflumilast and placebo groups (35% and 31%, respectively, and 32% and 31%, respectively) at the study end point, but more patients in the roflumilast groups than in the placebo groups withdrew in the first 12 weeks after randomisation. In both studies, the pre-specified primary end points were achieved and were similar in magnitude. The pre-bronchodilator $FEV_1$ increased, in the pooled analysis, by 48 mL with roflumilast compared with placebo ($P < 0.0001$). The rate of moderate or severe exacerbations per patient per year was 1.14 with roflumilast and 1.37 with placebo (reduction, 17%; $P < 0.0003$), and the difference in rates was independent of concomitant treatment with long-acting $\beta_2$-agonist. The time to the first moderate or severe exacerbation was significantly

prolonged in the roflumilast group ($P = 0.0185$). Of the pre-specified secondary end points, a statistically significant improvement was only seen in TDI focal score ($P = 0.0009$), although the difference was less than the generally accepted clinically important difference.

Fabbri *et al.* (10) have reported, also in a single publication, two additional efficacy studies of roflumilast in patients with moderate to severe COPD treated with long-acting bronchodilators. These studies complemented the results of the companion 1-year trails (9) where almost half of the patients had used inhaled long-acting $\beta_2$-agonists, and the beneficial effects of roflumilast were still seen in this sub-group of patients. However, the use of bronchodilators was not randomised in the 1-year trials, hence the need for further studies. In the first of these trials, after a run-in period of 4 weeks, patients with moderate to severe COPD were randomly assigned to receive in one study roflumilast 500 μg once daily plus salmeterol inhalation twice daily ($n = 466$) or matching placebo plus salmeterol inhalation twice daily ($n = 467$) (mean post-bronchodilator $FEV_1$, 55% of predicted). In the other very similar study, patients were randomly assigned to either roflumilast 500 μg plus tiotropium inhalation once daily ($n = 371$) or placebo plus tiotropium once daily ($n = 372$) (mean post-bronchodilator $FEV_1$, 56% of predicted). The inclusion criteria in the two studies were very similar, but in contrast to the salmeterol plus roflumilast study, subjects recruited to the tiotropium plus roflumilast trial were more symptomatic because they were required to have chronic cough and sputum production and frequent use of as-needed short-acting $\beta_2$-agonists (at least 28 puffs per week) during the run-in period (10). Both studies were concluded after 24 weeks, and the primary end point was changed from baseline in pre-bronchodilator $FEV_1$. Secondary end points included post-bronchodilator $FEV_1$ and FVC, TDI score, Shortness of Breath Questionnaire, rate of COPD exacerbations and use of rescue medication. A total of 744 subjects completed the salmeterol study, and 642 completed the tiotropium study; in both trials, the probability of treatment discontinuation was greater in patients treated with roflumilast. Compared with placebo, roflumilast consistently improved mean pre-bronchodilator $FEV_1$ by 49 mL ($P < 0.0001$) in patients treated with salmeterol and by 80 mL ($P < 0.0001$) in those treated with tiotropium. Similar improvements were noted in post-bronchodilator $FEV_1$ and FVC. In both trials, a trend towards improvement in number, severity and time to first exacerbation was observed in the roflumilast-treated groups, although neither of the trials had been powered for the analysis of exacerbations outcomes. Roflumilast also had beneficial effects on selected patient-reported outcomes in both studies, although more pronounced in the tiotropium plus roflumilast trial compared with the salmeterol plus roflumilast trial (10).

Further studies of the clinical efficacy of roflumilast in various subgroups of patients with COPD are likely to be published shortly (11, 12).

## Adverse effects of roflumilast

In the majority of published clinical studies of roflumilast, the total number of subjects reporting adverse events has been greater in the roflumilast-treated groups compared with the placebo-treated groups and, where different doses of roflumilast have been administered, has been dose-related (7–10). Diarrhoea, nausea, weight loss and decreased appetite have been the most commonly reported treatment-related adverse events (7–10). Diarrhoea has typically been reported by approximately 9% of patients treated with roflumilast 500 μg once daily compared with 3% of those treated with placebo (8–10). Compared with placebo, nausea has been reported twice as often by patients treated with roflumilast. Weight loss has been observed in up to 12% of patients treated with roflumilast, with most of the change occurring in the first 6 months of treatment. In the two trials reported by Fabbri *et al.* (10), a gradual reduction in mean body weight was observed in the roflumilast-treated groups (roflumilast plus salmeterol trial −2.0 kg and roflumilast plus tiotropium trial −1.8 kg, compared with +0.2 and +0.3 kg, respectively, in the placebo-treated groups), with no significant differences between patients in different body mass index categories. The weight loss appears to be related to decreased appetite, as well as nausea and diarrhoea.

Based on the presently available published clinical trials, no safety concerns related to mortality, cardiovascular events, including arrhythmias or frequency of pneumonias have been reported (7–10).

## Discussion

The available clinical studies strongly suggest that roflumilast has potentially beneficial effects in patients suffering from COPD, particularly when added to long-acting bronchodilators in more symptomatic patients (9, 10). Roflumilast is likely to act mainly by mechanisms unrelated to bronchodilation, as also

suggested by its effect when added to long-acting bronchodilators on both post-bronchodilator lung function, and it might therefore have disease-modifying effects in COPD (10, 12).

Furthermore, roflumilast does not cause rapid bronchodilation in patients with COPD, although airway function does improve with regular administration over a period of days to weeks (8–10), in keeping with an anti-inflammatory effect. The observed improvement in pre-bronchodilator $FEV_1$ and the reduction in incidence of acute exacerbations (9, 10) further support the assumption of an anti-inflammatory mechanism of action.

The magnitude of the reported improvement in $FEV_1$ because of roflumilast is less than 100 mL and therefore does not meet the required difference for a bronchodilator to be considered effective (13). However, this might indicate a meaningful improvement in lung function when taking into account that subjects were selected for their non-responsiveness to short-acting bronchodilators and/or concomitant use of long-acting bronchodilators (7–10). Moreover, the magnitude of the bronchodilator effect and of inhaled corticosteroids on lung function is influenced by the initial pre-treatment lung function (14), and the later studies with roflumilast are in keeping with this. Indeed, the lung function changes reported here are similar to those seen with inhaled corticosteroids in comparable patient populations.

The reduction in exacerbation rate was significant in the long-term studies powered for acute exacerbations of COPD as a co-primary end point (9). This effect appears to be greatest in patients with more symptomatic disease and a history of more severe exacerbations (7–9, 12), although the study by Fabbri *et al.* (10) suggest that roflumilast might also be beneficial in patients with less severe COPD. Several studies of COPD have previously demonstrated a reduction in rate of acute exacerbations for treatment with long-acting $\beta_2$-agonist, long-acting anti-cholinergic drugs, inhaled corticosteroids and their combinations, and, although the mechanism underlying this reduction in exacerbation rate is not fully understood, a reduction in frequency and severity of exacerbations appears to be a requirement for an anti-inflammatory drug.

Although the published studies provide evidence of the clinical benefit of roflumilast in patients suffering from COPD, several issues remain to be addressed before the place of PDE4 inhibitors in the treatment of COPD has been clarified. Primarily, there is no available evidence about the clinical efficacy of roflumilast added to a combination of inhaled corticosteroids and long-acting bronchodilators. As roflumilast, as discussed above, is supposed to act mainly as an anti-inflammatory drug (12), it is very important to know if its benefit in reducing acute exacerbations of COPD will persist when compared with a combination of inhaled corticosteroids and long-acting bronchodilators, or may have an additive effect to that of combination therapy with inhaled corticosteroid and long-acting $\beta_2$-agonist. Furthermore, the side effects of roflumilast are an issue, although the gastrointestinal problems, including weight loss, and headache mainly occur within the first weeks of treatment and, in most cases, resolve on continued treatment. If roflumilast is not more effective than inhaled corticosteroids in reducing the rate of exacerbations, the side effects must be weighed against the reported increased risk of pneumonia in COPD patients treated with inhaled corticosteroids (15, 16).

In conclusion, the available studies suggest that roflumilast is beneficial for maintenance treatment of patients with severe COPD with chronic cough and sputum production and a history of frequent acute exacerbations as add-on to treatment with long-acting bronchodilators. Initially, roflumilast may therefore find its role as an alternative to inhaled corticosteroids in more symptomatic COPD patients with frequent exacerbations.

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