

## HOT TOPICS

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#### **Reduction of Exacerbations by the PDE4 Inhibitor Roflumilast - the Importance of Defining Different Subsets of Patients with COPD**

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#### **BACKGROUND**

Avoiding exacerbations is a very important goal in the overall management of patients with chronic obstructive pulmonary disease (COPD). Frequent exacerbations of COPD result in higher mortality, poorer quality of life, increased airway inflammation, and a more rapid decline in lung function versus those with less frequent exacerbations.<sup>1</sup> COPD exacerbations are associated with increased airway and systemic inflammation and physiological changes, especially the development of hyperinflation. They are triggered mainly by respiratory viruses and bacteria, which infect the lower airway and increase airway inflammation. Some patients are particularly susceptible to exacerbations, and show worse health status and faster disease progression than those who have infrequent exacerbations.<sup>1</sup>

Identification of treatments that decrease the frequency of exacerbations is an important goal and it has been suggested that agents with anti-inflammatory properties may be beneficial for decreasing these events in patients with COPD.<sup>2</sup> Inhibition of phosphodiesterase (PDE)-4 may have clinically important anti-inflammatory effects in COPD. This enzyme was identified as a major therapeutic target in respiratory diseases because it is the predominant isoenzyme involved in the metabolism of 3', 5' cyclic adenosine monophosphate (cAMP) in the majority of inflammatory cells, including macrophages, neutrophils, and CD8+ lymphocytes.<sup>3</sup> Inhibition of PDE-4 blocks the hydrolysis of cAMP, leading to elevated intracellular cAMP levels and, thus,

suppression of the proinflammatory activity of these cells.<sup>3</sup> Clinical trial results have shown that the PDE-4 inhibitor roflumilast is effective for decreasing exacerbations and improving pulmonary function in patients with COPD.<sup>4</sup> However, COPD is a heterogeneous disease with multiple phenotypes and it is important to determine subgroups of patients in which a given therapy has the greatest benefit.<sup>5,6</sup>

The study reviewed addressed this issue using results from two 12-month studies. The goal of the analysis was to define a subset of patients with COPD who are likely to respond to roflumilast, and in particular, to experience a decrease in the frequency of exacerbations with this treatment.<sup>7</sup>

## **HIGHLIGHTS OF STUDY DESIGNS AND RESULTS**

### **Study Designs**

The results analysed were from two 12-month, randomized, double-blind, parallel group studies. Diagnosis of COPD was based on American Thoracic Society (ATS) criteria in one trial and Global Initiative for Chronic Obstructive Lung Disease (GOLD) in the second study. Patients ( $\geq 40$  years of age) were current or ex-smokers ( $\geq 10$  pack-years) who were clinically stable with no exacerbations and no changes in COPD treatment within 4 weeks prior to first baseline visit. Post-bronchodilator FEV<sub>1</sub> was required to be  $\leq 50\%$  predicted and the post-bronchodilator FEV<sub>1</sub>:FVC ratio was  $\leq 0.70$ .<sup>7</sup>

Each study began with a 4-week, single-blind run-in period during which patients received placebo. Patients were then randomly assigned to roflumilast 500  $\mu\text{g}$  once daily or placebo for 52 weeks. Patients were allowed to continue treatment with SAMA and ICS ( $\leq 1000$   $\mu\text{g}$  beclomethasone dipropionate or equivalent) if taken on a regular basis at a constant daily dose for at least 3 months prior to study entry. About 60% of patients concomitantly received ICS during the studies.<sup>7</sup>

The primary endpoint was prebronchodilator FEV<sub>1</sub> and the rate of moderate or severe exacerbations per patient per year was defined by the need for oral or parenteral corticosteroid treatment, hospitalization, or death.<sup>7</sup> The main secondary lung function endpoint was post-bronchodilator FEV<sub>1</sub>.

### **Results**

Of 3630 patients enrolled into the run-in period, 2686 patients met the inclusion criteria and were randomized to treatment; 1905 patients completed the studies.<sup>7</sup>

The rate of moderate-to-severe exacerbations in the pooled analysis was 14.3% lower with roflumilast compared with placebo (0.52 versus 0.61 exacerbations per year;  $P=0.026$ ). There

were several subgroups in which the exacerbation rate was significantly lower with roflumilast versus placebo. These included men (18.7% reduction in exacerbation rate with roflumilast versus placebo,  $P=0.018$ ), patients with chronic bronchitis with or without emphysema (26.2% reduction,  $P=0.001$ ), patients receiving concomitant ICS (18.8% reduction,  $P=0.014$ ), patients receiving concomitant short-acting anticholinergic treatment (18.3% reduction  $P=0.012$ ), and patients with baseline cough or sputum scores  $\geq 1$  (20.9% reduction,  $P=0.006$  and 17.8% reduction,  $P=0.030$ , respectively). Treatment with roflumilast produced significantly improvements in pre- and post-bronchodilator FEV<sub>1</sub> in all patient subgroups (both  $P<0.0001$ ).<sup>7</sup>

## COMMENT

Two important findings from this study have particularly important implications for consideration of COPD phenotypes and selection of therapy in clinical practice. First, roflumilast was most effective for decreasing the frequency of exacerbations in patients with chronic bronchitis. Chronic bronchitis is an inflammatory sub-phenotype COPD; and among adults <50 years old, chronic bronchitis may represent an early marker of susceptibility to the effects of cigarette smoking on systemic inflammation and long-term risk for COPD and all-cause mortality.<sup>8,9</sup> It has also been reported that about one-half of patients with chronic bronchitis and COPD also have metabolic syndrome and that this is associated with increased systemic inflammatory markers, independent of lung function impairment.<sup>10</sup> Results from a small-scale study in 38 patients with COPD have indicated that roflumilast has pulmonary anti-inflammatory effects, including reducing numbers of neutrophils and eosinophils and soluble markers of neutrophilic and eosinophilic inflammatory activity in induced sputum.<sup>11</sup> These effects may contribute to the benefit of roflumilast in patients with a highly inflammatory COPD phenotype.

The second important finding from this post-hoc analysis is that addition of roflumilast has significant incremental benefit in decreasing the frequency of exacerbations in patients who are already receiving ICS. Meta-analysis of clinical trial results has shown that ICS has significant benefit in decreasing the risk for exacerbations in patients with COPD, including those with severe disease.<sup>12</sup> And from ECLIPSE we know that 22% of patients with stage 2 disease, 33% with stage 3, and 47% with stage 4 still have frequent exacerbations despite to the current available treatment options<sup>13</sup>. The results from the analysis carried out by Rennard et al.<sup>7</sup> suggest that addition of roflumilast to therapy may provide a further decrease in these events and might be considered for addition to treatment in patients receiving ICS, but are still experiencing exacerbations.

## REFERENCES

1. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370:786-796.
2. Han MK, Martinez FJ. Pharmacotherapeutic approaches to preventing acute exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2011;8:356-362.
3. Cazzola M, Picciolo S, Matera MG. Roflumilast in chronic obstructive pulmonary disease: evidence from large trials. *Expert Opin Pharmacother*. 2010;11:441-449.
4. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694.

5. Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. *Am J Respir Crit Care Med*. 2010;182:598-604.
6. Hersh CP. Pharmacogenetics of chronic obstructive pulmonary disease: challenges and opportunities. *Pharmacogenomics*. 2010;11:237-247.
7. Rennard SI, Calverley PM, Goehring UM, Bredenbröker D, Martinez FJ. Reduction of exacerbations by the PDE4 inhibitor roflumilast-the importance of defining different subsets of patients with COPD. *Respir Res*. 2011;12:18.
8. Snoeck-Stroband JB, Lapperre TS, et al. Chronic bronchitis sub-phenotype within COPD: inflammation in sputum and biopsies. *Eur Respir J*. 2008;31:70-77.
9. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Chronic bronchitis before age 50 years predicts incident airflow limitation and mortality risk. *Thorax*. 2009;64:894-900.
10. Watz H, Waschki B, Kirsten A, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest*. 2009;136:1039-1046.
11. 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.
12. Puhan MA, Bachmann LM, Kleijnen J, Ter Riet G, Kessels AG. Inhaled drugs to reduce exacerbations in patients with chronic obstructive pulmonary disease: a network meta-analysis. *BMC Med*. 2009;7:2.
13. Hurst JR, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363:1128-1138.