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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the role of roflumilast in chronic obstructive pulmonary disease?

A: Roflumilast has been shown to reduce rates of acute exacerbation in patients with severe chronic obstructive pulmonary disease (COPD), ie, forced expiratory volume in 1 second (FEV_1) less than 50% with symptoms of chronic bronchitis and a history of exacerbations.

Roflumilast is a selective phosphodiesterase 4 (PDE4) inhibitor that acts on airway smooth muscle cells and various inflammatory cells. By blocking PDE4, roflumilast raises cyclic adenosine monophosphate levels within these cells, curtailing the inflammatory response.[1,2]

Roflumilast is not a bronchodilator, although modest improvements in FEV_1 have been documented in clinical trials when it was used as maintenance therapy.

TRIALS OF ROFLUMILAST

Several trials have investigated the efficacy of roflumilast in COPD (**Table 1**).

The RECORD trial

The RECORD trial[1] in 2005 was the first large randomized controlled trial of roflumilast in moderate to severe COPD. At a dose of 500 µg orally daily, there was a modest but statistically significant improvement in the postbronchodilator FEV_1. There was also improvement in the St. George Respiratory Questionnaire score in the treatment arm, but this was not statistically significant. The study also found a reduction in acute exacerbations of COPD with roflumilast, which was a secondary end point.[1]

The results of this study spurred interest in roflumilast as well as criticism of the design of the study. First, COPD patients on inhaled maintenance therapy such as an inhaled corticosteroid and long-acting beta-agonist combination or a long-acting muscarinic antagonist had their medications held during the study. Second, the average FEV_1 was 54% of predicted, indicative of a study population with less severe disease.[1]

The RATIO trial

Taking into account the results of the RECORD trial, the RATIO trial[3] in 2007 recruited patients with more severe COPD—ie, Global Initiative for Chronic Obstructive Lung Disease (GOLD) class III and IV—and included the rate of acute exacerbations as a primary end point. Maintenance therapy with inhaled corticosteroids was continued in patients already taking them. However, long-acting beta-agonists and long-acting muscarinic antagonist therapies were held.[3]

Again, roflumilast improved postbronchodilator FEV_1 compared with placebo. A reduction in acute exacerbations was seen but was not statistically significant except in subgroup analysis, where a statistically significant reduction in acute exacerbations was noted for patients with very severe (GOLD class IV) COPD.[3]

Post hoc analysis from the RATIO trial suggested that patients with chronic bronchitis and patients with a history of frequent exacerbations were more likely to respond to roflumilast.[2]

The EOS and HELIOS trials

In 2009, the results of the EOS and HELIOS trials of roflumilast in patients with severe

The most common adverse effects of roflumilast: diarrhea, weight loss, and nausea

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TABLE 1

Studies discussed in this article

AURA
Effect of Roflumilast on Exacerbation Rate in Patients With Chronic Obstructive Pulmonary Disease (BY217/M2-124)[5]

EOS
Effect of Roflumilast on Lung Function in Chronic Obstructive Pulmonary Disease Patients Treated With Salmeterol (BY217/M2-127)[4]

HELIOS
Effect of Roflumilast in Chronic Obstructive Pulmonary Disease) Patients Treated With Tiotropium (BY217/M2-128)[4]

HERMES
Effect of Roflumilast on Exacerbation Rate in Patients With Chronic Obstructive Pulmonary Disease (BY217/M2-125)[5]

RATIO
Effect of 1-Year Treatment With Roflumilast in Severe Chronic Obstructive Pulmonary Disease[3]

REACT
Effect Of Roflumilast On Exacerbations In Patients With Severe Chronic Obstructive Pulmonary Disease Uncontrolled By Combination Therapy: A Multicentre Randomised Controlled Trial[6]

RECORD
Roflumilast—An Oral Anti-inflammatory Treatment for Chronic Obtructive Pulmonary Disease: A Randomised Controlled Trial[1]

COPD were published.[4] These trials allowed continuation of long-acting beta-agonists and muscarinic antagonists. The prebronchodilator FEV_1 improved modestly when roflumilast was added to a long-acting bronchodilator. These studies ran for only 24 weeks, and the rate of acute exacerbations was not a primary end point, although the results did show a trend toward reduction of exacerbations.[4]

The AURA and HERMES trials

Also in 2009 was the publication of the results of two 52-week placebo-controlled trials (AURA and HERMES) of roflumilast in patients with severe COPD with chronic bronchitis and a history of frequent exacerbations.[5] Maintenance therapy with long-acting beta-agonists was continued, whereas inhaled corticosteroids and long-acting muscarinic antagonists were held. Statistically significant improvements in prebronchodilator FEV_1 and reduction in the rate of exacerbations were observed in the roflumilast group (17% reduction, 95% confidence interval 8–25, $P < .0003$).[5]

The REACT trial

The REACT trial[6] randomized 1,945 patients with severe COPD already on maximal recommended combination inhaled corticosteroid and long-acting beta-agonist therapy to receive either roflumilast or placebo. The patients' ratio of FEV_1 to forced vital capacity was less than 70%, their postbronchodilator FEV_1 was less than 50%, and they had chronic bronchitis and a history of at least two acute exacerbations during the past year. They had also been on combination therapy for the previous year. Patients who were on long-acting muscarinic-antagonist therapy (70% of the cohort) were included, and continued with their medication.

Patients were followed for 52 weeks. There was a significant reduction in the rate of exacerbations in the roflumilast group vs placebo (0.823 vs 0.959; risk ratio 0.858; 95% confidence interval 0.740–0.995; $P = .0424$).[6] As in previous trials, the roflumilast group showed an improvement in postbronchodilator FEV_1. The study also showed a reduction in hospital admissions in the treatment group.[6]

ADVERSE EFFECTS OF ROFLUMILAST

Roflumilast is known to have adverse effects significant enough to reduce compliance, the most common being diarrhea, weight loss, and nausea.[2,6,7] In the REACT trial,[6] 11% of patients in the roflumilast group vs 5% in the placebo group dropped out of the study because of adverse drug effects. Diarrhea was reported in 10% and weight loss in 9% of patients taking roflumilast. Weight loss has been shown to be reversible upon stopping roflumilast.[2] There has been no evidence of increased risk of death or serious adverse events in studies of roflumilast in patients with COPD.[2] However, the benefit-to-harm ratio suggests that roflumilast provides a net benefit only in patients at high risk of severe exacerbations.[7]

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