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ROFLUMILAST: A NEW PDE4 INHIBITOR FOR COPD

Jeremy Hyink, Pharm.D. Candidate

Chronic Obstructive Pulmonary Disease (COPD) affects an estimated 13 million people in the United States.[1] However, this number does not represent the significant amount of undiagnosed patients living with this condition. National surveys estimate the amount of people suffering from symptoms of chronic airway obstruction may be as high as 24 million.[2]

In 2009, chronic lower respiratory diseases, including COPD, surpassed cerebrovascular accidents as the third leading cause of death in the United States, accounting for 137,082 deaths.[3] Though the mortality data is significant, the morbidity associated with COPD is equally staggering. COPD is the second leading cause of disability in the United States, and has been responsible for 50 million hospital visits in the last 20 years.[4] Annually, 1.5 million emergency room visits and 15 million physician office visits are attributable to COPD. In 2003, the total economic burden of COPD was estimated at $37.2 billion, with $20.9 billion due to direct medical costs and $16.3 billion due to indirect morbidity and mortality costs.[5] As the incidence of COPD has increased, these costs have likely increased as well.

Phosphodiesterase 4 (PDE4) inhibitors represent a new treatment modality for COPD, and roflumilast is the first drug in this class to be approved in the U.S. Roflumilast was approved by the FDA on February 28th, 2011 as Daliresp®, marketed by Forrest Pharmaceuticals. Daliresp® is available as a once daily oral tablet of 500 mcg. The FDA-approved indication is the prevention of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. This article will review the pharmacology, pharmacokinetics, safety and efficacy, dosing, and cost of treatment with roflumilast.

Pharmacology

Inflammation in lung tissue is a key component in COPD, leading to obstruction, mucus hypersecretion, and progressive airway destruction. Inflammation is mediated by macrophages, neutrophils, and CD8+ T-lymphocytes.[6] PDE4 is a member of the enzyme superfamily of phosphodiesterases whose function is to hydrolyze 3'5'-cyclic adenosine monophosphate (cAMP) and 3'5'-cyclic guanosine monophosphate (cGMP) to the inactive 5'-monophophate. Raising intracellular levels of cAMP inhibits inflammatory cell functions, and the PDE4 enzyme subfamily is widely distributed in inflammatory cells of lung tissue. These two observations led researchers to investigate selective PDE4 inhibition as a means to reduce inflammation in reactive airway diseases such as COPD.[7]

Methylxanthines, most notably theophylline, have long been utilized for their non-selective PDE inhibition as adjunct therapy in COPD. Roflumilast and its active metabolite, roflumilast N-oxide, are potent and selective PDE4 inhibitors shown to increase intracellular cAMP

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levels in inflammatory cells, such as neutrophils, monocytes, dendritic cells, CD4+ T-cells, and bronchial smooth muscle cells.[8] Due to the inhibitory effect of cAMP on cell proliferation, PDE4 inhibitors such as roflumilast may also exhibit an anti-remodeling effect on the airways.[9]

Pharmacokinetics

Table 1 describes selected pharmacokinetic properties of roflumilast and its major metabolite, roflumilast N-oxide. Roflumilast is two-to-three times more potent than roflumilast N-oxide, but the plasma AUC of roflumilast N-oxide is, on average, 10-fold greater than that of roflumilast.[10] As a result, roflumilast N-oxide accounts for nearly 90% of the total PDE4 inhibitory activity of roflumilast.[11] Food does not affect total drug absorption, but does prolong time to maximum concentration (Tmax) of roflumilast by one hour.[10]

Special Populations

Roflumilast was studied in patients with mild-to-moderate hepatic impairment defined as Child-Pugh class A or B. When given roflumilast 250mcg once daily for 14 days, those classified as Child Pugh Class A had a 51% increase in the AUC of roflumilast, a 24% increase in the AUC of roflumilast N-oxide, and a 26% increase in the Cmax of roflumilast N-oxide. Child Pugh Class B patients experienced a 92% increase in the AUC of roflumilast, a 41% increase in the AUC of roflumilast N-oxide, and a 40% increase in the Cmax of roflumilast N-oxide. Based on these findings, clinicians should avoid the use of roflumilast in patients with moderate-to-severe hepatic impairment, and consider risk-benefit in using roflumilast in patients with mild hepatic impairment. [10]

No dose adjustment is necessary in patients with severe renal impairment.[10]

Roflumilast is classified as Pregnancy Category C, and should only be used when the benefit outweighs risk. Roflumilast has not been studied in nursing mothers and should be avoided in this population.[10]

Clinical Trials

In a small (n=38) crossover study, roflumilast reduced sputum neutrophils by 31% and eosinophils by 42% in COPD patients treated with 500 mcg orally once daily for one month.[12] Building on this data, Calverely et al. performed two simultaneous Phase III trials (M2-111, M2-112) involving patients with moderate-to-severe COPD (**Table 2**). In these parallel studies, a total of 2686 patients were randomly assigned to roflumilast 500mcg daily or placebo for 1 year. Primary efficacy endpoints were change in post-bronchodilator forced expiratory volume in 1 second (FEV_1) from baseline to endpoint and the number of moderate or severe exacerbations per patient per year. Treatment with roflumilast improved FEV_1 12 mL from baseline, whereas a deterioration of 26 mL from baseline was observed in the placebo group. This represents a significant increase in FEV_1 of 39 mL from baseline in the roflumilast group compared to placebo ($p<0.001$). However, no significant improvements were realized in the exacerbation endpoint in either group.[13] A *post-hoc* analysis by Rennard et al. found that patients who responded most favorably to roflumilast therapy were of the chronic bronchitis phenotype of COPD. Prior to randomization, these patients had higher cough or sputum scores and had more frequent exacerbations. The effect of roflumilast on patients with the emphysema phenotype was not significantly different from placebo.[14]

The results of the M2-111/M2-112 trials and their

Table 1 | Pharmacokinetic Properties of Roflumilast and Roflumilast N-Oxide[10]

Property	Roflumilast	Roflumilast N-Oxide
Absorption	F = 80% Cmax = 1 hr	Cmax = 8hr
Distribution	PPB = 99% Vd = 2.9L/kg	PPB = 97%
Metabolism	Primarily via CYP 1A2 and 3A4 and conjugation reactions to roflumilast N-oxide	
Elimination	$t_{1/2}$ = 17h Time to Cpss = 4 days 70% excreted in urine	$t_{1/2}$ = 30h Time to Cpss = 6 days

F = bioavailability, Cmax = maximum plasma concentration, PPB = plasma protein binding, Vd = volume of distribution, $t_{1/2}$ = half-life, Cpss = steady state plasma concentration

post-hoc analysis prompted researchers to test roflumilast in a patient population having a chronic bronchitis etiology of COPD. The M2-124 and M2-125 trials included patients classified as severe-to-very severe COPD (post-bronchodilator FEV1 ≤ 50% of predicted), who had cough and sputum production and at least one episode of exacerbation in the previous year requiring oral corticosteroids.[15] A 4-week run-in was performed where all patients took a placebo tablet in the morning; baseline rescue inhaler use was recorded. Patients were permitted during this period and throughout the study to use long acting β-agonists (LABAs) and short acting anticholinergics, but inhaled corticosteriods (ICS) or long acting anticholinergics were prohibited. Patients were allocated to treatment with either roflumilast 500 mcg or placebo in addition to their stable therapy, and were followed for 1 year. Primary endpoints were change in prebronchodilator FEV_1 from baseline and number of moderate and severe exacerbations. Exacerbations were defined as moderate if they required oral or parenteral corticosteroids and severe if they resulted in admission or death. The roflumilast groups in both trials experienced statistically significant improvements of both primary endpoints.[15]

Table 2 | Phase III Trials Involving Roflumilast[13-17]

Study	Design	Patients	Interventions	Key Findings
Rabe K, et al.[17] (2005) RECORD (M2-107)	MC, DB	N=1411; post-bronchodilator FEV_1 30-80% predicted	Roflumilast 250 mcg (n=576), roflumilast 500mcg (n=555), or PL (n=280) once daily x 24 weeks	Roflumilast ↑ post-bronchodilator FEV_1 97 mL vs. PL (@500 mcg dose). 500 mcg dose showed most improvement in FEV_1 and exacerbation rate vs. 250 mcg dose.
Calverley et al.[13] (2007) OPUS (M2-111)/ RATIO(M2-112)	MC, DB, PGS	N= 2686; post-bronchodilator FEV_1 ≤ 50% predicted	Roflumilast 500 mcg (n=1328) or PL (n=1361) x 1 year	Roflumilast ↑ post-bronchodilator FEV_1 39 mL vs. PL; Retrospective: roflumilast ↓ exacerbation rate 36% vs. PL in pts classified as GOLD Stage IV; Chronic bronchitis or pts with high cough/sputum scores show greatest benefit
Calverley et al.[15] (2009) AURA (M2-124)	MC, R, DB, PGS	N= 1523; post-bronchodilator FEV_1 ≤ 50%, chronic bronchitis symptoms, history of exacerbations	Roflumilast 500 mcg (n=765) or PL (n=758) once daily x 1 year	Roflumilast ↑ pre-bronchodilator FEV_1 39 mL vs. PL; roflumilast ↓ exacerbations (moderate or severe) 14.9% vs. PL; roflumilast ↑ post-bronchodilator FEV_1 49 mL vs. PL
Calverley et al.[15] (2009) HERMES (M2-125)	MC, R, DB, PGS	N= 1568; post-bronchodilator FEV_1 ≤ 50%, chronic bronchitis symptoms, history of exacerbations	Roflumilast 500 mcg (n=772) or PL (n=796) once daily x 1 year	Roflumilast ↑ pre-bronchodilator FEV_1 58 mL vs. PL; roflumilast ↓ exacerbations (moderate or severe) 18.5% vs. PL; roflumilast ↑ post-bronchodilator FEV_1 61 mL vs. PL
Fabbri et al.[16] (2009) EOS (M2-127)	MC, R, DB, PGS	N= 933; post-bronchodilator FEV_1 40-70% of predicted	Roflumilast 500 mcg (n=466) or PL (n=467) once daily x 24 weeks, in addition to salmeterol 50 mcg twice daily	Roflumilast ↑ pre-bronchodilator FEV_1 49 mL vs. PL; roflumilast ↑ post-bronchodilator FEV_1 60 mL vs. PL; significant ↓ in proportion of patients with exacerbation vs. PL; significant ↓ median time to 1st exacerbation (moderate and severe) vs. PL
Fabbri et al.[16] (2009) HELIOS (M2-128)	MC, R, DB, PGS	N= 743; post-bronchodilator FEV_1 40-70% of predicted	Roflumilast 500 mcg (n=371) or PL (n=372) once daily x 24 weeks, in addition to tiotropium 18 mcg once daily	Roflumilast ↑ pre-bronchodilator FEV_1 80 mL vs. PL; roflumilast ↑ post-bronchodilator FEV_1 81 mL vs. PL; significant ↓ in proportion of patients with exacerbation vs. PL

MC = multicenter, R = randomized, DB = double blind, PGS = parallel group study, PL = placebo FEV_1 = forced expiratory volume in 1 second

Bronchodilatation with LABAs and anticholinergics remain the preferred and most effective therapeutic options in COPD. The objectives of two parallel group studies (M2-127, M2-128) performed by Fabbri et al. were to determine the efficacy and safety of concomitant therapy with roflumilast and either a LABA or an anticholinergic.[16] M2-127 compared the addition of roflumilast or placebo to treatment with salmeterol, while M2-128 investigated roflumilast versus placebo in addition to tiotropium. Inclusion criteria for these trials were age older than 40, current or former smokers with at least a ten pack-year history, post-bronchodilator FEV_1 40-70% of predicted value, partial reversal with albuterol, and stable disease. Patient demographics between the two trials were similar, with the exception that patients recruited to the tiotropium trial were more symptomatic. A 4-week run-in period similar to the M2-124 and M2-125 trials was utilized. The primary endpoint in both studies was change in mean pre-bronchodilator FEV_1 from baseline. In the salmeterol trial, the roflumilast plus salmeterol group experienced a 39 mL increase in FEV_1 from baseline, while the placebo plus salmeterol group saw a 10 mL decrease in FEV_1 from baseline. In the tiotropium trial, the roflumilast plus tiotropium group realized a 65 mL increase in FEV_1 from baseline, whereas the placebo plus tiotroium group experienced a 16 mL decrease in FEV_1 from baseline. Similar improvements were realized in post-bronchodilator FEV_1. Researchers concluded that roflumilast maintains its efficacy in the presence of long acting bronchodilators, providing additive benefit to these medications.[16]

Adverse Reactions/Safety Concerns

The most common drug-related adverse reactions associated with roflumilast are listed in Table 3.

Psychiatric events, including insomnia, anxiety, and depression were more common with roflumilast than placebo. In a pooled analysis of over 6000 patients from clinical trials who received roflumilast, the incidences of insomnia, anxiety, and depression were reported at rates of 2.4%, 1.4%, and 1.2% in the roflumilast group versus 1.0%, 0.9%, and 0.9% in the placebo group.[18] Five incidents of attempted suicide occurred in those receiving roflumilast, with three successful, compared with one unsuccessful attempt in the placebo group. An FDA Advisory Panel concluded that this suicide event rate was too low to draw any conclusions, but physicians and patients should be informed of the rare events of suicidal behavior and patients should be monitored for psychiatric events.[19]

Weight loss was more prevalent in those taking roflumilast (7.5%) over those taking placebo (2.1%), with an average weight loss of 2 kg. Within 12 weeks of treatment discontinuation, many patients partially regained some of the lost weight.[7] The FDA Advisory Panel concluded that there was no increased morbidity associated with this weight loss, and that physicians and patients should be made aware of this possible side effect of roflumilast.[19]

Drug Interactions

As roflumilast is metabolized by CYP 3A4 and 1A2, drug interaction studies were performed with inhibitors and inducers of these enzymes. Co-administration of roflumilast with the strong 3A4 inhibitor, ketoconazole, increased the AUC of roflumilast 34%, but Cmax re-

Table 3 | Common Adverse Reactions of Roflumilast[18]

Adverse Reaction	Treatment	
	Roflumilast 500mcg (N=5766) n (%)	Placebo (N=5491) n (%)
Diarrhea	585 (10.1)	143 (2.6)
Weight decreased	394 (6.8)	101 (1.8)
Nausea	297 (5.2)	79 (1.4)
Psychiatric (insomnia, anxiety, depression)	344 (6.0)	164 (3.0)
Headache	266 (4.6)	110 (2.0)
Decreased appetite	125 (2.2)	22 (0.4)
Back Pain	176 (3.1)	117 (2.1)
Dizziness	139 (2.4)	65 (1.2)

mained unchanged. CYP 3A4 is responsible for the metabolism of roflumilast to roflumilast N-oxide. Since roflumilast N-oxide contributes 90% of PDE4 inhibitory activity, and PDE4 inhibition is correlated with the drug's safety and efficacy profile, researchers determined that no dose adjustment is necessary when roflumilast and ketoconazole are co-administered. At its highest recommended daily dose, ketoconazole does not affect exposure to roflumilast N-oxide, and thus does not alter the safety and efficacy of the parent drug.[20] However, concomitant administration with fluvoxamine, which inhibits multiple CYP enzyme pathways including 3A4 and 1A2, causes a significant increase in roflumilast N-oxide and roflumilast levels, and thus these two medications should not be given simulataneously.[21] Co-administration of roflumilast and the potent 3A4 inducer rifampin is not recommended, since resulting significant reductions in roflumilast PDE4 inhibition may reduce the effectiveness of roflumilast.[19]

Cost

The average retail cost of a one month supply of Daliresp® without insurance is $216.98, with a range of $207.00 - $233.95.

Summary

COPD is a chronic airway disease of increasing incidence associated with significant morbidity and mortality. Roflumilast, a newly approved once daily oral medication for COPD, is the first approved PDE4 inhibitor in the U.S. PDE4 inhibitors decrease inflammatory mediators in the lungs, therefore decreasing overall inflammation associated with the pathogenesis of COPD.[12] In clinical trials, patients with chronic bronchitis benefitted from roflumilast therapy, experiencing significantly greater increases in pre- and postbronchodilator FEV_1 compared with placebo, as well as reductions in COPD exacerbations.[14,15,16] Major adverse effects noted from pooled clinical trial data included diarrhea, weight decrease, and nausea.[18] In COPD patients with chronic bronchitis and cough and sputum production who continue to have exacerbations despite standard therapy, roflumilast may be an appropriate new option for adjunct therapy.

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Clinical Trial Update

Rivaroxaban | ROCKET-AF[1] was a randomized double-blind study evaluating the efficacy of rivaroxaban 20 mg daily (n = 6958) compared to dose-adjusted warfarin (goal INR 2.0-3.0, n = 7004) in patients with nonvalvular atrial fibrillation and a CHADS2 score of at least 2. Key exclusion criteria included a creatinine clearance (CrCl) < 30 mL/min; patients with a CrCl of 30-49 mL/min received 15 mg/d (21% of patients). The primary outcome (composite of ischemic and hemorrhage stroke and systemic embolism) was tested for non-inferiority in the per-protocol analysis and for superiority in the safety analysis. After a median follow-up of 590 days, rivaroxaban was found to be non-inferior to warfarin in reducing the risk for the primary endpoint in the per-protocol analysis (HR 0.79; 95% CI 0.66-0.96; $p < 0.001$) and superior to warfarin in the safety analysis ($p = 0.01$). Rivaroxaban reduced the risk for intracranial hemorrhage (HR 0.67; $p = 0.007$) but increased the risk for GI hemorrhage (HR 1.45; $p < 0.001$) and was associated with an increased risk for major bleeding (HR 1.04; $p = 0.58$) compared to warfarin. Rivaroxaban also trended towards reducing the risk of MI and death, although the risk reduction for both was not statistically significant. The mean time in the therapeutic range (TTR) for warfarin-treated patients was 55%.

Apixaban | ARISTOTLE[2] was a randomized double-blind trial comparing apixaban 5 mg BID (n = 9120) to dose-adjusted warfarin (goal INR 2.0-3.0, n = 9081) in patients with nonvalvular atrial fibrillation and a CHADS2 score of at least 1. Key exclusion criteria included a CrCL < 25 mL/min. Patients meeting two of the following criteria were given a dose of 2.5 mg BID: age $\geq$ 80 years, body weight $\leq$ 60 kg, or a serum creatinine (SCr) $\geq$ 1.5 mg/dL; this lower dose was used in roughly 4.5% of patients. The primary outcome was the composite of ischemic or hemorrhagic stroke and systemic embolism, tested for both non-inferiority and superiority. After a median follow-up of 1.8 years, apixaban was found to be superior to warfarin in reducing the risk for the primary outcome (HR 0.79; 95% CI 0.66-0.95; $p < 0.001$ for non-inferiority, $p = 0.01$ for superiority). Apixaban also reduced the risk for major bleeding at all locations (HR 0.69; $p < 0.001$), death from any cause (HR 0.89; $p = 0.047$), and hemorrhagic stroke (HR 0.51; $p < 0.001$), and trended towards a reduction in ischemic or unknown stroke (HR 0.92; $p = 0.42$). The mean TTR for warfarin was 62.2%.

Be on the lookout for future PharmaNotes discussing these novel anticoagulants and their landmark trials.

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