Roflumilast: A Phosphodiesterase-4 Inhibitor for the Treatment of Severe Chronic Obstructive Pulmonary Disease

Nathan A. Pinner, PharmD[1,2]; Leslie A. Hamilton, PharmD[1]; and Anthony Hughes, PharmD[1]

[1]Department of Pharmacy Practice, Auburn University Harrison School of Pharmacy, Auburn, Alabama; and [2]Department of Family Medicine, University of Alabama College of Community Health Sciences, Tuscaloosa, Alabama

ABSTRACT

Background: Roflumilast is a newly approved phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and a history of exacerbations.

Objective: The objective of this article is to review the pharmacology, clinical efficacy, and tolerability of roflumilast in the treatment of COPD.

Methods: Articles were identified using MEDLINE (1966–August 1, 2011) and EMBASE (1947–August 1, 2011). Searches were conducted using the terms *roflumilast* and *COPD*. Included in the search were all English-language clinical trials that were randomized, had durations of >6 weeks, and studied the effects of roflumilast on the forced expiratory volume in 1 second (FEV_1) or rates of exacerbations in patients with COPD. Abstracts from the annual meetings of the American Thoracic Society, American College of Chest Physicians, and European Respiratory Society were also searched to identify relevant publications. In addition, all pertinent studies evaluating the pharmacokinetics and pharmacodynamics of roflumilast were included.

Results: A total of 6 clinical trials (4 publications) evaluating the efficacy of roflumilast were identified and included. For the treatment of COPD, roflumilast was associated with a significant improvement in lung function (increase in FEV_1 of 36–88 mL) when compared with placebo. Roflumilast also reduced the rate of exacerbations in subsets of patients with chronic cough and a history of exacerbations. Overall, health-related quality of life was not significantly affected. Adverse effects were common in clinical trials, with 9% to 16% of patients discontinuing therapy as a result. The most frequently reported adverse effects were gastrointestinal issues, headache, and weight loss. Suicide-related adverse effects have occurred in 5 patients receiving roflumilast and 1 patient receiving placebo.

Conclusion: Roflumilast significantly improved FEV_1 in clinical trials but had inconsistent reductions in the rates of exacerbations. Comparative studies with recommended therapies for COPD, particularly inhaled corticosteroids, are needed to better assess the role of roflumilast in the management of COPD. (*Clin Ther.* 2012;34:56–66)

Key words: chronic bronchitis, COPD, phosphodiesterase-4 inhibitors, roflumilast.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. From 1970 to 2002, while death rates from the other leading causes of death decreased, rates of death due to COPD doubled.[1] COPD is characterized by chronic airflow obstruction that is not fully reversible and progresses at a rate greater than that of the general population. Cigarette smoking is the most common risk factor, but others exist, such as $alpha_1$-antitrypsin deficiency, occupational chemical exposure, and air pollution.[2]

Pharmacologic treatments are successful in reducing symptoms and exacerbations, improving health status, and increasing exercise tolerance. Medications employed in the long-term management of COPD include short- and long-acting β_2-agonists, short- and long-acting anticholinergics, methylxanthines, and inhaled corticosteroids.[2] None of the existing pharmacologic

Accepted for publication December 13, 2011.
doi:10.1016/j.clinthera.2011.12.008
0149-2918/$ - see front matter

options alone or in combination have been shown to affect the long-term decline in lung function or to reduce mortality.[3,4] Thus, there is a need for new agents that may have disease-modifying properties.

Selective phosphodiesterase-4 (PDE4) inhibitors have been in development for several years.[5] Theophylline, a nonselective phosphodiesterase inhibitor, has long been used for the treatment of COPD, but owing to a narrow therapeutic index, adverse effects, limited efficacy, and multiple drug interactions, its use has declined.[6,7] A member of the phosphodiesterase family, PDE4 is expressed in airway smooth muscle and in immune and proinflammatory cells.[8] PDE4 is the sole cyclic adenosine monophosphate (cAMP) metabolizing phosphodiesterase found in eosinophils, monocytes, and neutrophils.[8] Roflumilast and roflumilast N-oxide are selective inhibitors of PDE4 and do not affect the other PDE isozymes.[6] Inhibition of PDE4 reduces the inactivation of cAMP, which functions to decrease the activation of immune and inflammatory cells.[8]

Roflumilast is currently approved by the US Food and Drug Administration (FDA) for the treatment of severe COPD associated with chronic bronchitis and a history of exacerbations.[9] Roflumilast is available in 500-μg tablets, and the recommended dosing is 1 tablet daily. The objective of this article was to perform a concise, systematic review of the clinical efficacy and tolerability data leading to the approval of roflumilast. A nonsystematic review of the pharmacokinetic and pharmacodynamic data is also included.

METHODS

Articles for clinical efficacy were identified by systematically searching MEDLINE (1966–August 1, 2011) and EMBASE (1974–August 1, 2011) using the terms *roflumilast* and *COPD*. The search was limited to English-language, human, randomized controlled trials. Trials were included for the clinical efficacy review if they had a duration of at least 6 weeks and studied the effects of roflumilast on forced expiratory volume in 1 second (FEV_1) or rates of exacerbations in patients with COPD. Two authors performed the searches and selected the articles for inclusion in the clinical efficacy section (N.A.P., A.H.). Any discrepancies were resolved by the third author (L.A.H.). Abstracts and proceedings from the annual meetings of the American Thoracic Society, American College of Chest Physicians, and European Respiratory Society were searched to identify additional relevant publications. Abstract data were included if they provided additional information concerning the adverse effects of roflumilast not reported in the original publications of the clinical trials. In addition, all pertinent studies evaluating the pharmacokinetic properties and pharmacodynamics of roflumilast were nonsystematically included in this review.

RESULTS

The search of *roflumilast* and *COPD* returned 124 and 300 articles, respectively, from MEDLINE and EMBASE. When limited to human, English-language, and randomized controlled trials, MEDLINE returned 13 articles and EMBASE 16. After evaluating for clinical outcomes and duration, 6 trials (4 articles) were identified in MEDLINE and 4 (3 articles) in EMBASE. After eliminating duplicates the total number of trials included in the clinical efficacy review was 6 (4 articles).

Clinical Pharmacology

Pharmacokinetics

The absolute bioavailability of roflumilast is 79% following oral administration.[10] Roflumilast is then metabolized by cytochrome P450 (CYP) 3A4 and 1A2 isozymes to its active metabolite, roflumilast N-oxide. The C_{max} for roflumilast is achieved at 1 hour and at 4 hours for roflumilast N-oxide after repeated dosing.[11] Food reduces the C_{max} by 40% and delays the time until it is reached by about 1 hour. The resulting AUC for roflumilast and roflumilast N-oxide after food is comparable, and thus the drug can be given without regard to meals.[12] The mean AUC of roflumilast N-oxide exceeds that of roflumilast by a factor of 10 to 12.[10,11] Roflumilast N-oxide has similar PDE4 inhibition to roflumilast, and because of its higher presence in plasma, it accounts for approximately 90% of the pharmacologic effects.[13] Both roflumilast and roflumilast N-oxide exhibit dose-proportional, linear pharmacokinetic properties, with a doubling of the dose resulting in a doubling of the C_{max} and AUC.[11] The $t_{½}$ for roflumilast ranges from 14 to 18 hours and for roflumilast N-oxide from 20 to 22 hours.[10,11,14,15]

The volume of distribution after intravenous infusion is 2.9 L/kg, indicating a high degree of tissue distribution.[10] Studies have not been published that assess the plasma protein binding of roflumilast and roflumilast N-oxide, but the package labeling reports 99 and 97%, respectively.[9] Roflumilast N-oxide is further metabolized by CYP 3A4, 2C19, or glucuronidation to

Table I. Summary of ranges of reported pharmacokinetic (PK) data for roflumilast and roflumilast N-oxide in healthy adult subjects following a single 500-μg oral dose.[10–12,22]

PK Parameters	Roflumilast	Roflumilast N-Oxide
C_{max} (μg/L)	5.3–8.3	8.8–13.1
$AUC_{0-\infty}$ (μg × h/L)	31–61	350–646
$t_{½}$ (h)	10.3–28.0	19.6–32.4
T_{max} (h)	1.0–1.5	4.0–12.3
V_d (L/kg)[10]	2.92	
Bioavailability[10]	0.79	

inactive metabolites.[16,17] Table I summarizes the pharmacokinetic parameters of roflumilast and roflumilast N-oxide.

Pharmacodynamics

To assess the antiinflammatory potential of roflumilast, a randomized, double-blind, placebo-controlled, crossover study was conducted with the primary objective of comparing the difference in percentage of sputum neutrophils between roflumilast and placebo.[18] Secondary objectives of this study were to assess various other inflammatory markers, immune cells, and lung function. Thirty-eight patients, aged 45 to 75 years, who had moderate-to-severe COPD (FEV_1 35%–75%) for at least 1 year, were current or ex-smokers (for at least 6 months) with a smoking history of 10 pack-years or more, and had sputum neutrophilia (≥45% nonsquamous cells) and no recent exacerbation of COPD, were randomized to roflumilast 500 μg or placebo once daily. Long-acting bronchodilators, theophylline (2 weeks), and inhaled and/or oral corticosteroids were discontinued before inclusion in the study. However, short-acting bronchodilators were allowed during the study.

Compared with placebo, the roflumilast treatment resulted in statistically significant reductions in absolute numbers of eosinophils (−50.0%; $P < 0.001$), neutrophils (−35.5%; $P = 0.002$), and lymphocytes (−34.8%; $P = 0.022$); however, the reduction in percentage of neutrophils was not significant ($P = 0.31$). Significant improvements in pre- and postbronchodilator FEV_1 of 80 mL ($P < 0.001$) and 69 mL ($P = 0.018$), respectively, were reported. Inflammatory markers neutrophil elastase, eosinophil cationic protein, and IL-8 were all reduced significantly, as was α_2-macroglobulin (a marker of microvascular leakage). A significant reduction in tumor necrosis factor-α (TNF_{α}) concentration of 10.4% ($P = 0.047$) was reported after ex vivo stimulation with lipopolysaccharide. However, concentrations of E-selectin, another systemic marker of inflammation, were not reduced significantly. Of note, inflammation worsened during the placebo arm of the study, with increases in sputum neutrophils, eosinophils, neutrophil elastase, and α_2-macroglobulin above baseline values. Pre- and postbronchodilator FEV_1 was reduced during the placebo arm to below baseline values. The absolute increase from baseline in pre- and postbronchodilator FEV_1 was approximately 60 mL and 40 mL, respectively.

In this population, roflumilast reduced inflammatory cells and markers of inflammation in the sputum and provided modest improvements in FEV_1. Improvement in lung function is likely due to the effects on inflammation, as PDE4 inhibitors have not exhibited direct bronchodilating effects in previous studies.[13,19,20]

Drug-Drug Interactions

Since roflumilast is metabolized by CYP 3A4, 2C19, and 1A2, multiple possibilities for drug-drug interactions exist. Both the formation and degradation of roflumilast N-oxide are dependent on the cytochrome P450 system. Owing to the potential for alterations in the AUC for roflumilast and/or roflumilast N-oxide, the "total PDE4 inhibitory activity" (tPDE4i) has been established to compare overall pharmacologic impact of inhibitors and inducers of cytochrome P450 isozymes.[21] Inhibitors of these isozymes have the potential to decrease the clearance of roflumilast, decrease formation of roflumilast N-oxide, or decrease the clearance of roflumilast N-oxide. Studies have been conducted with inhibitors specific to each isozyme, as well as with some nonselective inhibitors, to better characterize the potential for drug-drug interactions with roflumilast.[16,22–25] Table II summarizes the results from the drug-drug interaction studies. One study assessed the effects of oral erythromycin 500 mg 3 times daily added to roflumilast 500 μg daily in healthy volunteers (n = 16). Erythromycin, a moderate inhibitor of CYP 3A4, inhibited the formation of roflumilast

Table II. Summary of drug interaction data for roflumilast and roflumilast N-oxide.[16,17,22–25,28–30]

Studied Drugs	Regimen	Roflumilast			Roflumilast N-oxide			Total PDE4 Inhibitory Activity
		AUC	C_{max}	$t_{½}$	AUC	C_{max}	$t_{½}$	
CYP Inhibitors								
Erythromycin (3A4)	SS erythromycin; SD R (500 μg)	+71%	+40%	+10 h	+3%	–34%	+12 h	+9%
Ketoconazole (3A4)	SS ketoconazole; SD R (500 μg)	+99%	+23%	+16 h	+3%	−38%	+12 h	+9%
Fluvoxamine (1A2, 2C19, 3A4)	SS fluvoxamine; SD R (500 μg)	+156%	+12%	+31 h	+52%	−20%	+34 h	+59%
Cimetidine (3A4, 1A2, 2C19)	SS cimetidine; SD R (500 μg)	+85%	+46%	+7 h	+27%	−4%	+11 h	+48%
Enoxacin (1A2)	SS enoxacin; SD R (500 μg)	+55%	+20%	+6 h	+22%	−14%	+13 h	+25%
CYP Inducer								
Rifampicin (3A4 and others)	SS rifampicin; SD R (500 μg)	−79%	−68%	−10 h	−56%	+30%	−14 h	−58%
Pulmonary Medications								
Budesonide	Administered concomitantly	−1%	+8%	+2 h	−8%	−12%	+1.5 h	NR
Montelukast	SS R (500 μg daily); SD montelukast	−2%	−4%	+4 h	−1%	−1%	−5 h	NR
Antacid								
Magnesium hydroxide/aluminum hydroxide	Administered concomitantly	+4%	−11%	No change	−1%	−8%	+1.5 h	NR

CYP = cytochrome P450; NR = not reported; PDE4 = phosphodiesterase-4; R = roflumilast; SD = single dose; SS = steady state.

N-oxide; increased the C_{max}, AUC, and $t_{½}$ of roflumilast; increased the AUC of roflumilast N-oxide; and caused a 9% increase in the tPDE4i activity.[22] Ketoconazole, a strong inhibitor of CYP 3A4, had comparable effects to erythromycin on the pharmacokinetic properties of roflumilast. Roflumilast AUC was doubled, but the AUC of roflumilast N-oxide increased only 3%. The tPDE4i activity also increased 9% when administered with ketoconazole.[16] Following administration with fluvoxamine, a mixed inhibitor of CYP 1A2, 2C19, and 3A4, the AUC of both roflumilast and roflumilast N-oxide increased 2.5-fold and 1.5-fold, respectively.[23] This result is in contrast to that of the previous studies of CYP 3A4 inhibitors that reported increases in roflumilast AUC but only minor increases in roflumilast N-oxide AUC.[16,22] Owing to the increases in AUC, the tPDE4i increased by approximately 60%. The effects of fluvoxamine on 2C19 are thought to contribute to the increase in tPDE4i activity.[23] Cimetidine, a mixed CYP 3A4, 1A2, and 2C19 inhibitor, caused comparable increases in AUC to roflumilast (90% increase) and roflumilast N-oxide (30% increase) as well as increased the tPDE4i activity by 50%.[24] The CYP 1A2 inhibitor enoxacin caused increases in the AUC of roflumilast and roflumilast N-oxide, although to a lesser extent than the mixed inhibitors fluvoxamine and cimetidine.[23–25] The effect of enoxacin on tPDE4i activity was less, an increase of 27%.[25] The package labeling recommends that caution be used when roflumilast is prescribed with any of the previously discussed medications.[9] Other inhibitors of CYP 3A4, 1A2, and 2C19 should also be initiated cautiously in patients receiving roflumilast. The impact of extended therapy with cytochrome P450 inhibitors is unknown, and patients should be monitored closely.

Drugs that induce cytochrome P450 enzymes may be expected to decrease the total AUC to roflumilast and roflumilast N-oxide. Coadministration of rifampicin, an inducer of several cytochrome P450 enzymes, most notably CYP3A4, with roflumilast led to an 80% and 68% reduction in roflumilast and roflumilast N-oxide AUC, respectively, and a 58% reduction in the tPDE4i activity.[17] Comparable reductions in the AUC and tPDE4i activity would be expected to occur with other cytochrome P450 enzyme inducers. Thus, the use of rifampicin or other potent cytochrome P450 enzyme inducers with roflumilast is not recommended.[9,17]

Roflumilast and roflumilast N-oxide have been studied to assess their impact on cytochrome P450 enzymes as well as P-glycoprotein. Neither roflumilast nor roflumilast N-oxide demonstrated altered disposition of midazolam (CYP 3A4 substrate) or digoxin (P-glycoprotein substrate).[26,27] Montelukast and budesonide, medications that are likely to be coadministered with roflumilast, have also been studied, and dose adjustments are not currently recommended.[9,28,29]

Antacids and food may affect the absorption and bioavailability of drugs. On investigation of the coadministration or subsequent administration of magnesium hydroxide/aluminum hydroxide–containing antacid with roflumilast, no significant differences in the pharmacokinetic properties of roflumilast or roflumilast N-oxide were found.[30]

Special Populations

Patients with mild (Child-Pugh A)-to-moderate (Child-Pugh B) cirrhosis were studied to determine the impact on the pharmacokinetic properties of roflumilast. The average total AUC was 51% and 92% higher for roflumilast and 24% and 41% higher for roflumilast N-oxide in patients with mild and moderate cirrhosis, respectively. This result correlated with an increase in tPDE4i activity of 26% for mild cirrhosis and 46% for moderate cirrhosis.[31] It is currently recommended that roflumilast be used cautiously in patients with mild hepatic impairment and be avoided in patients with moderate-to-severe liver impairment.[9]

Recently, patients with severe renal disease not receiving hemodialysis were administered a single dose of roflumilast (500 μg) to assess the impact on the pharmacokinetic properties of roflumilast. The AUC was 20% and 7% lower in patients with renal disease (mean creatinine clearance [Cl_{CR}] = 25.5 mL/min) than in matched patients with normal renal function (mean Cl_{CR} = 102.3 mL/min) for roflumilast and roflumilast N-oxide, respectively. The $t_{½}$, however, was 19% and 30% higher in patients with renal disease than in those with normal renal function for roflumilast and roflumilast N-oxide, respectively.[32] Based on these data, it does not appear that a dosage adjustment is necessary in patients with severe renal disease who are not receiving hemodialysis. Although it has not been studied, the high degree of protein binding will likely prohibit roflumilast from being effectively removed via hemodialysis.[32] The package labeling does not recommend a dosage adjustment in patients with

renal disease, nor does it recommend an adjustment for patients based on age, race, or gender. Roflumilast is rated as pregnancy category C.[9]

Efficacy

To determine the clinical efficacy of roflumilast, 6 prospective, randomized, double-blind, placebo-controlled trials have been performed (**Table III**).[33–36] The end points primarily investigated were changes in lung function, health-related quality of life, and rates of exacerbations.

One Phase III, multicenter, double-blind, placebo-controlled trial randomly assigned 1411 current or former smokers with stable, moderate-to-severe COPD (FEV_1 30%–80%) to either 250 μg or 500 μg of roflumilast or placebo daily.[33] Patients were excluded if they had experienced an exacerbation of their COPD that necessitated the prescription of systemic corticosteroids or required hospital treatment for COPD in the 4 weeks preceding the run-in period. During the study, patients were allowed the use of salbutamol for rescue therapy, fixed daily doses of short-acting anticholinergics, and oral corticosteroids to treat exacerbations. All other respiratory medications were prohibited and were withdrawn 4 weeks before randomization. The primary outcomes were the changes in postbronchodilator FEV_1 and health-related quality of life (assessed by the St. George's Respiratory Questionnaire [SGRQ]) at 24 weeks compared with the numbers at baseline. Improvement in FEV_1 was reported within the first 4 weeks of treatment with both doses of roflumilast. This improvement was maintained throughout the 24-week study period. Postbronchodilator FEV_1 was increased by 74 mL and 97 mL ($P < 0.0001$ for both) compared with placebo and by 29 mL ($P = 0.0134$) and 51 mL ($P < 0.0001$) compared with the baseline figures for roflumilast 250 μg and 500 μg, respectively. The improvement in SGRQ total score, when compared with results using placebo, was not significant for either dose of roflumilast. Mean number of exacerbations per patient was 1.13, 1.03, and 0.75 for the placebo, roflumilast 250 μg, and roflumilast 500 μg groups, respectively. The reduction in mean exacerbations per patient was significantly lower with the 500 μg roflumilast group than with the placebo group ($P = 0.0029$, one-sided) but not with the roflumilast 250 μg group.

Calverly et al, in a randomized multicenter, multinational, double-blind, placebo-controlled, parallel-group study, randomly assigned 1513 patients with severe COPD (mean postbronchodilator FEV_1 41% predicted) to receive either 500 μg oral roflumilast or matching placebo for 1 year (M2-112).[34] The primary end point was the change in postbronchodilator FEV_1 over the 1-year period and the number of moderate-to-severe exacerbations per patient per year. Inhaled corticosteroids and short-acting anticholinergics were allowed to be continued, and salbutamol was allowed as a rescue medication. All other COPD medications were discontinued before the run-in period. At 1 year, the difference in postbronchodilator FEV_1 from baseline, between roflumilast and placebo, was 39 mL ($P = 0.001$). The overall rate of moderate or severe exacerbations did not significantly differ between groups (0.86/patient/y and 0.92/patient/y for roflumilast- and placebo-treated patients, respectively). Exacerbations per patient-year occurred at a rate of 1.01 and 1.59 ($P = 0.024$) in patients with stage IV COPD treated with roflumilast or placebo, respectively. There was no significant difference in the improvement in health-related quality of life as measured by the SGRQ between the groups. Roflumilast-treated patients had a mean reduction of the SGRQ score by 1.7 units, whereas placebo-treated patients reduced the score by 2.0 units ($P = 0.651$). A comparable number of patients experienced a clinically significant reduction of the SGRQ score of 4 units in each group (295 for roflumilast and 308 for placebo).

The M2-124 and M2-125 studies were 2 identical placebo-controlled, double-blind, multicenter trials conducted to assess the effects of roflumilast and placebo on FEV_1 and rates of exacerbations in patients with severe COPD ($FEV_1 \leq 50\%$ predicted) and a history of exacerbations requiring systemic corticosteroids.[35] Patients were stratified according to smoking status and use of long-acting β2-agonists (allowed during study period) and then randomly assigned to roflumilast 500 μg (n = 1537) or matching placebo (n = 1554) daily. Inhaled corticosteroids, theophylline, and long-acting anticholinergics were not allowed during the study period. The reported difference in prebronchodilator FEV_1 compared with that of placebo was 39 mL ($P = 0.0003$) and 58 mL ($P < 0.0001$) in the M2-124 and M2-125 trials, respectively. The rate of moderate-to-severe exacerbations per patient-year for the roflumilast group compared with that for the

Table III. Summary of major findings for roflumilast clinical trials.

Trial	Patient Number	Design	Study Population	Treatments	Primary End Point(s)	Secondary End Point(s)
Rabe et al[33]	1411	Phase III, randomized, double-blind, placebo-controlled, multicenter	Moderate COPD (post-BD FEV_1 30%–80%)	Placebo (n = 280) 250 μg (n = 576) 500 μg (n = 555) daily for 24 wk	Post-BD FEV_1*: 250 μg, 74 mL 500 μg, 97 mL $P < 0.0001$ SGRQ score, P = NS	Pre-BD FEV_1*: 250 μg, 64 mL, $P = 0.0006$ 500 μg, 88 mL, $P < 0.0001$ Mean no. exacerbation (any type) per patient Placebo, 1.13 250 μg, 1.03 500 μg, 0.75
Calverley et al[34] (M2-112)	1513	Randomized, double-blind, placebo-controlled, multicenter, multinational, parallel group	Severe COPD ($FEV_1 \leq$ 50%)	Placebo (n = 753) 500 μg (n = 760) daily for 52 wk	Post-BD FEV_1*, 39 mL, $P = 0.001$ Reduction of moderate or severe exacerbations, P = NS	Improvement in SGRQ score P = NS Pre-BD FEV_1*, 36 mL, $P < 0.002$ Post-BD*: FEV_6, 53 mL, $P < 0.010$ FVC, 48 mL, P = NS FEF_{25-75}, 21 mL, $P < 0.004$ GOLD Stage IV exacerbation rate reduced, 1.014 (R) vs 1.588 (P), P = 0.024
Calverley et al[35] (M2-124 and M2-125)	3091	Randomized, double-blind, placebo-controlled, multicenter	Severe COPD ($FEV_1 \leq$ 50%)	Placebo (n = 1554) 500 μg (n = 1537) daily for 52 wk	Pre-BD FEV_1*, 48 mL, $P = 0.0001$ Reduced rate of moderate or severe exacerbations, 1.14 (R) vs 1.37 (P), $P = 0.0003$	Post-BD FEV_1*, 55 mL, $P = 0.0001$ Time to death from any cause P = NS C-reactive protein concentration P = NS TDI focal score, $P = 0.0009$
Fabbri et al[36] (M2-127 and M2-128)	1676	Randomized, double-blind placebo-controlled, multicenter, multinational	Moderate-to-severe COPD (post-BD FEV_1 40%–70%) In addition, the tiotropium arm required the presence of chronic cough and frequent use of rescue inhalers	Roflumilast plus salmeterol (R+S): Placebo (n = 467) 500 μg (n = 466) Roflumilast plus tiotropium (R+T): Placebo (n = 372) 500 μg (n = 371) daily for 24 wk	Pre-BD FEV_1*: R+S: 49 mL, $P <$ 0.0001 R+T: 80 mL, $P <$ 0.0001	Post-BD FEV_1*: R+S, 60 mL, $P < 0.0001$ R+T, 81 mL, $P < 0.0001$ Post- BD FVC *: R+S, 58 mL, $P = 0.0028$ R+T, 101 mL, $P = 0.0004$ TDI score† SOBQ† Use of rescue medications† Exacerbation rates (all types) were not different

BD = bronchodilator; COPD = chronic obstructive pulmonary disease; SGRQ = St. George's Respiratory Questionnaire; SOBQ = Shortness of Breath Questionnaire; TDI = Transition Dyspnea Index.
*Value is the difference between placebo and treatment spirometry parameters.
†TDI ($P = 0.0032$), SOBQ ($P = 0.0051$), and use of rescue medication ($P = 0.0004$) were only significant for the roflumilast plus tiotropium arm.

placebo group was 1.08 versus 1.27 ($P = 0.0278$) for the M2-124 study and 1.21 versus 1.49 ($P = 0.0035$) for the M2-125 study, respectively. Rates of severe exacerbations (defined as involving hospital admission or death) did not differ significantly between the 2 groups in either study or the pooled analysis. Differences in median time until the first moderate or severe exacerbation were not statistically significant in either study alone but were in the pooled analysis (hazard ratio [HR] = 0.89; $P=0.0185$). The median time until the second moderate or severe exacerbation was significantly extended in both the M2-124 (HR = 0.79; $P = 0.0290$) and M2-125 (HR = 0.79; $P = 0.0214$) studies. Improvements in the transition dyspnea index were statistically significant in both studies when compared with the placebo results but were not improved by a mean of 1 unit, the degree of improvement prespecified as clinically significant.[35]

Two additional 1-year trials sought to assess the effects of roflumilast, compared with those of placebo, on FEV_1 and exacerbation rates when used in combination with the long-acting bronchodilator salmeterol (M2-127) or tiotropium (M2-128).[36] Both trials enrolled patients with moderate-to-severe COPD (FEV_1 40%–70% predicted), but patients in the M2-128 trial must have been receiving tiotropium for the previous 3 months and had chronic cough and sputum production with frequent use of short-acting β_2-agonists (defined as ≥28 inhalations per week). Patients in the M2-127 trial must not have had an exacerbation requiring systemic corticosteroids in the previous month, but this was not an exclusion for the M2-128 trial. Short-acting β_2-agonists were allowed for rescue, but no respiratory medications except for the study medications were allowed once enrolled. The prebronchodilator FEV_1 was 49 mL and 80 mL greater in the roflumilast group when compared with that of placebo in the M2-127 and M2-128 trials, respectively ($P < 0.0001$ for both). The rate of all types of exacerbations did not differ significantly in either trial. Median time until first exacerbation varied between the 2 trials. For instance, the time until first moderate or severe exacerbation was prolonged in the M2-127 trial (HR = 0.6; $P = 0.0067$) but not in the M2-128 trial. The median time to any exacerbation was prolonged in the M2-128 trial (HR = 0.7; $P = 0.0264$) but not in the M2-127 trial. When compared with the results with placebo, a statistically significant improvement in symptoms was reported for the M2-128 trial but was not different in the M2-127 trial.

All clinical trials have reported statistically significant improvements in FEV_1, ranging from 36 to 88 mL, when compared with placebo.[33–36] This difference is small but is comparable to that reported previously with the inhaled corticosteroid fluticasone (42–59 mL)[3,37] and the long-acting bronchodilator salmeterol (38–47 mL)[3,37] but less than that reported with tiotropium (90–140 mL).[4,38,39] These increases in FEV_1 have been reported in trials in which roflumilast is administered alone,[35] in combination with long-acting bronchodilators salmeterol and tiotropium,[36] and inhaled corticosteroids.[34] What remains undetermined is the impact roflumilast may have in patients managed with a combination of bronchodilators and inhaled corticosteroids. Studies in this area are needed, as this population would benefit from additional improvements in lung function.

Reductions in exacerbation rates have been inconsistent in roflumilast trials. Three 1-year trials in patients with severe to very severe COPD have been conducted. The earliest trial (M2-112) did not detect a difference in the annual rate of moderate-to-severe exacerbations, but a significant reduction was detected in both the M2-124 and M2-125 trials.[34–36] The latter trials recruited patients with chronic cough and sputum production and a history of an exacerbation requiring corticosteroids in the previous year; these trials excluded the use of inhaled corticosteroids, whereas the M2-112 trial did not. Thus, roflumilast is indicated for use only in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[9]

Tolerability

Adverse Effects

The most common adverse effects observed with roflumilast were gastrointestinal disturbances (nausea, diarrhea, weight loss, decreased appetite) and headache (**Table IV**).[33–36] Withdrawal due to adverse effects in clinical trials ranged from 9% to 16% in roflumilast-treated patients and from 5% to 10% in placebo-treated patients.[33–36] Diarrhea, nausea, and headache were reported to resolve in about 4 weeks. However, weight loss was maintained for the duration of the study period. Mean weight loss for all patients receiving roflumilast 500 μg was 2.1

Table IV. Ranges of select adverse effects from clinical trials with roflumilast.[33–36]

Adverse Effect	Reported Rates of Occurrence
Nausea	3%–5%
Diarrhea	8%–9%
Headache	2%–6%
Weight loss	6%–12%
Insomnia	2%

kg.[40] In a subset of patients who reported weight loss as an adverse event, mean weight change was −6.26 kg.[41] Clinical trials have not reported the degree of weight loss in patients reporting it as an adverse effect, only as a mean of the entire population.[35,36] The package labeling states that 7% of patients experienced a >10% weight loss, so patients should be monitored carefully when initiating roflumilast.[9] Finally, weight loss was greater in patients reporting gastrointestinal adverse events or headache (2.60 kg) than in patients who did not experience these types of adverse events (2.02 kg).[35]

Psychiatric adverse events have also been reported, the most common being insomnia.[9] Approximately 2% of all patients treated with roflumilast experienced insomnia.[33–36] Five patients who were taking roflumilast experienced suicide-related adverse events compared with only 1 who received placebo.[40] In documents submitted to the FDA, the suicide-related adverse events included 2 attempted and 3 completed suicides in roflumilast-treated patients and 1 attempted suicide in placebo-treated patients.[42] In an analysis of roflumilast use in patients aged >65 years, adverse events were found to occur more frequently.[43]

Roflumilast is associated with several adverse effects uncommon to existing COPD therapies. Future studies of longer duration are necessary to determine the risk associated with the psychiatric effects and weight loss. Specifically, studies should evaluate patients with weight loss exceeding 10% of their body weight to establish those at risk. Until more is known, patients should be monitored closely for decreases in weight and psychiatric symptoms.

Precautions and Contraindications

Roflumilast is contraindicated only in moderate-to-severe liver impairment (Child-Pugh B and C). Precautions related to its use include coadministration with strong inducers of cytochrome P450 enzymes, its effects on body weight, and the possibility of psychiatric events.[9]

Limitations

The search was limited to English language articles only, which may have meant the omission of additional studies of roflumilast. In addition, post hoc analyses were also excluded from the clinical efficacy review, as these can only be considered hypothesis generating. However, post hoc analyses were allowed when reviewing the tolerability of roflumilast. A key limitation in reviewing roflumilast was the lack of published data regarding its more severe adverse effects. Much of the data for these adverse effects (weight loss and suicide-related events) were gathered from documents submitted to the FDA, and inclusion of post hoc and abstract data were needed to further define the risks associated with roflumilast. The pharmacokinetic and pharmacodynamic review was done in a nonsystematic manner, which may have led to selection bias. This was done to include studies representative of the pharmacokinetic and pharmacodynamic properties of roflumilast without including an overwhelming amount of data. Finally, several clinical trials remain unpublished that are identified as "completed" when searching ClinicalTrials.gov.[44] The results of these studies are needed for a more complete understanding of the effects of roflumilast on clinical outcomes in COPD.

CONCLUSIONS

Roflumilast improved FEV_1 to a degree comparable to that of inhaled corticosteroids in clinical trials, but its effects on rates of exacerbations and quality of life measures have not been as consistent. Roflumilast is currently recommended only for patients with severe COPD associated with chronic cough and a history of exacerbations. Further comparative studies of longer duration with other COPD therapies are needed to better determine the most appropriate role for roflumilast in the treatment of COPD. Studies more fully assessing drug interactions and adverse effects are also needed to better define the risk of maintenance therapy. Patients initiated on roflumilast should be monitored closely for

weight decrease and the development of psychiatric symptoms.

ACKNOWLEDGMENTS

Drs. Pinner and Hughes were responsible for the literature search and design. All authors participated in reviewing the literature and drafting the manuscript. Dr. Pinner performed all revisions with the approval of all coauthors.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of the article.

REFERENCES

1. Jemal A, Ward E, Hao Y, et al. Trends in the leading causes of death in the United States, 1970–2002. *JAMA*. 2005;294: 1225–1229.
2. Rabe KF, Hurd S, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, GOLD Executive Summary. *Am J Respir Crit Care Med*. 2007;176:532–555.
3. Calverly PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356:775–789.
4. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543–1554.
5. Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. *Lancet*. 2005; 365:167–175.
6. Hatzelmann A, Morcillo EJ, Lungarella G, et al. The preclinical pharmacology of roflumilast–a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2010; 23:235–256.
7. Hendeles L, Weinberger M, Johnson G. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics Principles of Therapeutic Drug Monitoring*. San Francisco, Calif: Applied Therapeutics Inc; 1980: 95–138.
8. Torphy TJ. Phoshodiesterase isozymes. *Am J Respir Crit Care Med*. 1998;157:351–370.
9. Daliresp [package insert]. St. Louis, Mo: Forrest Pharmaceuticals; 2010.
10. Bethke TD, Lahu G. High absolute bioavailability of the new oral phosphodiesterase-4 inhibitor roflumilast. *Int J Clin Pharmacol Ther*. 2011;49:51–57.
11. Bethke TD, Böhmer GM, Hermann R, et al. Dose-proportional intraindividual single- and repeated-dose pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor. *J Clin Pharmacol*. 2007;47:26–36.
12. Hauns B, Hermann R, Hünnemeyer A, et al. Investigation of a potential food effect on the pharmacokinetics of roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, in healthy subjects. *J Clin Pharmacol*. 2006;46:1146–1153.
13. Bundschuh DS, Eltze M, Barsig J, et al. In vivo efficacy in airway midels of roflumilast, a novel orally active PDE4 inhibitor. *J Pharmacol Exp Ther*. 2001;297:208–290.
14. Huennemeyer A, Hauns B, David M, et al. Pharmacokinetics and safety of roflumilast, a once-daily, oral, selective PDE4 inhibitor, and its active metabolite roflumilast N-oxide in healthy subjects. *J Allergy Clin Immunol*. 2004;113: S222.
15. Manegold A, Hauns B, David M, et al. Pharmacokinetic characteristics of roflumilast administered in gradually increasing doses of 500 μg to 1000 μg are dose-linear in healthy subjects. *Eur Respir J*. 2002;20:S108.
16. Lahu G, Huennemeyer A, von Richter O, et al. Effect of single and repeated doses of ketoconazole on the pharmacokinetics of roflumilast and roflumilast N-oxide. *J Clin Pharmacol*. 2008;48:1339–1349.
17. Nassr N, Huennemeyer A, Herzog R, et al. Effects of rifampicin on the pharmacokinetics of roflumilast and roflumilast N-oxide in healthy subjects. *Br J Clin Pharmacol*. 2009;68:580–587.
18. Grootendorst DC, Gauw SA, Verhoosel RM, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax*. 2007;62:1081–1087.
19. Grootendorst DC, Gauw SA, Baan R, et al. Does a single dose of the phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? *Pulm Pharmacol Ther*. 2003; 16:115–120.
20. Grootendorst DC, Gauw SA, Benschop N, et al. Efficacy of the novel phosphodiesterase 4 inhibitor BAY 19-8004 on lung function and airway inflammation in asthma and chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2003;16:341–347.
21. Hermann R, Lahu G, Hauns B, et al. Total PDE4 inhibitory activity: a concept for evaluating pharmacokinetic alterations of roflumilast and roflumilast N-oxide in special populations and drug-drug interactions. *Eur Respir J*. 2006; 28:436s. Abstract.
22. Lahu G, Huennemeyer A, Herzog R, et al. Effect of repeated dose of erythromycin on the pharmacokinetics of roflumilast and roflumilast N-oxide. *Int J Clin Pharmacol Ther*. 2009;47:236–245.
23. von Richter O, Lahu G, Huennemeyer A, et al. Effect of fluvoxamine on the pharmacokinetics of roflumilast and roflumilast N-oxide. *Clin Pharmacokinet*. 2007;46:613–622.
24. Bohmer GM, Gleiter CH, Morike K, et al. No dose adjustment on coadministration of the PDE4 inhibitor

roflumilast with a weak CYP3A, CYP1A2, and CYP2C19 inhibitor: an investigation using cimetidine. *J Clin Pharmacol*. 2011;51:594–602.
25. Lahu G, Nassr N, Herzog R, et al. Effect of steady-state enoxacin on single-dose pharmacokinetics of roflumilast and roflumilast N-oxide. *J Clin Pharmacol*. 2011;51:586–593.
26. Nassr N, Lahu G, von Richter O, et al. Lack of a pharmacokinetic interaction between steady-state roflumilast and single-dose midazolam in healthy subjects. *Br J Clin Pharmacol*. 2006;63:365–370.
27. Eckermann G, Lahu G, Nassr N, et al. Absence of pharmacokinetic interaction between roflumilast and digoxin in healthy adults. *J Clin Pharmacol*. 2011 Jan 21 [Epub ahead of print].
28. Hermann R, Siegmund W, Giessmann T, et al. The oral, once-daily phosphodiesterase 4 inhibitor roflumilast lacks relevant pharmacokinetic interactions with inhaled budesonide. *J Clin Pharmacol*. 2007; 47:1005–1013.
29. Böhmer G, Nassr N, Wenger M, et al. The targeted oral, once-daily phosphodiesterase 4 inhibitor roflumilast and the leukotriene receptor antagonist montelukast do not exhibit significant pharmacokinetic interactions. *J Clin Pharmacol*. 2009;49: 389–397.
30. Nassr N, Lahu G, Hünnemeyer A, et al. Magnesium hydroxide/aluminum hydroxide-containing antacid does not affect the pharmacokinetics of the targeted phosphodiesterase 4 inhibitor roflumilast. *J Clin Pharmacol*. 2007;47:660–666.
31. Hermann R, Nassr N, Lahu G, et al. Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. *Clin Pharmacokinet*. 2007;46:403–416.
32. Bethke TD, Hartmann M, Hunnemeyer A, et al. Influence of renal impairment on the pharmacokinetics of oral roflumilast: an open-label, parallel-group, single-center study. *Int J Clin Pharmacol Ther*. 2011;49: 491–499.
33. Rabe KF, Bateman ED, O'Donnell D, et al. Roflumilast–an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 2005;366:563–571.
34. Calverley PM, Sanchez-Toril F, McIvor A, et al. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2007; 176:154–161.
35. Calverley PM, Rabe KF, Goehring U, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomized clinical trials. *Lancet*. 2009;374:685–694.
36. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomized clinical trials. *Lancet*. 2009; 374:695–703.
37. Calverly PM, Pauwels R, Vestbo J, et al. Combined salmetrol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomized controlled trial. *Lancet*. 2003;361:449–456.
38. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. *Ann Intern Med*. 2005;143: 317–326.
39. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010; 182:155–162.
40. Gross N, Calverly PM, Fabbri LM, et al. Characterization of safety with roflumilast, an oral phosphodiesterase-4 inhibitor for the treatment of COPD. *Chest*. 2010;138:466A.
41. Martinez FJ, Rabe KF, Wouters EFM, et al. Time course and reversibility of weight decrease with roflumilast, a phosphodiesterase 4 inhibitor. *Am J Respir Crit Care Med*. 2010:A4441.
42. US Food and Drug Administration. Daxas (roflumilast) in chronic obstructive pulmonary disease. FDA advisory committee briefing document. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PulmonaryAllergyDrugsAdvisoryCommittee/UCM207379.pdf. Accessed November 3, 2011.
43. Hanania NA, Dransfield MT, Goehring UM, et al. Efficacy of roflumilast in elderly patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2011:A3087.
44. ClinicalTrials.gov. Roflumilast search page. http://www.clinicaltrials.gov/ct2/results?term=roflumilast. Accessed December 7, 2011.

Address correspondence to: Nathan A. Pinner, PharmD, University Medical Center, Box #870374, Tuscaloosa, AL 35406. E-mail: nap0003@auburn.edu