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Original article

Comparison of roflumilast, an oral anti-inflammatory, with beclomethasone dipropionate in the treatment of persistent asthma

Background: Roflumilast is an oral, once-daily phosphodiesterase 4 inhibitor with anti-inflammatory activity in development for the treatment of asthma. Roflumilast was compared with inhaled beclomethasone dipropionate (BDP) in patients with asthma.
Methods: In a double blind, double-dummy, randomized, noninferiority study, 499 patients (forced expiratory volume in 1 s [FEV_1] = 50–85% predicted) received roflumilast 500 μg once daily or BDP 200 μg twice daily (400 μg/day) for 12 weeks. Lung function and adverse events were monitored.
Results: Roflumilast and BDP significantly improved FEV_1 by 12% (270 ± 30 ml) and 14% (320 ± 30 ml), respectively ($P < 0.0001$ *vs* baseline). Roflumilast and BDP also significantly improved forced vital capacity (FVC) ($P < 0.0001$ *vs* baseline). There were no significant differences between roflumilast and BDP with regard to improvement in FEV_1 and FVC. Roflumilast and BDP showed small improvements in median asthma symptom scores (–0.82 and −1.00, respectively) and reduced rescue medication use (−1.00 and −1.15 median puffs/day, respectively; $P < 0.0001$ *vs* baseline). These small differences between roflumilast and BDP were not considered clinically relevant. Both agents were well tolerated.
Conclusions: Once daily, oral roflumilast 500 μg was comparable with inhaled twice-daily BDP (400 μg/day) in improving pulmonary function and asthma symptoms, and reducing rescue medication use in patients with asthma.

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Key words: asthma; beclomethasone; ICS; PDE4 inhibitor; roflumilast.

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Asthma is a chronic inflammatory airway disease with significant morbidity and mortality that is increasing in prevalence worldwide (1). Inhaled corticosteroids (ICS) are considered the standard of care in the treatment of asthma. The ICS beclomethasone dipropionate (BDP) is an established treatment in asthma (2, 3). However, low patient compliance is a constant problem with ICS therapy (4). In addition, ICS therapies, such as beclomethasone, are associated with systemic and local side effects (5, 6). To help address these issues, oral anti-inflammatory therapies are being investigated in the treatment of asthma.

Phosphodiesterases are a family of enzymes involved in the degradation of cyclic adenosine monophosphate (cAMP), which is a natural modulator of inflammation and a potential target for new anti-inflammatory therapeutics (7–10). Phosphodiesterase 4 (PDE4) is expressed in inflammatory cells (e.g. T lymphocytes, eosinophils, and macrophages) involved in the pathophysiology of asthma and other obstructive airway diseases (11). Inhibition of PDE4 activity results in maintenance of appropriate cAMP levels, resulting in down-regulation of the inflammatory processes in cells involved in the pathophysiology of asthma (11–13).

Roflumilast is an oral PDE4 inhibitor. *In vitro* and *in vivo* studies have demonstrated that roflumilast inhibits tumor necrosis factor alpha synthesis in monocytes, monocyte-derived dendritic cells, and macrophages, and inhibits CD4+ T-cell proliferation and cytokine production (e.g. interleukin-2 and interleukin-4), leukotriene B4 synthesis, and reactive oxygen species formation from leukocytes (14, 15). The high systemic availability of orally administered roflumilast and the prolonged half-life of its active metabolite, roflumilast *N*-oxide, favor a once-daily dosing regimen (16).

The objective of this study was to compare the efficacy and safety of once-daily oral roflumilast 500 μg with those of BDP 200 μg twice daily (400 μg/day) in patients with asthma.

Patients and methods

Patients

All patients provided written informed consent, and this study complied with the ethical standards of regional and national legal regulations. Inclusion criteria: patients age 12–70 years with a history of asthma as defined by the National Institutes of Health, (17) stable asthma with no change in treatment, no exacerbations, and no lower airway infections within 4 weeks before baseline. Randomization criteria included a forced expiratory volume in 1 s (FEV_1) between 50 and 85% of predicted when salbutamol was withheld ≥4 h before measurement, average use of ≥1 puff/day salbutamol during the 7 days before randomization, and an average asthma symptom score ≥1 over a 24-hour period during the 7 days before randomization. In addition, patients were required to have either reversible airway obstruction (≥15% increase in FEV_1 15–30 min after inhalation of 200–400 μg salbutamol) or a diurnal peak expiratory flow (PEF) variability of ≥15% during ≥3 days of the last 7 days preceding randomization.

Exclusion criteria included poorly controlled asthma (i.e. occurrence within 4 weeks prior to start of study of at least one of the following: use of oral glucocorticoids, hospitalization because of deterioration of asthma control or exacerbation, treatment of asthma in an emergency department), COPD, current heavy smoking (>10 cigarettes/day and or >5 pack years) or previous history of smoking (>5 pack years), and regular use of >8 puffs/day of rescue medication prior to start of study.

Study design

The study was a randomized, double blind, double-dummy, parallel-group, multicenter, noninferiority study. After a single-blind placebo baseline period of 1–3 weeks, eligible patients were randomized 1 : 1 to receive either (A) an oral roflumilast 500 μg tablet once daily in the morning and two puffs of placebo administered via MDI in the morning and in the evening for 12 weeks; or (B) an oral placebo tablet once daily in the morning and BDP 400 μg daily administered via MDI as two 100 μg puffs delivered in the morning and in the evening for 12 weeks. Salbutamol was permitted as rescue medication, and oral, nasal, and ophthalmic antihistamines were allowed as needed during the study. All other respiratory medications—including ICS, anticholinergics, theophylline, and inhaled long-acting beta $(\beta)_2$-agonists—were withdrawn at the start of the study.

Patient assessments

Pulmonary function was measured during the baseline period and at weeks 3, 6, 9, and 12 of treatment. Asthma symptom scores and rescue medication use were recorded daily in patient diaries. The primary efficacy variable was change from baseline in FEV_1 at the end of treatment. Secondary variables included change from baseline in forced vital capacity (FVC) and spirometric PEF, morning and evening PEF from patient diary cards, asthma symptom scores, and concomitant use of salbutamol as rescue medication. Measurements of FEV_1 and FVC were taken using a spirometer (MicroLab 3300 customized Version 1.3; Micro Medical Ltd., Rochester, Kent, UK) according to American Thoracic Society recommendations (18). The highest value from three technically satisfactory maneuvers was recorded. Reversibility of FEV_1 was assessed by measuring immediately before and 15 min after inhalation of 200 μg salbutamol from an MDI. In the case of an insufficient response (i.e. <15% of prebronchodilator value), a second dose of 200 μg salbutamol from an MDI was administered and a second measurement obtained after 15 min. Morning and evening PEF values were recorded by patients on diary cards. Three measurements were taken using a PEF meter (Mini Wright^{TM} Peak Flow Meter; Clement Clarke International Ltd., Essex, UK) and the highest value was used for further evaluation.

Asthma symptoms were assessed by evaluating nighttime and daytime asthma symptom scores. A 5-point scale was used for nighttime scores, with a score of 0 indicating no symptoms and a score of 4 indicating a bad night with the patient awake most of the night because of asthma. A 5-point scale also was used for daytime asthma scores, with a score of 0 indicating no symptoms and a score of 4 indicating that asthma was very bad and the patient was unable to carry out daily activities as usual.

Adverse events (AEs) observed by the investigator and/or reported by the patient were recorded. Adverse events occurring during the trial that were fatal, life threatening, resulted in persistent or significant disability or incapacity, required hospitalization or prolongation of hospitalization, or corresponded to a congenital anomaly were classified as serious AEs.

Statistical methods

All efficacy and safety assessments were performed in the intention-to-treat (ITT) population, unless otherwise specified. The per-protocol population was defined as patients who had no protocol violations, including violation of entry criteria. Percent-of-predicted values were calculated according to the formula from the European Respiratory Society (19). A last observation carried forward method was used for last visit analysis. To analyze the change from baseline in FEV_1, FVC, and PEF from patient diaries, an analysis of covariance was performed with the factors/covariates treatment, sex, center, value at baseline, and age. Data for lung function measurements are provided as least squares mean ± SE of the mean. Nonparametric test procedures were applied for symptom scores and daily use of rescue medication. Pratt's modification of the Wilcoxon signed-rank test was applied for within-group comparisons, and the Mann–Whitney *U*-test was applied for between-treatment comparisons. Descriptive statistics were used for AEs. Roflumilast was considered noninferior if the lower limit of the 95% confidence interval (CI) of the difference between roflumilast and BDP did not exceed the prespecified noninferiority acceptance limits (for FEV_1 and FVC, −200 ml; for PEF, −25 l/min). A sample size of 200 randomized patients per group was calculated to provide 93% power and a two-sided significance level of 0.05.

Results

Patients

A total of 633 patients were screened from 51 centers in four countries, of which 499 patients (ITT population) were randomized to receive roflumilast ($n = 253$) or BDP ($n = 246$) treatment (Fig. 1). There were no significant differences in demographics or baseline characteristics between the two treatment groups (Table 1). Approximately 50% of each group was male and the baseline mean FEV_1 percent predicted was similar between groups (72–73%). Use of respiratory medications before study inclusion was similar between the roflumilast and BDP groups. Inhaled short-acting β_2-agonists (74 and 77%, respectively) and inhaled glucocorticosteroids (56 and 57%, respectively) were the most frequently used

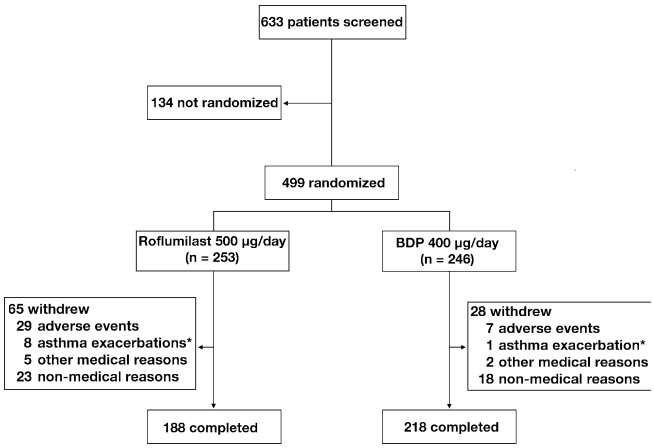

Figure 1. Patient disposition. BDP, beclomethasone dipropionate. *An asthma exacerbation requiring treatment with oral glucocorticosteroids accompanied by a decrease in FEV_1 ≥20% from baseline, a decrease in morning PEF ≥30% from baseline during ≥3 of the 7 days directly preceding a study visit, or use of salbutamol > 8 puffs/day during ≥3 of the 7 days directly preceding a study visit.

Table 1. Demographic and baseline characteristics for the ITT population

Characteristics*	500 µg/day roflumilast ($n = 253$)	400 µg/day BDP ($n = 246$)
Sex (male : female) (%)	46 : 54	48 : 52
Median age, years (range)	42 (12–70)	44 (12–70)
Nonsmokers : Ex-smokers (%)	72 : 28	68 : 32
Mean FEV_1, l ± SD	2.30 ± 0.66	2.28 ± 0.61
Mean FEV_1, predicted (%)	73 ± 10	72 ± 10
Reversibility: mean change in FEV_1 ± SD (%)	23 ± 10	24 ± 10
Asthma severity (%)		
Mild (FEV_1≥80% predicted)	26	27
Moderate (FEV_1 >60 and <80% predicted)	59	59
Severe (FEV_1 ≤ 60% predicted)	13	14
Morning PEF ± SD (diary), mean and l/min	347 ± 110	354 ± 95
Median asthma symptom score	2.29†	2.00‡
Median rescue medication use, puffs/day	2.29	2.57§
Patients previously treated with ICS (%)	60	62
Mean µg dose, BDP equivalents (range)	411 (100–500)	425 (100–500)

*Lung function variables, symptom scores, and rescue medication use measured before randomization.
†$n = 251$.
‡$n = 245$.
§$n = 243$. BDP, Beclomethasone dipropionate; Ex-smoker, Nonsmoker with ≤ 5 pack years; FEV_1, Forced expiratory volume in 1 s; ITT, Intention to treat; ICS, Inhaled corticosteroids; PEF, Peak expiratory flow; SD, Standard deviation.

medications. The per-protocol population ($n = 421$) included 207 patients in roflumilast group and 214 patients in BDP group. A total of 406 patients completed the study: 188 patients treated with roflumilast and 218 patients treated with BDP (Fig. 1). The most common reason for treatment discontinuation overall was non-medical reasons, reported for 23 patients treated with roflumilast and 18 patients treated with BDP.

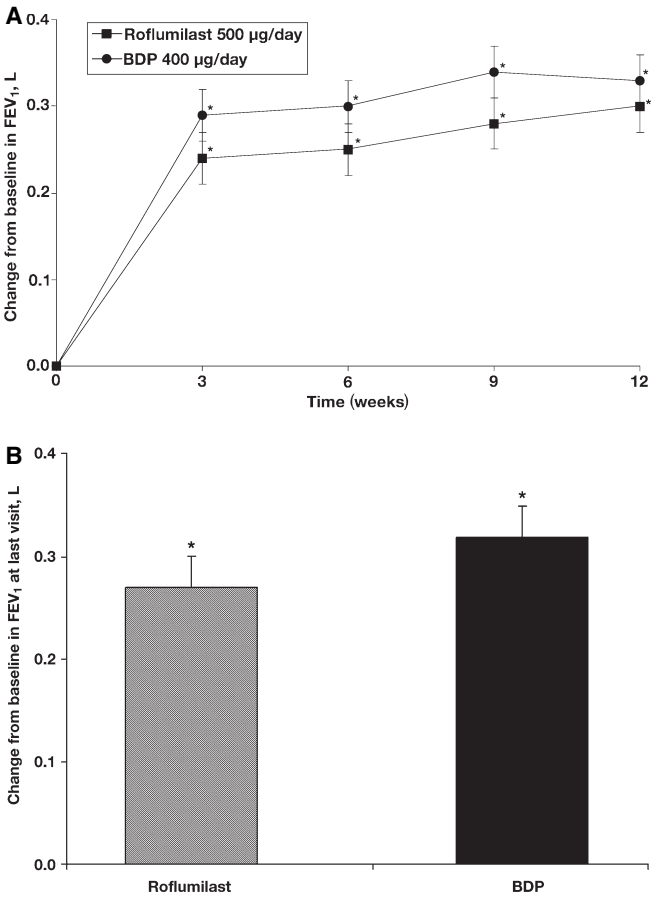

Figure 2. Oral roflumilast 500 µg once daily was comparable with inhaled beclomethasone dipropionate (BDP) 400 µg/day (200 µg twice daily) in improving FEV_1 from baseline both (A) over time and (B) at the last visit. FEV_1, Forced expiratory volume in 1 s. Data is least squares mean ± SE of the mean. *$P < 0.0001$ *vs* baseline at last visit for roflumilast or BDP. There was no significant difference between roflumilast and BDP for any time point ($P > 0.05$).

Efficacy

Pulmonary function. Roflumilast and BDP improved FEV_1 during this 12-week study (Fig. 2A). A significant improvement was noted at the first time point measured (week 3) and was maintained throughout the study for both treatment groups. Roflumilast improved FEV_1 from baseline by 270 ± 30 ml, and BDP improved FEV_1 by 320 ± 30 ml, indicating a 12 and 14% improvement in FEV_1, respectively ($P < 0.0001$ *vs* baseline for both; Fig. 2B), with no significant difference between the two groups (95% CI, −120–30; $P = 0.21$ for difference between groups). Results from a per protocol analysis confirmed this improvement in FEV_1: roflumilast ($n = 153$) improved FEV_1 from baseline by 300 ± 40 ml, and BDP ($n = 173$) improved FEV_1 by 370 ± 30 ml, indicating a 13 and 16% improvement in FEV_1, respectively ($P < 0.0001$ *vs* baseline for both),

with no significant difference between the two groups (95% CI, −160–30; $P = 0.16$ for difference between groups). The use of ICS prior to the study did not significantly affect patients' response to roflumilast or BDP. In patients who used ICS, roflumilast improved FEV_1 from baseline by 230 ml, and BDP improved FEV_1 by 310 ml, with no significant difference between the two groups ($P = 0.07$ for difference between groups). Likewise, in patients who did not use ICS, roflumilast and BDP improved FEV_1 from baseline by 340 and 320 ml, respectively ($P = 0.75$ for difference between groups).

Roflumilast and BDP significantly improved FVC from baseline by 270 ± 30 and 330 ± 30 ml, respectively ($P < 0.0001$ *vs* baseline for both), with no significant difference between the two groups (95% CI, −130–30; $P = 0.19$ for difference between groups). Similar results were observed in the per-protocol population.

Roflumilast and BDP consistently improved morning and evening PEF, with further improvements from baseline observed during each week of treatment (data not shown). Roflumilast improved morning and evening PEF from baseline by 17 ± 3.5 and 13 ± 3.5 l/min, respectively ($P \leq 0.0002$ *vs* baseline). Treatment with BDP improved morning and evening PEF from baseline by 27 ± 3.5 and 21 ± 3.5 l/min, respectively ($P < 0.0001$ *vs* baseline). The 10 l/min difference in morning PEF (95% CI, −19.45 to −0.64; $P = 0.04$ for difference between groups) and 8 l/min difference in evening PEF (95% CI, −17.36–1.44; $P = 0.10$ for difference between groups) were not considered clinically meaningful. Similar improvements were observed in the per-protocol analysis, with a 5 l/min difference in morning PEF (95% CI, −16.25–5.48; $P = 0.33$ for difference between groups) and a 5 l/min difference in evening PEF (95% CI, –16.11–5.41; $P = 0.33$ for difference between groups) between the two treatments.

Asthma symptom scores and use of rescue medication. In addition to improvements in lung function parameters, improvements in asthma symptom scores (Fig. 3A) and a reduction in rescue medication use (Fig. 3B) were observed in both treatment groups. Roflumilast improved median asthma symptom scores from baseline by −0.82 ($P < 0.0001$) compared with −1.00 for BDP ($P < 0.0001$), with no significant difference between the two treatments ($P = 0.09$ for difference between groups). Roflumilast also reduced median rescue medication use by −1.00 puffs/day ($P < 0.0001$) compared with −1.15 puffs/day for BDP ($P < 0.0001$), with a statistically greater decrease (0.15 puffs/day) in rescue medication use with BDP ($P = 0.0171$). The 0.15-puffs/day differences in rescue medication use between the two groups were not considered clinically meaningful. Furthermore, based on the per-protocol analysis, there was no statistically significant difference between roflumilast and BDP (−1.29 puffs/day and −1.29 puffs/day, respectively; $P = 0.34$ for difference between groups).

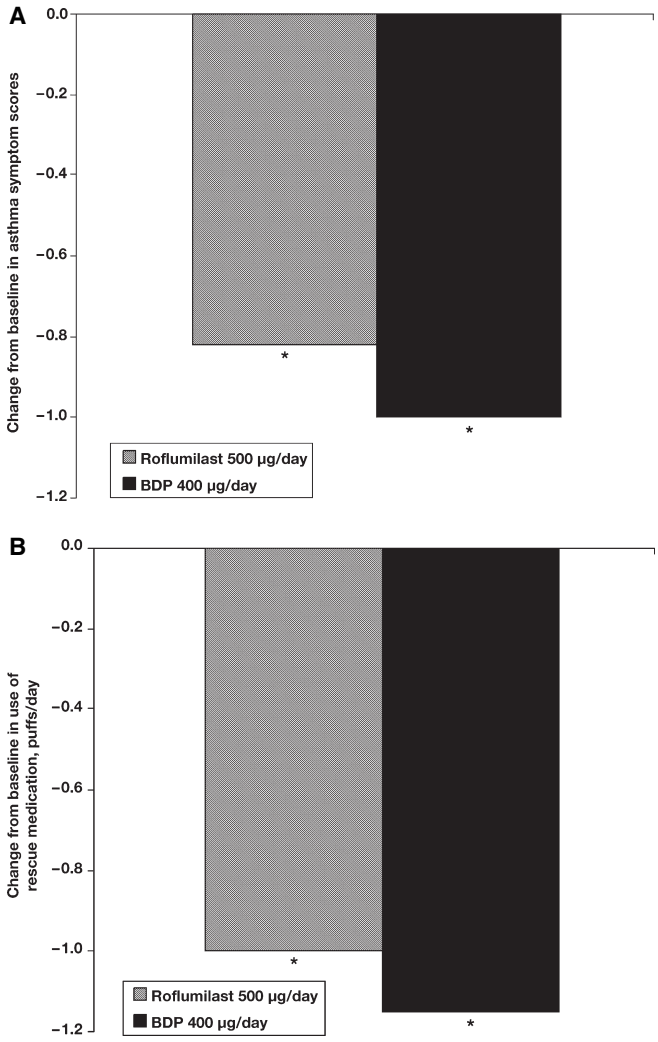

Figure 3. Oral roflumilast 500 µg once daily and inhaled beclomethasone dipropionate (BDP) 400 µg/day (200 µg twice daily) both demonstrated improvements from baseline in (A) total asthma symptom scores and (B) use of rescue medication. Data are median ± SE of the mean. *$P < 0.0001$ *vs* baseline. There was no significant difference in asthma symptoms scores ($P = 0.09$) and a significant difference in rescue medication use ($P = 0.0171$) between roflumilast and BDP at last visit.

Safety evaluation

The median duration of drug exposure was 84 days in each treatment group, indicating that a majority of patients received study medication throughout the 12-week treatment period. The majority of AEs in the roflumilast and BDP groups were considered either not related to study drug [119 of 193 (62%) AEs for roflumilast and 84 of 108 (78%) AEs for BDP] or unlikely related to study drug [32 of 193 (17%) AEs for roflumilast and 15 of 108 (14%) AEs for BDP] by the investigator. The most frequently reported AEs in patients were asthma worsening (9%) and nausea (6%)

Table 2. Adverse events by treatment group

Adverse event*	Patient, *n* (%)	
	500 μg/day Roflumilast ($n = 253$)	400 μg/day BDP ($n = 246$)
Asthma†	24 (9)	10 (4)
Nausea	16 (6)	3 (1)
Upper respiratory tract infection	11 (4)	9 (4)
Bronchitis	11 (4)	5 (2)
Rhinitis	10 (4)	7 (3)
Headache	9 (4)	3 (1)
Diarrhea	8 (3)	0

*Adverse events occurring in ≥3% of patients in any treatment group.
†Included wheezing, asthma exacerbations, and asthma worsening.
BDP, Beclomethasone dipropionate.

in the roflumilast group and asthma worsening (4%) and upper respiratory tract infection (4%) in the BDP group (Table 2). Most AEs were mild to moderate in intensity. Thirteen patients (5%) in roflumilast group and four patients (2%) in BDP group experienced asthma exacerbations, with nine and one patients in roflumilast and BDP groups, respectively, subsequently discontinuing from the study. Three (1%) patients treated with roflumilast and 2 (1%) patients treated with BDP reported serious AEs, and all were considered unrelated to study medication. There were no deaths during the study and no clinically meaningful changes in vital signs, electrocardiogram, or clinical laboratory parameters.

Discussion

Airway inflammation plays an important role in the pathophysiology of asthma, and ICS are a mainstay in current asthma management (20). However, many ICS may not fully penetrate into the small airways (21) (a key site of chronic inflammation), and some patients with asthma are insensitive or resistant to ICS therapy (22). Additionally, patient compliance (23), problems with inhaler techniques, and potential safety risks with long-term ICS therapy remain concerns (24). Oral therapies have been developed to address potential issues with inhaled therapies. Montelukast and zafirlukast are oral leukotriene receptor antagonists indicated as controller therapy for asthma. Although clinical benefits of these agents have been demonstrated, the evidence of their ability to control the multiple aspects of the inflammatory milieu of asthma is somewhat limited, particularly *vs* ICS (25–27). Therefore, additional pharmacologic agents have been investigated to target the inflammatory processes involved in the pathophysiology of asthma and other chronic airway diseases, such as COPD.

Key cells contributing to chronic airway inflammation express PDE4, an enzyme that degrades cAMP. Roflumilast inhibits PDE4 activity and *in vitro* and *in vivo* studies have shown that roflumilast and its active metabolite, roflumilast *N*-oxide, have anti-inflammatory activity affecting several pathways involved in airway inflammation (14, 15, 28). Roflumilast inhibits chemokine and cytokine secretion from several key inflammatory cell types, such as eosinophils, macrophages, and dendritic cells, thereby inhibiting inflammatory mediators implicated in the pathophysiology of asthma (14, 15, 28).

This study was designed to compare once-daily oral roflumilast 500 μg *vs* BDP 400 μg/day, a commonly prescribed ICS for the treatment of asthma. Treatment with roflumilast and BDP resulted in improvements in lung function parameters. Roflumilast was comparable with BDP in improving FEV_1, FVC, and evening PEF compared with baseline values. Roflumilast and BDP were also well tolerated during this study. Improvements observed for BDP were comparable with data from previously published ICS studies (29).

Roflumilast 500 μg and BDP 400 μg improved asthma symptoms and reduced rescue medication use. The reduction in rescue medication use from baseline was −1.00 and −1.15 puffs/day for roflumilast and BDP, respectively (difference of 0.15 puffs/day). The limited improvement may be related to the relatively low median baseline values for the roflumilast and BDP groups determined prior to randomization, 2.29 and 2.57 puffs/day, respectively, leaving little room for improvement. Asthma controller therapies, such as ICS, were discontinued during the baseline period, however a short baseline or medication washout period could possibly explain the low report of rescue medication use. The small difference in use of rescue medication between roflumilast and BDP was not considered clinically meaningful.

A placebo arm may have clarified potential differences between roflumilast and BDP with respect to improvement in efficacy parameters and inclusion of a placebo arm would have further strengthened the study. However, we did not expect to see a difference between the two treatment groups, and felt that addition of a placebo arm would incur unnecessary risk for patients with asthma. If we had in fact observed a difference between the two active treatments, we would not have been able to assess the magnitude of the difference. In this respect, a placebo arm would have been beneficial. Further, it is common for ethics committees to restrict approval of placebo-controlled studies of this size and design. Therefore, although it does not have a placebo group for comparison over time, this study does achieve the primary goal of establishing the noninferiority between roflumilast and BDP in patients with asthma.

Long-term compliance with ICS therapy has been an ongoing issue (4, 23, 30, 31). In addition, inadequate patient techniques for administering inhaled medications are associated with poor asthma control (32). Roflumilast is administered once daily as an oral tablet compared with the twice-daily inhalations required for BDP and other commonly administered ICS. Therefore, roflumilast

may provide a simplified, more convenient dosing regimen compared with ICS.

In conclusion, this study demonstrates that oral roflumilast 500 μg/day is comparable with the cornerstone asthma therapy, ICS (BDP 400 μg/day), in improving FEV_1, FVC, and asthma symptoms. This study is encouraging and further supports roflumilast as an effective anti-inflammatory therapy for asthma.

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