Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial

Klaus F Rabe, Eric D Bateman, Denis O’Donnell, Stephan Witte, Dirk Bredenbrocker, Thomas D Bethke

Summary

Background Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation associated with chronic inflammation. There are few treatment options for the disease. This study assessed the efficacy and safety of roflumilast, a phosphodiesterase-4 inhibitor, in patients with moderate to severe COPD.

Methods This phase III, multicentre, double-blind, randomised, placebo-controlled study was undertaken in an outpatient setting. 1411 patients with COPD were randomly assigned roflumilast 250 μg (n=576), roflumilast 500 μg (n=555), or placebo (n=280) given orally once daily for 24 weeks. Primary outcomes were postbronchodilator FEV₁, and health-related quality of life. Secondary outcomes included other lung function parameters and COPD exacerbations. Analyses were by intention to treat.

Findings 1157 (82%) patients completed the study; 32 (11%) withdrew from the placebo group, 100 (17%) from the roflumilast 250 μg group, and 124 (22%) from the roflumilast 500 μg group. Postbronchodilator FEV₁ at the end of treatment significantly improved with roflumilast 250 μg (by 74 mL [SD 18]) and roflumilast 500 μg (by 97 mL [18]) compared with placebo (p<0.0001). Improvement in health-related quality of life was greater with roflumilast 250 μg (–3·4 units [0·6]) and roflumilast 500 μg (–3·5 units [0·6]) than with placebo (–1·8 units [0·8]), although the difference between treatment groups were not significant. The mean numbers of exacerbations per patient were 1·13 (2·37), 1·03 (2·33), and 0·75 (1·89) with placebo, roflumilast 250 μg, and roflumilast 500 μg, respectively. Most adverse events were mild to moderate in intensity and resolved during the study.

Interpretation Roflumilast is a promising candidate for anti-inflammatory COPD treatment because it improved lung function and reduced exacerbations compared with placebo. Long-term studies are needed to fully assess the effect on health-related quality of life.

Introduction Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality in adults worldwide. A meta-analysis showed that the overall prevalence is between 4% and 10%. COPD is the fifth leading cause of death worldwide, and its increasing prevalence and limited treatment options suggest that it will become the third leading cause of death by the year 2020. As defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scientific committee, COPD is a disease characterised by airflow restriction that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The disease is usually related to cigarette smoking, but other causative factors, such as exposure to air pollution, exist.

Airflow obstruction in COPD arises as a result of chronic inflammation and structural changes in small airways and lung parenchyma. The inflammation is characterised by increased numbers of neutrophils, macrophages, and cytotoxic T cells, as well as by the presence of multiple inflammatory mediators such as cytokines, chemokines, and growth factors. The recognition that chronic inflammation is a key pathophysiological mechanism in COPD provided the rationale for the use of inhaled corticosteroids as a treatment option. However, corticosteroids have little effect on inflammatory processes associated with COPD, and even high doses of these drugs do not reduce the progression of the disease. Bronchodilators, such as β₂-agonists or anticholinergics, provide some symptomatic relief, but there is a definite unmet medical need to develop agents that specifically target chronic inflammation associated with COPD.

The search for an anti-inflammatory treatment for COPD is now focusing on inhibitors of phosphodiesterase 4, the major hydrolase of cyclic adenosine monophosphate (cAMP) in inflammatory cells. Inhibition of phosphodiesterase 4 increases intracellular cAMP concentrations. The rise in concentrations of cAMP can lead to activation of protein kinase A, resulting in phosphorylation and inactivation of target transcription factors, which ultimately result in reduction of cellular inflammatory activity. Targeted inhibition of phosphodiesterase 4 is thought to elicit anti-inflammatory effects in patients with asthma or COPD. Phosphodiesterase-4 inhibitors could potentially provide better anti-inflammatory activity than corticosteroids because corticosteroids do not...
suppress neutrophil activation or production of cytokines and chemokines.\textsuperscript{8}

Roflumilast is a targeted inhibitor of phosphodiesterase 4 and is given once daily via the oral route. The anti-inflammatory potential of roflumilast has been proven in vitro and in animal models and includes inhibition of the synthesis of leukotriene B\textsubscript{4} and reactive oxygen species in neutrophils as well as inhibition of TNF-\alpha release by mononuclear cells.\textsuperscript{11,12} Roflumilast also inhibits T-cell proliferation, cytokine production, and cell infiltration of the lungs.\textsuperscript{11,12} Preliminary clinical data suggest that roflumilast could improve lung function in patients with COPD while being well tolerated.\textsuperscript{11} We undertook a large clinical phase III, randomised, multicentre, multinational, double-blind, placebo-controlled study to assess whether once-daily roflumilast (250 \textmu g or 500 \textmu g) given orally for 24 weeks has a clinically meaningful effect on lung function and health-related quality of life when compared with placebo in patients with moderate to severe COPD.

**Methods**

**Patients**

All patients were recruited from an outpatient setting. Inclusion criteria for patients were: history of COPD >12 months, as defined by GOLD guidelines;\textsuperscript{14} age 40 years or older; current smoker or ex-smoker (>1 year of smoking cessation) with a smoking history of >10 pack-years; postbronchodilator FEV\textsubscript{1} (forced expiratory volume in 1 s) of 30–80% of predicted value; postbronchodilator FEV\textsubscript{1}/FVC (forced vital capacity) ratio <70%; reversibility of FEV\textsubscript{1} of <12% and/or <200 mL after 400 \textmu g inhaled salbutamol; and stable clinical disease status with no change in COPD treatment during the 4 weeks before the run-in period (described later).

Patients were excluded from study enrolment if they were diagnosed with asthma or other relevant lung diseases (eg, lung cancer, bronchiectasis); if they were on long-term oxygen treatment; or if they had a recent exacerbation that required a course of systemic corticosteroids, emergency room treatment, or hospital admission (within 4 weeks before the run-in period). Patients were also excluded from study enrolment if they had a respiratory tract infection within 4 weeks before the run-in period, known alpha-1-antitrypsin deficiency, or regularly used more than eight puffs of rescue medication per day. Study approval was obtained from governing ethics committees for each study centre, and all patients provided written informed consent.

**Procedures**

This parallel-group study was undertaken from April, 2002, to June, 2003 in 159 centres in Australia, Austria, Belgium, Canada, France, Germany, Hungary, Ireland, South Africa, Spain, and the UK. After a 4-week, single-blind run-in period, during which patients received placebo and salbutamol as rescue medication, patients were randomly assigned a study treatment if they had a respiratory tract infection within 4 weeks before the run-in period, known alpha-1-antitrypsin deficiency, or regularly used more than eight puffs of rescue medication per day. Study approval was obtained from governing ethics committees for each study centre, and all patients provided written informed consent.

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**Figure 1: Trial profile**

Two patients randomised to roflumilast 250 mg did not take any study medication and were therefore excluded from the intention-to-treat analysis. QoL = health-related quality of life. *Remaining patients had no valid final FEV\textsubscript{1} measurement. †Two questionnaires were required for QoL assessment. Patients with an incomplete or missing questionnaire at either baseline or at final follow up were excluded from the final analysis.
postbronchodilator FEV\(_1\) between 30% and 80% of predicted and if their medication compliance during this period was >80% and <125% (as assessed by tablet count). Treatment was assigned by the investigators with sequential study numbers according to a block randomisation list in ratios of 2: 2: 1 (roflumilast 500 μg: roflumilast 250 μg: placebo). The randomisation sequence was generated by ALTANA Pharma AG in a blinded manner; no person involved in data analysis had knowledge of the randomisation sequence. Treatment was given once daily in the morning for 24 weeks. Placebo tablets and packaging were identical to that of roflumilast. Medication boxes were labelled with the study protocol number, randomisation number, and visit code; coding prevented the investigator and people at the study centre from knowing which medication was given.

Concomitant respiratory medications allowed throughout the study were salbutamol, as rescue medication, and short-acting anticholinergics for treatment of exacerbations during the active treatment phase. All other respiratory medications (eg, inhaled corticosteroids) were withdrawn 4 weeks before randomisation.

The primary outcome variables were postbronchodilator FEV\(_1\) and St. George’s respiratory questionnaire (SGRQ) total score and were calculated as the change from baseline to the endpoint (last observation carried forward). Secondary outcome measures were change from baseline in postbronchodilator FEV\(_1\), postbronchodilator FVC, postbronchodilator forced expiratory volume in the first 6 s (FEV\(_6\)), postbronchodilator forced expiratory flow between 25% and 75% of the vital capacity (FEF\(_{25–75}\)), and number of COPD exacerbations.

We recorded adverse events as part of the safety assessment using standard International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP).

Pulmonary function tests were done at the first run-in visit, at week 2 of run-in, at randomisation (ie, baseline), and at weeks 4, 8, 12, 16, 20, and 24 of the treatment period according to American Thoracic Society recommendations. A centralised spirometer (MasterScope CT, VIASYS Healthcare GmbH, Hoechberg, Germany) was used at each study site, and measurements were undertaken both before and 30–45 min after inhalation of a 400 μg dose of salbutamol. Measurements were taken at the same time of day within a 4-h window, based on the time of the measurement at baseline visit. Patients were asked to withhold salbutamol for at least 4 h and short-acting anticholinergics for at least 6 h before each measurement. For FEV\(_1\) and FVC, the highest value from three technically acceptable attempts was chosen for analysis. The ratio of FEV\(_1\) to FVC was calculated from the highest value for FEV\(_1\) and FVC. FEV\(_1\) and FEF\(_{25–75}\) values were taken from the best-test curve, defined as the value with the largest sum of FEV\(_1\) and FVC. We calculated percent-of-predicted values according to the recommendations for spirometry of the European Respiratory Society. Throughout the study, an expert at VIASYS assessed the quality of blinded spirometry data, and only technically acceptable flow-volume loops were investigated.

We assessed health-related quality of life at week 2 of run-in, at baseline, and at weeks 12 and 24 of the treatment period using the validated SGRQ questionnaire. The SGRQ is a disease-specific instrument composed of 76 items that are weighted to produce three subcomponent scores: symptoms, activity, and impacts. The total score is calculated from mathematical addition of these subcomponents and provides a global assessment of a patient’s respiratory health. The total score ranges from 0 to 100, with a score of 100 indicating maximum disability. A difference of 4–8 units versus a control (eg, placebo) is regarded as a clinically relevant improvement in health-related quality of life.

Exacerbations were classified according to severity grades. Our definition of mild exacerbations was modified from that of Szafranski and colleagues as an increase in bronchodilator use on 2 or more consecutive days.

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**Table 1: Demographics and baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo n=280</th>
<th>Roflumilast 250 μg n=575</th>
<th>Roflumilast 500 μg n=555</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63 (40–82)</td>
<td>65 (40–86)</td>
<td>64 (42–87)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>207 (74%)</td>
<td>419 (73%)</td>
<td>410 (74%)</td>
</tr>
<tr>
<td>Female</td>
<td>73 (26%)</td>
<td>157 (27%)</td>
<td>145 (26%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>279 (100%)</td>
<td>573 (100%)</td>
<td>550 (99%)</td>
</tr>
<tr>
<td>Height, cm (SD)</td>
<td>169 (8.4)</td>
<td>169 (8.3)</td>
<td>168 (8.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>76 (16.5)</td>
<td>75 (15.7)</td>
<td>75 (16.2)</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>26 (5.0)</td>
<td>26 (4.7)</td>
<td>26 (5.0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>125 (45%)</td>
<td>267 (46%)</td>
<td>254 (46%)</td>
</tr>
<tr>
<td>Ex-smokers n (%)</td>
<td>155 (53%)</td>
<td>309 (54%)</td>
<td>301 (54%)</td>
</tr>
<tr>
<td>Pack-years</td>
<td>43 (22.0)</td>
<td>43 (24.5)</td>
<td>41 (20.6)</td>
</tr>
<tr>
<td>Prebronchodilator FEV(_1), L</td>
<td>1.45 (0.48)</td>
<td>1.40 (0.47)</td>
<td>1.41 (0.49)</td>
</tr>
<tr>
<td>Postbronchodilator FEV(_1), L</td>
<td>1.57 (0.48)</td>
<td>1.52 (0.47)</td>
<td>1.50 (0.48)</td>
</tr>
<tr>
<td>Prebronchodilator FEV(_1), % predicted</td>
<td>51 (13.8)</td>
<td>50 (13.4)</td>
<td>51 (13.7)</td>
</tr>
<tr>
<td>Postbronchodilator FEV(_1), % predicted</td>
<td>55 (15.3)</td>
<td>54 (13.0)</td>
<td>54 (13.3)</td>
</tr>
<tr>
<td>Reversibility change in FEV(_1), %</td>
<td>9.6 (13.1)</td>
<td>9.6 (12.0)</td>
<td>9.1 (13.1)</td>
</tr>
<tr>
<td>Postbronchodilator FVC, L</td>
<td>3.17 (0.86)</td>
<td>3.08 (0.83)</td>
<td>3.08 (0.85)</td>
</tr>
<tr>
<td>FEV(_1)/FVC, %</td>
<td>50 (11)</td>
<td>50 (12)</td>
<td>50 (12)</td>
</tr>
<tr>
<td>Prebronchodilator FEV(_1), L</td>
<td>2.86 (0.75)</td>
<td>2.77 (0.71)</td>
<td>2.76 (0.70)</td>
</tr>
<tr>
<td>Postbronchodilator FEV(_1), L</td>
<td>0.62 (0.30)</td>
<td>0.60 (0.33)</td>
<td>0.59 (0.30)</td>
</tr>
<tr>
<td>Pretudy medication for COPD, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhaled short-acting β, agonists</td>
<td>142 (51.1%)</td>
<td>301 (52%)</td>
<td>267 (48%)</td>
</tr>
<tr>
<td>Inhaled short-acting anticholinergics</td>
<td>94 (34%)</td>
<td>211 (37%)</td>
<td>208 (38%)</td>
</tr>
<tr>
<td>Xanthines</td>
<td>72 (26%)</td>
<td>157 (27%)</td>
<td>143 (26%)</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>47 (17%)</td>
<td>130 (23%)</td>
<td>124 (22%)</td>
</tr>
<tr>
<td>Inhaled long-acting β, agonists</td>
<td>37 (13%)</td>
<td>76 (13%)</td>
<td>92 (17%)</td>
</tr>
<tr>
<td>Concomitant short-acting anticholinergics, n (%)</td>
<td>100 (36%)</td>
<td>259 (40%)</td>
<td>228 (41%)</td>
</tr>
</tbody>
</table>

Data are expressed as mean and SD, unless otherwise stated. FEV\(_1\)=forced expiratory volume in 1 s; FVC=forced vital capacity; FEV\(_6\)=forced expiratory flow between 25% and 75% of the vital capacity; COPD=chronic obstructive pulmonary disease.
who had at least one post-baseline efficacy assessment available. The primary comparison in the study was
to detect a significant difference between roflumilast
500 μg versus placebo for FEV₁ and SGRQ. If roflumilast 500 μg was shown to be better than
placebo, roflumilast 250 μg was compared with placebo and roflumilast 500 μg was compared with the 250 μg
group. At a one-sided level of 0·025, a sample size of
400 patients in each roflumilast dose group and
200 patients in the placebo group was needed to
establish 90% power, based on a two-sample \( t \) test, to
provide a difference between group means of about
70 mL, assuming a SD of 250 mL in all treatment
groups. We undertook all statistical analyses using SAS
Windows NT version 8.2 (SAS Institute, Cary, NC,
USA). The within-treatment and between-treatment
differences for the primary and secondary lung function
variables as well as SGRQ were assessed with an
analysis of covariance (ANCOVA) with the factors and
covariates of treatment, sex, (pooled) centre, value at
randomisation, smoking status at study entry, and age
included in the model. In case of missing values the last
observation carried forward imputation technique was
applied. Based on the differences between the values
from endpoint (ie, to the last value analysis), we did
randomisation tests using pair-wise contrasts. Adjusted
means and 95% CI were given for treatment differences.
For within-group and between-group comparisons, the
two-sided tests were done at a level of
\( \alpha=0·05 \) (corresponding to 0·025 one-sided). The number of
COPD exacerbations was analysed with the Jonckheere-
Terpstra test for trend, and the number of patients with
COPD exacerbations was analysed with the Cochran-
Armitage test for trend. Descriptive statistics were used
for adverse events.

**Role of the funding source**

This study was supported by ALTANA Pharma AG,
Konstanz, Germany. The sponsor managed the data and
undertook all final analyses. Authors had full access to all
data and were involved in data interpretation and
preparation of the manuscript in collaboration with the
sponsor. K F Rabe had final responsibility for the
decision to submit for publication.

**Results**

Figure 1 shows the trial profile. Two patients randomly
assigned roflumilast 250 μg did not take any study
medication and were therefore excluded from the
intention-to-treat population. 1157 patients completed
the trial. Table 1 shows the baseline characteristics for the
three treatment groups.

**Table 1. Baseline characteristics for the three treatment groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (SD)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roflumilast 500 μg</td>
<td>40 (10)</td>
<td>35 (25-50)</td>
</tr>
<tr>
<td>Roflumilast 250 μg</td>
<td>40 (10)</td>
<td>35 (25-50)</td>
</tr>
<tr>
<td>Placebo</td>
<td>40 (10)</td>
<td>35 (25-50)</td>
</tr>
</tbody>
</table>

**Figure 2: Change from baseline in postbronchodilator (A) and prebronchodilator (B) FEV₁ over time**

Data are least squares means ± standard errors. FEV₁=forced expiratory volume in 1 s. *p<0.05 versus baseline.
Improvement with roflumilast was noted within the first 4 weeks; deterioration with placebo began at 8 weeks. Roflumilast 250 μg and 500 μg significantly increased FEV₁ from baseline at all visits during the 24-week treatment period (p<0.05 at each visit); this improvement was also significantly greater when compared with placebo (p<0.03) for both roflumilast groups. At 24 weeks, the improvement in FEV₁ from baseline compared with placebo (p=0.03) for both roflumilast groups was also significantly greater when compared with placebo (p<0.03) for both roflumilast groups. At 24 weeks, the improvement in FEV₁ from baseline compared with placebo was 74 mL (SD 18) for roflumilast 250 μg and 97 mL (18) for roflumilast 500 μg (table 2). There were no differences between current smokers and ex-smokers in the roflumilast treatment groups (data not shown). A post-hoc subanalysis showed that postbronchodilator FEV₁ in patients with moderate COPD (FEV₁ >50% of predicted) significantly increased in both roflumilast groups compared with placebo, with differences of 87 mL (23) with 250 μg (p=0.0001) and 103 mL (23) with 500 μg (p<0.0001). In patients with severe COPD (FEV₁ <50% of predicted), postbronchodilator FEV₁ by 52 mL (27) compared with placebo (figure 2B). At 24 weeks, roflumilast significantly improved postbronchodilator FEV₁ from baseline compared with placebo, with a difference of 64 mL (18) with 250 μg and 88 mL (18) with 500 μg (table 2). Improvements in FEV₁ were also noted with both doses of roflumilast, whereas a decline was recorded with placebo (figure 2B). At 24 weeks, roflumilast significantly improved prebronchodilator FEV₁, versus placebo, with a difference of 64 mL (18) with 250 μg and 88 mL (19) with 500 μg (table 2). Improvements in FEV₁, were maintained when patients who withdrew from the study were excluded from the analysis (data not shown). Additionally, a dose–dependent association was recorded for both prebronchodilator and postbronchodilator FEV₁, although the difference between the roflumilast doses was not significant.

For the other secondary lung function parameters a similar pattern of results was recorded; postbronchodilator FVC, FEV₁, and FEF₁,·₁<sub>50</sub> improved in the roflumilast treatment groups versus the placebo group at the last visit (p<0.05). Postbronchodilator FVC significantly increased in both roflumilast groups compared with placebo, with differences of 71 mL (31) with 250 μg and 114 mL (31) with 500 μg. Significant improvements from baseline with roflumilast 250 μg and 500 μg compared with placebo were also noted for postbronchodilator FEV₁, and FEF₁,·₁<sub>50</sub> (table 2).

Health-related quality of life assessed by SGRQ, a

![Figure 3: Change from baseline in St. George’s respiratory questionnaire total score (A) and component scores (B) at week 24](image)

Data are least squares means ± standard errors. *p<0.05, **p<0.01, ***p<0.001 versus baseline; ns=not significant.
The percentage of patients with diarrhoea during each time period.

**Figure 4:** Onset of diarrhoea

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=280</th>
<th>Roflumilast 250 μg</th>
<th>Roflumilast 500 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of exacerbations</td>
<td>317</td>
<td>593</td>
<td>418</td>
</tr>
<tr>
<td>Total number of patients with exacerbations</td>
<td>97 (35%)</td>
<td>207 (76%)</td>
<td>157 (78%)</td>
</tr>
<tr>
<td>Mean number of exacerbations per patient (SD)</td>
<td>Overall 1.13 (2.37)</td>
<td>1.03 (2.33)</td>
<td>0.75 (1.89)</td>
</tr>
<tr>
<td></td>
<td>Mild 0.83 (2.25)</td>
<td>0.71 (2.13)</td>
<td>0.48 (1.74)</td>
</tr>
<tr>
<td></td>
<td>Moderate 0.28 (0.64)</td>
<td>0.30 (0.66)</td>
<td>0.25 (0.62)</td>
</tr>
<tr>
<td></td>
<td>Severe 0.02 (0.12)</td>
<td>0.02 (0.14)</td>
<td>0.03 (0.19)</td>
</tr>
<tr>
<td>Number of patients with exacerbations</td>
<td>Mild 56 (20%)</td>
<td>115 (20%)</td>
<td>75 (14%)</td>
</tr>
<tr>
<td></td>
<td>Moderate 58 (21%)</td>
<td>123 (21%)</td>
<td>99 (18%)</td>
</tr>
<tr>
<td></td>
<td>Severe 5 (2%)</td>
<td>12 (2%)</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Number of patients who received concomitant oral corticosteroids</td>
<td>51 (18%)</td>
<td>111 (19%)</td>
<td>97 (18%)</td>
</tr>
</tbody>
</table>

**Table 3:** Chronic obstructive pulmonary disease exacerbations

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=280</th>
<th>Roflumilast 250 μg</th>
<th>Roflumilast 500 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients experiencing ≥1 adverse event</td>
<td>174 (62%)</td>
<td>382 (66%)</td>
<td>370 (67%)</td>
</tr>
<tr>
<td>COPD exacerbation*</td>
<td>65 (23%)</td>
<td>135 (23%)</td>
<td>113 (20%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>39 (7%)</td>
<td>47 (7%)</td>
<td>46 (8%)</td>
</tr>
<tr>
<td>Diarrhoea NOS</td>
<td>6 (2%)</td>
<td>28 (5%)</td>
<td>50 (9%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14 (5%)</td>
<td>27 (5%)</td>
<td>23 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1%)</td>
<td>16 (3%)</td>
<td>27 (5%)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). *Only moderate and severe exacerbations were reported as adverse events. COPD=chronic obstructive pulmonary disease; NOS=not otherwise specified.

**Table 4:** Adverse events occurring in at least 5% of patients in any treatment group

coprimary variable, showed improvements (ie, decreased score) with both placebo and roflumilast treatment (figure 3A). The changes from baseline in SGRQ total score were −3·4 units (SD 0·6; p=0·0001) for roflumilast 250 μg, −3·5 units (0·6; p<0·0001) for roflumilast 500 μg, and −1·8 units (0·8; p=0·002) for placebo. The improvement in SGRQ total score, compared with placebo, was −1·7 units (0·8) with roflumilast 500 μg and −1·6 units (0·9) with roflumilast 250 μg; however, these differences were not statistically significant (p=0·053 and p=0·077, respectively). Scores in the subcomponents of activity, impacts, and symptoms also improved with roflumilast treatment compared with baseline (all p values <0·01), with the symptoms scores showing the largest improvement of −3·6 units (1·1) with placebo, −6·0 units (0·9) with roflumilast 250 μg, and −4·6 units (0·9) with roflumilast 500 μg (figure 3B). Subcomponent scores did not differ between the roflumilast groups compared with placebo.

The percentage of patients who had any exacerbation was lower in the roflumilast 500 μg group than in the 250 μg or placebo groups during the 24 weeks of treatment (p value for trend test=0·0114, one-sided; table 3). Roflumilast treatment also reduced the overall mean number of exacerbations per patient when compared with placebo, which were 1·13, 1·03, and 0·75 in the placebo group, roflumilast 250 μg group, and roflumilast 500 μg group, respectively (p=0·0009, one-sided). Comparison of these mean exacerbation rates showed that the rate of total exacerbations was 34% lower in the roflumilast 500 μg group than in the placebo group. This difference in the overall mean exacerbation rate was primarily due to the difference in mild exacerbations (p=0·004, one-sided), with a 42% difference in the mean number of mild exacerbations per patient observed with roflumilast 500 μg compared with placebo. The mean number of moderate and severe exacerbations per patient was low and closely similar between groups.

The most common adverse events reported by the investigator during the study were moderate or severe exacerbations of COPD and nasopharyngitis (table 4). The frequency of headache was low and was much the same across all treatment groups, with 4% of patients in each treatment group reporting headache. Diarrhoea, which occurred more often in the roflumilast treatment groups, arose most commonly within the first 4 weeks of treatment and was generally mild to moderate in intensity (figure 4). Adverse events regarded as likely to be related to study medication by the investigator were reported in 12 (4%) patients treated with placebo, 46 (8%) patients treated with roflumilast 250 μg, and 92 (17%) patients treated with roflumilast 500 μg. Diarrhoea was the most common adverse event deemed likely to be related to study medication, occurring in none, 13 (2%), and 34 (6%) patients treated with placebo, roflumilast 250 μg, and roflumilast 500 μg, respectively. The next most common adverse event was nausea, reported in none, six (1%), and 18 (3%) patients treated with placebo, roflumilast 250 μg, and roflumilast 500 μg, respectively. Headaches were thought to be at least likely related to study medication in one (<1%), four (1%), and ten (2%) patients, respectively. Vomiting was rare, occurring in only one patient treated with roflumilast 250 μg and one patient.
treated with roflumilast 500 μg. There were no apparent clinically meaningful changes in vital signs, electrocardiogram measurements, or clinical laboratory parameters during treatment with roflumilast.

Most adverse events resolved during the course of the study (>90%). Discontinuations due to adverse events were higher in the roflumilast 500 μg group (15% of patients) than in the roflumilast 250 μg group (10%) or in the placebo group (8%). COPD exacerbation was the most common adverse event leading to withdrawal, occurring in eight (3%), 25 (4%), and 18 (3%) patients in the placebo, roflumilast 250 μg, and roflumilast 500 μg treatment groups, respectively. Serious adverse events were reported by 21 (8%), 41 (7%), and 53 (10%) patients. The most frequent serious adverse event was COPD exacerbation in each treatment group. The percentage of patients who withdrew because of serious adverse events was much the same between treatment groups (4%, 5%, and 6% of patients in the placebo, roflumilast 250 μg, and roflumilast 500 μg treatment groups, respectively). There was no pattern or trend relating the incidence or cause of serious adverse events to roflumilast.

Discussion

Chronic inflammation is generally regarded as a central mechanism in the pathogenesis of COPD.1 The significant morbidity and mortality associated with the disease, combined with the lack of effective treatments, warrant the development of drugs that target the underlying chronic inflammation rather than solely the clinical symptoms of COPD. Inhibition of phosphodiesterase 4 has been shown to inhibit the inflammatory processes associated with COPD, and thus represents a promising new treatment approach.

Roflumilast, at doses of 250 μg or 500 μg, given once daily, was effective in patients with moderate to severe COPD. The phosphodiesterase-4 inhibitor significantly improved postbronchodilator FEV1 throughout the 24-week treatment period, while a decline was recorded in the placebo. When assessed at each study visit, roflumilast 500 μg consistently provided an improvement versus placebo. At the end of the treatment period, the 500 μg dose improved FEV1 by 97 mL when compared with placebo. These data are encouraging given that in another study,19 treatment with inhaled fluticasone propionate 500 μg twice daily in a similar patient population (prebronchodilator FEV1 of about 45% of predicted versus about 51% in our study) resulted in a 50 mL improvement in postbronchodilator FEV1 over 6 months compared with placebo. Since FEV1 is thought to predict prognosis and overall mortality in patients with COPD,20 the improvements in lung function recorded in our study are encouraging.

Consistent with the results seen for postbronchodilator FEV1, prebronchodilator FEV1, and postbronchodilator FVC improved with roflumilast but deteriorated with placebo. Roflumilast has been shown to have no direct bronchodilating properties in animal models.7 In patients with COPD, the phosphodiesterase-4 inhibitor cilomilast has been shown to have no acute bronchodilatory activity.21 Additionally, in a double-blind, randomised, three-period study (n=15), FEV1 measured periodically for up to 6 h did not improve with roflumilast 500 μg or 1000 μg compared with placebo.22 This information, together with the consistent improvements in postbronchodilator lung function parameters in patients with COPD, suggests that the treatment effect of roflumilast is the result of the anti-inflammatory activity of the drug21,22,23-25 and not due to bronchodilation provided through airway smooth-muscle relaxation. However, we acknowledge that this study was not designed to specifically assess the anti-inflammatory activity of roflumilast.

We reduced observer bias for FEV1 by use of independent and blinded review of all spirometric measurements. Accidental bias is expected to be low because of the size, global enrolment, and inclusion criteria of the study. Furthermore, consistent with EMEA recommendations,24 we stratified randomisation according to smoking status. Therapeutic effectiveness in COPD should be based not only on lung function parameters but also on the overall assessment of the patients’ well-being.2 Besides improving lung function, roflumilast treatment improved health-related quality of life, as assessed by the SGRQ total score. Roflumilast 250 μg and 500 μg improved SGRQ total score from baseline by 3·4 units and 3·5 units, respectively, similar to the improvements in health-related quality of life reported in studies of the efficacy of inhaled corticosteroids in patients with COPD. Calverley and co-workers17 reported improvements of less than 3 units at 6 months in patients treated with inhaled corticosteroids. Additionally, improvements of 3–4 units were reported in studies of the efficacy of combination treatment (eg, inhaled corticosteroids in combination with a long-acting β agonist) in patients with COPD.15,19,27 Previously reported COPD studies of 6 months’ duration showed short-term placebo-induced improvements in quality of life, but these did not reach clinical significance.22,23 Over longer periods of follow-up, progressive deterioration in health status in patients treated with placebo is seen.28 Thus, long-term studies (1 year or more) are needed to show the full benefit of roflumilast compared with placebo in improving health-related quality of life.

The mechanisms leading to COPD exacerbations are unclear, but a further amplification of the inflammatory process could be implicated.7 This theory implies that the ability of roflumilast to target the underlying pulmonary inflammation could translate into a reduction of COPD exacerbations. Indeed, patients treated with roflumilast 500 μg had a 34% reduction in the mean number of total exacerbations...
per patient, which was primarily driven by a reduction in mild exacerbations. The inclusion criteria were designed to target a study population with clinically stable COPD (GOLD stages II and III). Patients, therefore, might have a low incidence of moderate and severe exacerbations and a drug effect could primarily influence the occurrence of mild exacerbations. Not unexpectedly, the reduction in exacerbations was primarily due to a decrease in the number of mild exacerbations per patient by 42% versus placebo. Importantly, the occurrence of moderate and severe exacerbations did not increase in the presence of decreasing mild exacerbations. Another major feature of most COPD exacerbations is an increase in dyspnoea, which is often a consequence of worsening of hyperinflation, characteristic of advanced COPD.11 Roflumilast-induced improvements in FEV\textsubscript{1}, as well as in FVC and FEV\textsubscript{1}, might reduce the degree of hyperinflation and, consequently, reduce dyspnoea and exacerbations.7,12 Further studies that specifically investigate the effect of roflumilast on small airway calibre are warranted.

Historically, archetypical phosphodiesterase-4 inhibitors, such as rolipram, led to dose-limiting gastrointestinal adverse events that hindered clinical development. Moreover, non-targeted, broad-spectrum phosphodiesterase inhibitors, such as theophylline, are associated with cardiac arrhythmias. No cardiac rhythm disorders related to study medication were reported in this study. Roflumilast might provide an acceptable therapeutic ratio with a favourable side-effect profile. Roflumilast was well tolerated in this study. Gastrointestinal side-effects occurred early during treatment and were generally mild to moderate and self-limited. The incidence of gastrointestinal side-effects was of a frequency that was similar to or lower than the numbers reported for cilomilast.13 Furthermore, only 1% of patients treated with roflumilast 250 μg and 4% of patients treated with roflumilast 500 μg discontinued treatment because of diarrhoea or nausea (data not shown). Additionally, the percentage of patients remaining in the study who experienced diarrhoea decreased over time. Overall, the lack of cardiac effects and the low incidence of drug-related adverse events help to differentiate roflumilast from other phosphodiesterase-4 inhibitors.

In conclusion, roflumilast was effective in improving lung function and reducing exacerbations in a population of patients with moderate to severe COPD. The phosphodiesterase-4 inhibitor class shows promise as a new therapeutic strategy for patients with COPD.
Articles

institution has received payment. He has served on advisory boards for the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyowa Hakko, Hoffmann-La Roche, Aventis, and MSD. He has received honoraria for lectures delivered at meetings organised by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyowa Hakko, and MSD. D O’Donnell did not report any conflict of interest. S Witte, D Bredenbröker, and T Bethke are employees of ALTANA Pharma and own a limited amount of ALTANA stock.

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References
6 Konstanz, Germany.
32 Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV(06) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 2000; 162: 917–19.