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

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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

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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