Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials

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Summary

Background Patients with chronic obstructive pulmonary disease (COPD) have few options for treatment. The efficacy and safety of the phosphodiesterase-4 inhibitor roflumilast have been investigated in studies of patients with moderate-to-severe COPD, but not in those concomitantly treated with longacting inhaled bronchodilators. The effect of roflumilast on lung function in patients with COPD that is moderate to severe who are already being treated with salmeterol or tiotropium was investigated.

Methods In two double-blind, multicentre studies done in an outpatient setting, after a 4-week run-in, patients older than 40 years with moderate-to-severe COPD were randomly assigned to oral roflumilast 500 μg or placebo once a day for 24 weeks, in addition to salmeterol (M2-127 study) or tiotropium (M2-128 study). The primary endpoint was change in prebronchodilator forced expiratory volume in 1 s (FEV_1). Analysis was by intention to treat. The studies are registered with ClinicalTrials.gov, number NCT00313209 for M2-127, and NCT00424268 for M2-128.

Findings In the salmeterol plus roflumilast trial, 466 patients were assigned to and treated with roflumilast and 467 with placebo; in the tiotropium plus roflumilast trial, 371 patients were assigned to and treated with roflumilast and 372 with placebo. Compared with placebo, roflumilast consistently improved mean prebronchodilator FEV_1 by 49 mL ($p<0·0001$) in patients treated with salmeterol, and 80 mL ($p<0·0001$) in those treated with tiotropium. Similar improvement in postbronchodilator FEV_1 was noted in both groups. Furthermore, roflumilast had beneficial effects on other lung function measurements and on selected patient-reported outcomes in both groups. Nausea, diarrhoea, weight loss, and, to a lesser extent, headache were more frequent in patients in the roflumilast groups. These adverse events were associated with increased patient withdrawal.

Interpretation Roflumilast improves lung function in patients with COPD treated with salmeterol or tiotropium, and could become an important treatment for these patients.

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Introduction

Pharmacotherapy for chronic obstructive pulmonary disease (COPD) improves lung function and reduces symptoms and exacerbations, but has limited clinical efficacy so that patients often remain symptomatic.[1–3] Bronchodilator medications are important for the management of COPD. When required daily, regularly administered longacting inhaled bronchodilators are preferred to regularly administered shortacting bronchodilators, and are given to the patient to reduce and prevent symptoms and exacerbations. The principal longacting inhaled bronchodilators are β_2 agonists (formoterol and salmeterol) and the anticholinergic drug tiotropium.[1–3]

Because regularly administered longacting bronchodilators have limited effects on symptoms and exacerbations,[1–6] many patients with COPD need additional treatment. The combination of one of the two longacting β_2 agonists and tiotropium is recommended for patients with COPD that is moderate to very severe who remain symptomatic despite regular treatment with a single longacting bronchodilator.[1–3] Similarly, theophylline is recommended as a second-choice treatment to supplement longacting bronchodilators, even though this recommendation is supported by results from only one small randomised clinical trial.[7] The addition of inhaled glucocorticosteroids to longacting β_2 agonists (combination with tiotropium has not been adequately assessed) further reduces symptoms and exacerbations, and improves lung function, particularly in patients with severe or very severe COPD.[4,8–10] Thus, inhaled glucocorticosteroids are recommended in combination with longacting bronchodilators for patients with COPD that is severe to very severe who have recurrent exacerbations.[1–3] However, inhaled glucocorticosteroids have limited effect in these patients, and their long-term use is associated with a small but significant increase in the risk of pneumonia that is of clinical concern.[4,11,12] Apart from improvements in bronchodilators and inhaled glucocorticosteroids, no novel treatment for COPD is expected to become available for several years.[5,13]

See Online for webappendix

Phosphodiesterase-4 (PDE4) inhibitors are a new class of anti-inflammatory drugs that have shown efficacy and acceptable tolerability in preclinical and clinical studies in patients with COPD.[14,15] A second-generation PDE4 inhibitor roflumilast has been shown to provide effective inhibition of chemotaxis, leucocyte activation, and cytokine production in vitro and in animal models of COPD,[15] and reduce the number of neutrophils and eosinophils in the sputum of patients with COPD.[16] In two large, randomised clinical studies undertaken in patients with COPD that was moderate to severe[17] or severe to very severe,[18] roflumilast consistently improved lung function. By contrast, the positive effect of roflumilast on exacerbations in moderate-to-severe disease[17] was not noted in patients with severe disease, though subgroup analysis did show a reduction in exacerbation rate in patients with very severe COPD.[18] In two randomised trials in symptomatic patients with severe COPD and a history of exacerbations, Calverley and colleagues[19] confirmed after 1 year the positive effects of roflumilast on both lung function and exacerbations independent of the patient's smoking status or use of concomitant medication such as inhaled longacting β_2 agonists.

To find out whether roflumilast provides benefit to patients who are regularly treated with longacting inhaled bronchodilators, we investigated its effects in patients with COPD who were regularly treated with salmeterol or tiotropium.

Methods

Setting

The salmeterol plus roflumilast (M2-127) trial was done in 135 centres in ten countries, whereas the tiotropium plus roflumilast (M2-128) trial was done in 85 centres in seven countries.

Patients

We recruited patients with moderate-to-severe COPD, which was defined spirometrically,[1–3] from an outpatient setting to investigate the effect of roflumilast concomitantly with salmeterol or tiotropium. The main inclusion criteria were age older than 40 years, current or former smokers (≥1 year of smoking cessation) with a smoking history of at least ten pack-years, postbronchodilator forced expiratory volume in 1 s (FEV_1) of 40–70% of predicted value,[20] a postbronchodilator FEV_1 to forced vital capacity (FVC) ratio of less than or equal to 0·70, partial reversibility to albuterol (400 µg; increase in baseline FEV_1 of ≤12% or 200 mL), and stable disease. By contrast with the salmeterol plus roflumilast trial, patients recruited to the tiotropium plus roflumilast trial were more symptomatic because they had to have chronic cough and sputum production, and frequent use of as-needed shortacting β_2 agonists (at least 28 puffs per week) during the run-in period while they were being treated with tiotropium for at least 3 months before enrolment. Inclusion and exclusion criteria are provided in the webappendix (p 10).

Both studies were approved by local ethical review committees and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Interventions

In an initial, 4-week run-in, patients in both studies were given placebo tablets once a day in the morning. They recorded their use of shortacting bronchodilators, and cough and sputum production on daily diary cards. In this initial study phase, patients, but not investigators, were unaware of the treatment they were assigned to. Patients who took at least 80% of prescribed placebo tablets without evidence of a moderate or severe exacerbation of COPD during the run-in period were randomly assigned to roflumilast 500 µg once a day in the morning or placebo for the subsequent 24 weeks.

Randomisation and masking

The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients to treatment. In the double-blind treatment phase, all individuals involved in the studies were unaware of treatment assignment. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling—tablets were identical in appearance. The sponsor and clinical research associate were notified if there was a clinical reason for an individual's treatment to be unmasked by the investigator with the interactive voice recognition system.

Besides salmeterol or tiotropium, no inhaled corticosteroids, shortacting anticholinergic drugs, other longacting bronchodilator drugs, theophylline, or other respiratory drugs were allowed after study enrolment.

After randomisation, patients were assessed every 4 weeks up to week 12, and every 6 weeks thereafter until week 24. At each visit, spirometric measurements were recorded before and 30 min after administration of bronchodilator (inhaled albuterol 400 µg). Additionally, we recorded any new exacerbations or adverse events, the patient's bodyweight, adherence to taking tablets, completeness of the daily diary records, use of shortacting β_2 agonists, and investigator-administered transition dyspnoea index (TDI)[21] and Shortness of Breath Questionnaire (SOBQ),[22] and dispensed study medication. Exacerbations were defined as mild if the patient needed an increase in rescue medication of at least three puffs per day on at least 2 consecutive days during the double-blind treatment period; moderate if the patient needed oral corticosteroids (not antibiotics); and severe if the patient needed treatment in hospital or died.

Study endpoints

The primary endpoint in both studies was change in mean prebronchodilator FEV_1 from baseline to each postrandomisation visit. Secondary endpoints in both trials included postbronchodilator FEV_1 and FVC, TDI score, SOBQ, rate of COPD exacerbations, and use of rescue medications (webappendix p 6).

At each visit, safety assessments included inquiries about the occurrence of adverse events. Bodyweight was measured with the same scales at each visit, height was measured with a stadiometer, and body-mass index (BMI) was calculated. At baseline and 24 weeks after randomisation, blood samples were taken for routine haematology and biochemistry tests and measurements of C-reactive protein (a possible marker of systemic inflammation in COPD), and an electrocardiogram (ECG) was done.

Statistical analysis

All reported data analyses were prespecified, and data are presented as mean and SD, unless otherwise indicated. Data for efficacy were evaluated with an intention-to-treat analysis in patients given at least one dose of study medication. Both studies were powered for the primary endpoint—ie, change in prebronchodilator FEV_1 from baseline, which was analysed by repeated-measures analysis of covariance.

The assumptions made for the primary endpoint on the basis of data gathered in a previous study[17] were compound symmetry structure with equal variance (common SD of 240 mL) for all five time points and both treatments, equal correlation of 0·6 between all pairs of time points for each patient, and normally distributed changes from baseline. The estimate of the treatment effect (50 mL) was based on clinical considerations and was in agreement with previous studies of inhaled glucocorticosteroids added to longacting β_2 agonists.[4,8] The sample size was calculated for the repeated-measures analysis of covariance model according to Chow and colleagues.[23] On the basis of assumptions outlined above and the use of a one-sided significance level of 2·5%, the power was 97% with a sample size of 469 patients per treatment group in the salmeterol plus roflumilast trial, and the power was 91% with a sample size of 350 patients per treatment group in the tiotropium plus roflumilast trial. The salmeterol plus roflumilast trial was originally powered for a traditional analysis of covariance model and not for a repeated-measures analysis of covariance model. After completion of recruitment, but before unmasking the studies, the statistical analysis model was changed to the more powerful repeated-measures analysis of covariance model, accounting for the larger number of patients recruited and the higher statistical power in the salmeterol plus roflumilast trial than in the tiotropium plus roflumilast trial. A conservative approach was taken for the main analysis of the repeated measurements of expiratory lung function variables,

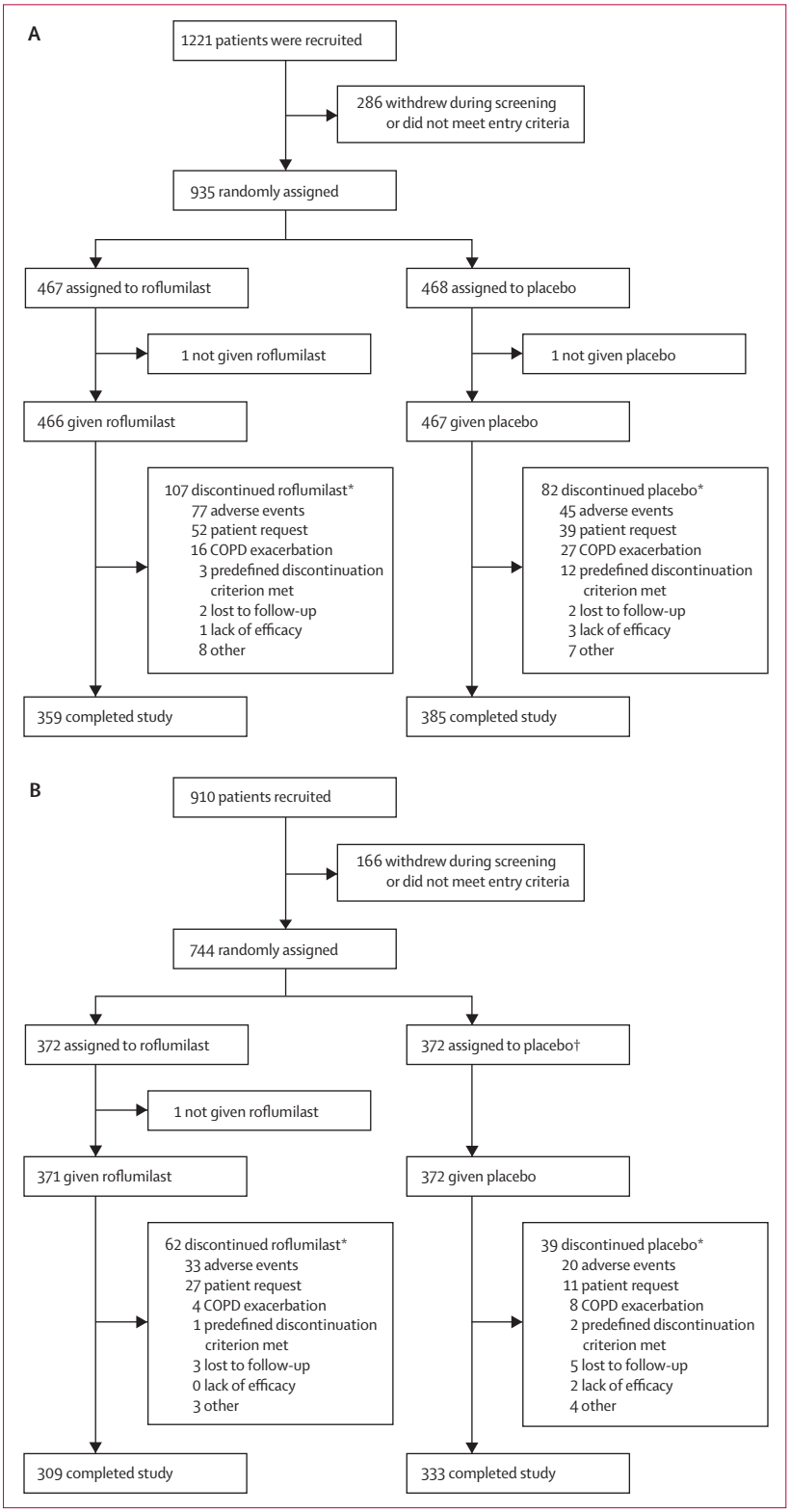


Figure 1: **Trial profiles of M2-127 (A) and M2-128 (B)**
COPD=chronic obstructive pulmonary disease. *Patients might have given more than one reason for discontinuation. †Three patients assigned to placebo were actually given roflumilast; 374 patients in the roflumilast group and 369 in the placebo group were included in the safety analysis in study M2-128.

	M2-127		M2-128	
	Salmeterol+roflumilast (n=466)	Salmeterol+placebo (n=467)	Tiotropium+roflumilast (n=371)	Tiotropium+placebo (n=372)
Age (years)*	65 (9)	65 (9)	64 (9)	64 (9)
Men	319 (68%)	299 (64%)	262 (71%)	267 (72%)
Cigarette pack-year*†	43 (22)	43 (22)	43 (22)	42 (22)
Smoking status*				
Current smoker	184 (39%)	184 (39%)	147 (40%)	146 (39%)
Former smoker	282 (61%)	283 (61%)	224 (60%)	226 (61%)
Chronic cough and sputum*	367 (79%)	362 (78%)	371 (100%)‡	372 (100%)‡
Prebronchodilator FEV_1 (L)§	1·43 (0·4)	1·41 (0·4)	1·47 (0·5)	1·49 (0·5)
Postbronchodilator FEV_1 (L)§	1·51 (0·4)	1·49 (0·4)	1·55 (0·5)	1·56 (0·5)
Prebronchodilator FEV_1 (% of predicted)§	51·9 (9·6)	52·4 (9·8)	53·3 (11·7)	53·4 (11·6)
Postbronchodilator FEV_1 (% of predicted)§	54·7 (9·1)	55·3 (9·2)	56·0 (11·6)	56·2 (11·6)
Postbronchodilator FEV_1/FVC (%)§	49·8 (9·4)	50·0 (9·7)	52·7 (10·3)	51·6 (9·9)
Use of as-needed relievers¶ (median, range)	1·4 (0–17·1)	1·7 (0–28·7)	4·7 (0–20·0)	4·6 (1·0–36·3)
COPD severity by FEV_1*||**				
Moderate	303 (65%)	324 (69%)	235 (63%)	240 (65%)
Severe	162 (35%)	141 (30%)	125 (34%)	119 (32%)

Data are mean (SD) or number (%), unless otherwise indicated. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease.*Measurements were taken at the beginning of the run-in period. †1 pack-year=20 cigarettes per day for 1 year. ‡Assumed from study inclusion criteria. §Measurements were taken at baseline. ¶Puffs per day in salmeterol plus roflumilast trial; puffs per week in tiotropium plus roflumilast trial. ||Based on the criteria of the Global initiative for chronic Obstructive Lung Disease. **Percentages do not add up to 100% because patients with mild or very severe COPD are not shown.

Table 1: **Baseline characteristics of the intention-to-treat populations assessed in the salmeterol plus roflumilast (M2-127) and tiotropium plus roflumilast (M2-128) trials**

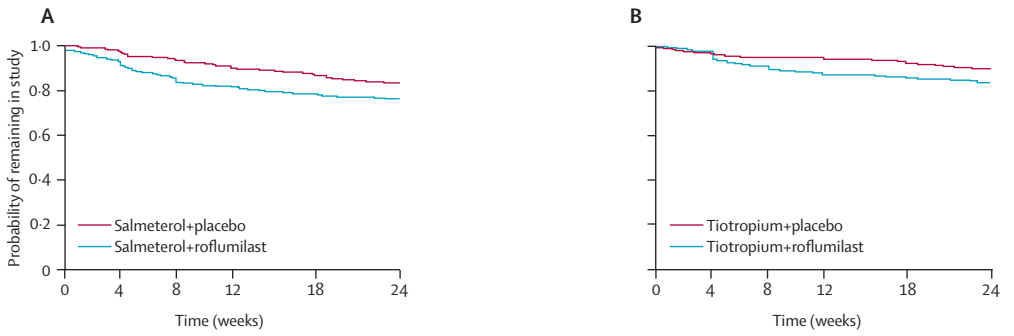


Figure 2: **Probability of treatment discontinuation in salmeterol plus roflumilast (M2-127) trial (A) and tiotropium plus roflumilast (M2-128) trial (B)**
*Patients still at risk at the beginning of the respective week; some patients in both studies had completed the study before week 24; two patients who were still in study M2-127 at week 24 were not considered, by the investigators, as having completed the study.

patient diary variables, SOBQ, and TDI scores, and no missing values were replaced in these two trials.

In both studies, the repeated-measures analysis of covariance model included the factors and covariates of treatment, value at baseline, age, sex, smoking status, country, time, and treatment-by-time interaction. Several statistical analyses were preplanned and done with the intent to assess the robustness of results with respect to the effect of differential dropouts and missing data. Adverse events were analysed with descriptive statistics and 95% CIs for the differences between treatment groups. The natural log-transformed C-reactive protein concentration (mean change from baseline to study end) was used for statistical analysis.

The studies are registered with ClinicalTrials.gov, number NCT00313209 for M2-127, and NCT00424268 for M2-128.

Role of the funding source

All authors (investigators [LMF, PMAC, JLI-A, FJM, and KFR] and employees of the sponsor [DSB and MB]) had full access to the data, and were responsible for the

decision to publish the report. The sponsor did not place any restrictions on authors about the statements made in the final report.

Results

The studies started in April, 2006 (first patient enrolled), and ended in January, 2008 (last assessment completed). In the salmeterol plus roflumilast trial, 933 patients were randomly assigned and treated; 744 patients completed the study (figure 1A). In the tiotropium plus roflumilast trial, 743 patients were randomly assigned and treated, and 642 completed the study (figure 1B). Table 1 shows the demographic and baseline characteristics of the two intention-to-treat study populations.

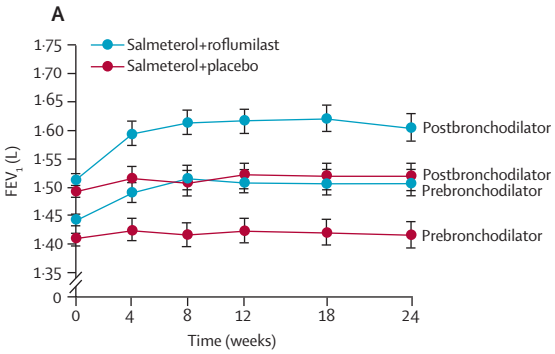
The study populations in the two trials did not differ. Most participants were elderly individuals, men, former smokers (more than 60%) with considerable previous tobacco consumption, and had moderate-to-severe airflow limitation (table 1). As expected, the use of shortacting β_2 agonists at baseline was higher in the tiotropium plus roflumilast trial than in the salmeterol plus roflumilast trial. Adherence to treatment was similar in all groups: the mean compliance was between 94% and 97%.

In both trials, the probability of treatment discontinuation was greater in patients treated with roflumilast (figure 2A and 2B). The prebronchodilator FEV_1 increased significantly in patients in the roflumilast groups in both studies (figure 3A and 3B; table 2). Similar improvements were noted in postbronchodilator FEV_1 and in prebronchodilator and postbronchodilator FVC (table 2). The prebronchodilator changes in FEV_1 were similar in patients with different characteristics (eg, disease severity, sex, rescue use of shortacting bronchodilators, and current smoking status; webappendix p 27). The sensitivity analyses confirmed the robustness of the results for FEV_1 with respect to the effect of differential dropouts and missing data (data not shown).

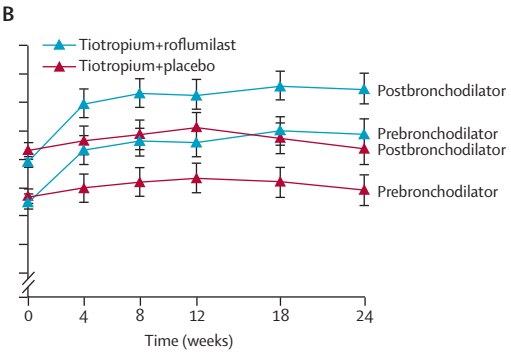
Roflumilast had a variable effect on symptomatic outcomes such as respiratory symptoms, use of rescue medications, and exacerbations in both trials (table 2). In general, the beneficial effect of roflumilast on some patient-reported outcomes (eg, TDI, SOBQ, use of rescue medication) was more pronounced in the tiotropium plus roflumilast trial than in the salmeterol plus roflumilast trial (table 2).

In the salmeterol plus roflumilast trial, 294 (63%) patients assigned to salmeterol plus roflumilast reported 671 adverse events and 276 (59%) assigned to salmeterol plus placebo reported 598 adverse events. In the tiotropium plus roflumilast trial, 172 (46%) patients in the tiotropium plus roflumilast group reported 373 adverse events and 150 (41%) in the tiotropium plus placebo group reported 287 adverse events. Most roflumilast-associated events affected the gastrointestinal and respiratory tracts.

The most frequently reported adverse event in both studies was COPD related (table 3). The number of patients with adverse events that were judged by the investigator to be related to treatment was 83 (18%) with salmeterol and roflumilast, 14 (3%) with salmeterol and placebo, 45 (12%) with tiotropium and roflumilast, and 6 (2%) with tiotropium and placebo. Diarrhoea, nausea, and weight loss were the most common treatment-related adverse events, with no major difference between



Number at risk*						
Prebronchodilator						
Salmeterol+roflumilast	466	455	410	389	374	359
Salmeterol+placebo	467	463	437	419	403	384
Postbronchodilator						
Salmeterol+roflumilast	466	450	410	387	372	359
Salmeterol+placebo	467	459	435	418	401	383



Number at risk*						
Prebronchodilator						
Tiotropium+roflumilast	371	364	343	325	318	310
Tiotropium+placebo	372	363	352	350	346	333
Postbronchodilator						
Tiotropium+roflumilast	371	363	341	323	316	310
Tiotropium+placebo	370	361	352	349	345	333

Figure 3: **Mean prebronchodilator and postbronchodilator forced expiratory volumes in 1 s (FEV_1) in salmeterol plus roflumilast (M2-127) trial (A) and tiotropium plus roflumilast (M2-128) trial (B)**
Error bars are SE. *Number of patients with data available; the number of patients reported here differs from the number at risk in figure 2 because some patients did not have their lung function measured at the end of the study, whereas others who did not complete the study had their function measured at week 24. Number of patients at risk for the baseline value (week 0) was not equal to the number in the intention-to-treat population (table 1) because some patients did not have a baseline value according to the definition from the statistical analysis plan.

	M2-127			M2-128		
	Salmeterol+ roflumilast	Salmeterol+ placebo	Salmeterol+roflumilast *vs* salmeterol+placebo	Tiotropium+ roflumilast	Tiotropium+ placebo	Tiotropium+roflumilast *vs* tiotropium+placebo
Lung function*						
Change in prebronchodilator FEV_1 (mL)	39 (9); n=456	−10 (9); n=463	Difference 49 (27 to 71); p<0·0001	65 (12); n=365	−16 (12); n=364	Difference 80 (51 to 110); p<0·0001
Change in postbronchodilator FEV_1 (mL)	68 (9); n=452	8 (9); n=460	Difference 60 (38 to 82); p<0·0001	74 (12); n=364	−7 (11); n=363	Difference 81 (51 to 110); p<0·0001
Change in prebronchodilator FVC (mL)	32 (15); n=456	−14 (14); n=463	Difference 47 (10 to 84); p=0·0128	54 (20); n=365	−41 (19); n=364	Difference 95 (47 to 143); p=0·0001
Change in postbronchodilator FVC (mL)	67 (15); n=452	10 (15); n=460	Difference 58 (20 to 95); p=0·0028	27 (23); n=364	−74 (22); n=363	Difference 101 (45 to 156); p=0·0004
Exacerbations†						
Mild, moderate, or severe (mean rate, per patient per year [95% CI])	1·9 (1·5 to 2·5); n=131	2·4 (1·9 to 3·1); n=159	RR 0·79 (0·58 to 1·08); p=0·1408	1·8 (1·3 to 2·5); n=82	2·2 (1·7 to 2·9); n=112	RR 0·84 (0·57 to 1·23); p=0·3573
Median time to first exacerbation (moderate or severe; days [IQR])	83·0 (41·0 to 102·0)	71·0 (33·0 to 109·0)	HR 0·6 (0·4 to 0·9); p=0·0067	80·5 (49·0 to 124·0)	74·5 (35·0 to 123·0)	HR 0·8 (0·5 to 1·1); p=0·1959
Median time to first exacerbation (mild, moderate, or severe events; days [IQR])	53·0 (10·0 to 85·0)	47·0 (17·0 to 96·0)	HR 0·9 (0·7 to 1·1); p=0·2707	50·0 (15·0 to 98·0)	37·0 (13·0 to 88·0)	HR 0·7 (0·5 to 1·0); p=0·0264
Proportion of patients with an exacerbation (moderate or severe)	51 (11%)	83 (18%)	RiR 0·60 (0·43 to 0·82); p=0·0015	42 (11%)	58 (16%)	RiR 0·73 (0·51 to 1·05); p=0·0867
Proportion of patients with an exacerbation (mild, moderate, or severe)	131 (28%)	159 (34%)	RiR 0·82 (0·68 to 0·99); p=0·0419	82 (22%)	112 (30%)	RiR 0·75 (0·59 to 0·95); p=0·0169
Further prespecified secondary analyses						
TDI focal score*	1·2 (0·1); n=454	1·1 (0·1); n=460	Difference 0·1 (−0·2 to 0·4); p=0·4654	1·4 (0·1); n=364	0·9 (0·1); n=364	Difference 0·4 (0·1 to 0·7); p=0·0032
Change in SOBQ*	−0·6 (0·7); n=454	−1·1 (0·7); n=461	Difference 0·5 (−1·2 to 2·2); p=0·5457	−3·4 (0·7); n=359	−0·7 (0·7); n=359	Difference −2·6 (−4·5 to −0·8); p=0·0051
Change from baseline in rescue medication (puffs per day)*	−0·01 (0·08); n=437	0·08 (0·08); n=442	Difference −0·09 (−0·28 to 0·11); p=0·3689	−1·56 (0·11); n=364	−1·05 (0·11); n=365	Difference −0·51 (−0·80 to −0·23); p=0·0004

Data are mean (SE), difference (95% CI), or point estimate (95% CI), unless otherwise indicated. n=number of patients with data available (or, for exacerbations, number of patients with at least one exacerbation). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. RR=rate ratio. HR=hazard ratio. RiR=risk ratio. TDI=transition dyspnoea index. SOBQ=Shortness of Breath Questionnaire. *Least squares mean (SE). †Estimated exacerbation rates were based on a Poisson regression model, HRs were based on a Cox proportional hazards model, RiRs were based on a log binomial regression model. Models included the treatment, age, sex, smoking status, country pool, and baseline postbronchodilator FEV_1 (only for the Poisson regression model).

Table 2: **Effect of treatment on primary and secondary functional and clinical outcomes in salmeterol plus roflumilast (M2-127) and tiotropium plus roflumilast (M2-128) trials**

the two studies. Compared with placebo, roflumilast was associated with increased withdrawal from the study; this increase was significant in the salmeterol plus roflumilast trial (p=0·0019) but not in the tiotropium plus roflumilast trial (p=0·0864; figure 2; webappendix p 14).

In both trials, similar gradual reductions were noted in mean bodyweight in the roflumilast groups during the 24 weeks of treatment (salmeterol plus roflumilast trial −2·0 kg; tiotropium plus roflumilast trial −1·8 kg), whereas there was little change in the salmeterol or tiotropium plus placebo groups (salmeterol plus roflumilast trial +0·2 kg; tiotropium plus roflumilast trial +0·3 kg; webappendix p 28). Weight loss was similar in the two trials and was not significantly different between patients in different BMI categories (webappendix p 15); in the salmeterol plus roflumilast trial only, weight loss associated with roflumilast was greater in patients with gastrointestinal adverse events or headache, or both (webappendix p 17).

Physical examinations, routine laboratory tests, C-reactive protein concentrations,[24] and ECGs did not show any clinically significant changes after administration of roflumilast in patients concomitantly treated with salmeterol or tiotropium (webappendix p 19).

Discussion

In patients with moderate-to-severe COPD treated with salmeterol or tiotropium, roflumilast improves lung function and some clinically relevant symptomatic outcomes. These results confirm the conclusions drawn from the findings of previous randomised clinical trials in which roflumilast was efficacious in patients with severe COPD who were not regularly treated with longacting bronchodilators.[17–19] Additionally, our results show that roflumilast maintains its clinical efficacy in patients with moderate-to-severe COPD who are already treated with longacting bronchodilators. However, these beneficial effects are also associated with some adverse effects of roflumilast.

The improvement in prebronchodilator and postbronchodilator FEV_1 suggests that the beneficial effect of roflumilast on lung function is additive to that achieved with bronchodilators, an effect that is probably

	M2-127*			M2-128		
	Salmeterol+ roflumilast (n=466)	Salmeterol+ placebo (n=467)	Salmeterol+roflumilast *vs* salmeterol+placebo (difference, 95% CI)	Tiotropium+ roflumilast (n=374)†	Tiotropium+ placebo (n=369)†	Tiotropium+roflumilast *vs* tiotropium+placebo (difference, 95% CI)
COPD	74 (16%)	111 (24%)	−7·89% (−13·2 to −2·58)	58 (16%)	67 (18%)	−2·65% (−8·30 to 3·00)
Weight loss	40 (9%)	5 (1%)	7·51% (4·59 to 10·44)	21 (6%)	2 (<1%)	5·07% (2·35 to 7·79)
Diarrhoea	38 (8%)	16 (3%)	4·73% (1·53 to 7·93)	33 (9%)	2 (<1%)	8·28% (5·04 to 11·52)
Nasopharyngitis	33 (7%)	35 (7%)	−0·41% (−3·96 to 3·14)	21 (6%)	20 (5%)	0·19% (−3·36 to 3·75)
Nausea	25 (5%)	1 (<1%)	5·15% (2·85 to 7·45)	11 (3%)	4 (1%)	1·86% (−0·42 to 4·14)
Headache	14 (3%)	5 (1%)	1·93% (−0·09 to 3·96)	8 (2%)	0	2·14% (0·40 to 3·87)
Back pain	13 (3%)	9 (2%)	0·86% (−1·30 to 3·02)	7 (2%)	5 (1%)	0·52% (−1·56 to 2·60)
Bronchitis	11 (2%)	15 (3%)	−0·85% (−3·18 to 1·47)	6 (2%)	10 (3%)	−1·11% (−3·46 to 1·25)
Tremor	10 (2%)	2 (<1%)	1·72% (0·06 to 3·37)	0	2 (<1%)	−0·54% (−1·56 to 0·48)
Decreased appetite	10 (2%)	1 (<1%)	1·93% (0·34 to 3·53)	3 (<1%)	0	0·80% (−0·37 to 1·98)
Insomnia	10 (2%)	1 (<1%)	1·93% (0·34 to 3·53)	6 (2%)	1 (<1%)	1·33% (−0·32 to 2·98)
Upper respiratory tract infection	9 (2%)	19 (4%)	−2·14% (−4·54 to 0·26)	4 (1%)	2 (<1%)	0·53% (−1·03 to 2·08)
Influenza	9 (2%)	11 (2%)	−0·42% (−2·50 to 1·65)	3 (<1%)	0	0·80% (−0·37 to 1·98)
Dyspnoea	2 (<1%)	14 (3%)	−2·57% (−4·44 to −0·70)	3 (<1%)	5 (1%)	−0·55% (−2·31 to 1·20)

Data are number (%), unless otherwise indicated. Adverse events are reported independently from investigator causality assessment. Patients might have had more than one adverse event. COPD=chronic obstructive pulmonary disease. *Incidence of adverse events in descending order. †Three patients assigned to placebo were given roflumilast; 371 patients in tiotropium+roflumilast group and 372 in the tiotropium+placebo group were included in the efficacy analysis in study M2-128.

Table 3: **Adverse events occurring in at least 2% of patients in one of the treatment groups in the salmeterol plus roflumilast (M2-127) and tiotropium plus roflumilast (M2-128) trials**

not primarily due to smooth muscle relaxation but to other mechanisms.[14,15,25–28] Roflumilast has no direct effect on smooth muscle in most animal models,[15,25,26] and, like other highly selective PDE4 inhibitors,[29,30] has no appreciable acute bronchodilator effect in people.[31] Also, roflumilast specifically inhibits PDE4, which is mainly expressed in inflammatory cells,[14,15] and has no appreciable inhibitory effect on PDE3 at the doses administered. The improvement in lung function obtained with the same dose used in our studies is associated with a reduction in numbers of sputum neutrophils and eosinophils in patients with COPD.[16] With consideration of all of the above, we postulate that suppression of inflammation is likely to be the mechanism of the improvement in lung function induced by roflumilast in our studies. However, no effect of roflumilast was noted on concentrations of C-reactive protein or number of circulating leucocytes, another potential biomarker of systemic inflammation. Thus, additional studies are needed to investigate the mechanism of improvement in lung function provided by roflumilast in patients given longacting bronchodilators.

The additive effect of roflumilast on lung function is small but occurs in patients who are already being treated with effective, longacting bronchodilators and who have been screened for limited acute bronchodilator reversibility, but who are not taking inhaled corticosteroids. The improvement in lung function induced by roflumilast in patients with COPD concomitantly treated with salmeterol, noted in the present study, is similar to the improvement in lung function induced by inhaled corticosteroids in patients with COPD of similar severity and functional characteristics who were treated with salmeterol.[4,8] Whether roflumilast would maintain this additive effect in patients concomitantly treated with longacting bronchodilators and glucocorticosteroids remains to be established.

The inclusion criteria for the tiotropium plus roflumilast trial led to the recruitment of more symptomatic patients with a higher use of as-needed medications than in the salmeterol plus roflumilast trial. The results from a post-hoc analysis of a previous study[18] suggested that these characteristics might increase the chance of detecting an effect of roflumilast on patient-reported outcomes such as dyspnoea and use of as-needed medications, and thus might explain the better efficacy of roflumilast that we noted in some patient-reported outcomes in tiotropium-treated patients than in salmeterol-treated patients. However, the designs of our studies do not allow an indirect comparison of efficacy and safety between the salmeterol plus roflumilast and tiotropium plus roflumilast combinations. It should be noted that the current studies were powered to detect improvement in lung function, and the 6-month treatment duration of these trials was too short to allow reliable detection of an effect on some patient-reported outcomes, such as exacerbations. Additionally, the rate of exacerbations per year recorded during the study was low (table 2), probably because patients had COPD that was moderate to severe rather

than severe to very severe, and because they were already treated with longacting bronchodilators that have been previously shown to reduce exacerbations.[32] Nevertheless, roflumilast did reduce some of the measures of exacerbation, particularly in patients treated with tiotropium, a result that must be interpreted cautiously because of the study design. Further studies are needed to investigate whether roflumilast has an additive effect on exacerbations when combined with longacting bronchodilators or used with a combination of inhaled bronchodilators and glucocorticosteroids. Although we acknowledge these limitations and the variable effects on patient-reported outcomes, we suggest that the consistent efficacy of roflumilast in terms of lung function lends support to the potential benefits of this treatment for patients with COPD that is moderate to severe who are already being treated with longacting bronchodilators.

PDE4 inhibitors have a well described adverse event profile.[14,15] In the two trials reported here, the prevalence of drug-related adverse events, including weight loss, was similar to that reported in patients irregularly taking longacting bronchodilators in other 12-month studies.[19] Weight loss was greater in patients treated with roflumilast who had gastrointestinal adverse events or headache, or both, than in individuals who did not, suggesting that it might be causally related to these adverse events.

The use of an oral, once-daily anti-inflammatory agent instead of inhaled corticosteroids as concomitant therapy to longacting bronchodilators might have advantages and disadvantages. Important advantages associated with roflumilast might be increased compliance with oral once-daily administration, particularly in addition to once-daily tiotropium, which is not available in combination with steroids, and no demonstrable increased risk of pneumonia.[12] By contrast, the adverse events associated with roflumilast constitute a disadvantage that could force some patients to discontinue this drug. The risks and benefits of the addition of roflumilast should be compared with a combination of bronchodilators or inhaled corticosteroids, or both, in large, well designed studies.

The adverse effects of roflumilast resemble some of those of theophylline, a drug with a weak and non-specific inhibitory effect on various phosphodiesterases and other pharmacological effects (eg, adenosine receptor antagonism).[33] The pronounced differences in molecular structure and pharmacology between roflumilast and theophylline suggest that the adverse effects might result from different mechanisms of action.[33]

Roflumilast improves lung function in patients with moderate-to-severe COPD who are already being treated with longacting bronchodilators (β_2 agonists or anticholinergic drugs), although with expected class-specific adverse events. Roflumilast could become an important, concomitant treatment for these patients.

Contributors

All authors were members of the steering committee and developed the design and concept of the studies, approved the statistical plans, interpreted the data, and wrote the report. LMF and KFR wrote the first draft of the report. DSB and MB coordinated data gathering, and MB did the statistical analysis. All authors vouch for the veracity and completeness of the data and the data analysis.

Conflicts of interest

LMF has served as a consultant to AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, Pfizer, and Sigma-Tau; been paid lecture fees by AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, and Pfizer; and received grant support from AstraZeneca, Boehringer Ingelheim, Menarini, Schering-Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Nycomed, Union Chimique Belge, Pfizer, Sigma-Tau, Italian Ministry of Health, and Italian Ministry for University and Research. PMAC has served on advisory boards for AstraZeneca, GlaxoSmithKline, Nycomed, and Novartis; received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim; and spoken at meetings supported by AstraZeneca, GlaxoSmithKline, and Nycomed. JLI-A has received honoraria for consultancies from AstraZeneca, Pfizer, and Almirall; and for medical presentations from Nycomed, AstraZeneca, Almirall, GlaxoSmithKline, Pfizer, and Boehringer Ingelheim. FJM has been a member of advisory boards for GlaxoSmithKline, Schering-Plough, Novartis, Nycomed, Genzyme, Forest/Almirall, Talecris, and Roche; on the speaker's bureau for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca; a member of steering committees for studies supported by Gilead, Actelion, Johnson & Johnson, United BioSource, and the National Institutes of Health; and an investigator in trials supported by Boehringer Ingelheim and Actelion. KFR has served as a consultant, participated in advisory board meetings and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline; received research funding from AltanaPharma, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GlaxoSmithKline during 2006–09; and served as a consultant, participated in advisory board meetings and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline. DSB and MB are employees of Nycomed.

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