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Clinical Question: In adults with COPD, does roflumilast reduce the frequency of exacerbations compared to standard therapies alone?

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Clinical Question

In adults with COPD does roflumilast reduce the frequency of exacerbations compared to standard therapies alone?

Search terms

Roflumilast, COPD, exacerbation

Limits

English, human, adults

Inclusion criteria

Systematic review, meta-analysis, randomized-control trial

Exclusion criteria

Studies older than 2010

Summary of the issues

Chronic Obstructive Pulmonary Disease (COPD) is characterized by inflammation in the lungs and airways leading to limitation of airflow. The disease is most commonly caused by cigarette smoke along with environmental pollutants producing a persistent inflammatory response in the lungs. The prevalence of COPD, associated morbidities and mortality, and contribution to healthcare cost make the disease a highly important area of research. In 1990 it was the sixth leading cause of death worldwide. [1] By 2002 it had risen to the fifth position and is expected to continue this upward trend to the fourth leading cause by 2030. [2] In the United States the annual direct cost of COPD is approximated to be $29.5 billion.

COPD is divided into four classes based on spirometry, symptom severity, and exacerbation risk. Exacerbations are a key feature of this disease. They contribute significantly to the overall cost, number of hospitalizations, and progression of the disease. Decreasing frequency and severity of exacerbations is one of the goals of therapy. [1]

The only known intervention to slow or prevent progression of the disease is smoking cessation. Pharmacotherapy for COPD is directed toward symptoms, quality of life, and exacerbation prevention. Current standard therapies are divided into two categories: bronchodilators and anti-inflammatory agents. The bronchodilators include beta-2 agonists, anticholinergics, and methylxanthines. Anti-inflammatory agents consist of inhaled and oral corticosteroids.

Isoenzyme phosphodiesterase 4 (PDE_4) inhibitors are a new class of medication in the management of COPD. They function by inhibiting the breakdown of cyclic adenosine monophosphate, which results in smooth muscle relaxation and inhibiting release of inflammatory mediators in the airways. Due to the dual mechanism of action, these new medications are a significant area of research for COPD treatment. [2] This review focuses on addition of PDE_4 inhibitors to standard therapies to decrease frequency of COPD exacerbations.

Summary of the evidence

Chong et al. performed a meta-analysis to study both the efficacy and safety of PDE_4 inhibitors in stable COPD management. There was a total of 29 randomized control trials (RCTs) included in the investigation: 15 studying roflumilast and 14 studying cilomast. Any trials that were investigating effects of a single dose of a PDE_4 inhibitor or use in acute exacerbation of COPD were excluded. The roflumilast and cilomilast studies had a total of 12,645 and 6,457 patients respectively. In these investigations a PDE_4 inhibitor was compared to placebo over the course of 12 to 52 weeks. Subjects included in the study met the following criteria: adults greater than 18 years of age with COPD, post-bronchodilator forced expiratory volume in one second(FEV1)/forced vital capacity (FVC) less than or equal to 0.7. COPD could be diagnosed based on criteria from the American Thoracic Society, European Respiratory Society, or Global Initiative for Chronic Obstructive Lung Disease. For this study primary outcomes included changes in lung function and quality of life, while incidence of exacerbations was evaluated as a secondary outcome. Although there was not a drastic change, the trials that evaluated COPD exacerbation frequency showed a statistically significant decrease. Compared to placebo, PDE_4 inhibitors led to a relative reduction of 23% in number of patients experiencing at least one exacerbation in 12 to 52 weeks. There was no significant difference in efficacy of roflumilast or cilomilast. The average number of exacerbations per patient per year was similarly decreased by 13% in the PDE_4 group (rate ratio 0.87). In one investigation there was a mean difference of −0.25 in number of exacerbations over a 24-week period. These findings demonstrate the ability of PDE_4 inhibitors to decrease COPD exacerbation frequency. [2]

Martinez et al. performed a recent RCT, not included in the previous meta-analysis. This study aimed to determine the effect of roflumilast on COPD exacerbation in patients with

severe COPD already on an inhaled corticosteroid (ICS)-long-acting beta-2 agonist (LABA) combination with or without a long-acting muscarinic agonist (LAMA). The trial was a 1-year, double-blind, placebo-controlled RCT with patients gathered from 201 centers in 21 countries. Inclusion criteria consisted of age ≥40 years, ≥20 pack-year smoking history, COPD with FEV1/FVC ≤0.7 and FEV1 <50% predicted, chronic bronchitis symptoms, and history of ≥two exacerbations in the past year. Patients also had to be on an ICS-LABA combination for at least one year prior with a fixed dose for 3 months or more. Subjects were randomized to treatment for one year with either roflumilast or placebo. The primary endpoint was the number of moderate-severe exacerbations per patient per year with number of severe exacerbations per patient per year as a secondary endpoint. Exacerbations requiring oral or parenteral steroids were defined as moderate, while severe exacerbations led to hospitalization or death. Findings of this study were similar to those in the meta-analysis by Chong et al. The rate ratio of moderate-to-severe exacerbations for the intention to treat (ITT) group and per protocol (PP) group was 0.868 and 0.806 respectively. The more significant findings of this trial not investigated in the previous meta-analysis were the rates of severe exacerbations and exacerbations leading to hospitalization. For severe exacerbations the ITT group rate ratio was 0.757, and the PP group was even lower at 0.668. The rate ratio for exacerbations leading to hospital admission was similarly decreased to 0.761. Like the previous study, this investigation shows that roflumilast has a statistically significant effect on frequency of exacerbations. [3]

There were other outcomes evaluated in both of these investigations that are also important to mention. Both studies showed that roflumilast increases FEV_1 by approximately 50mL. Despite this increase, there was no improvement in symptoms or quality of life. Similarly, there was no increase in exercise tolerance even with the improved FEV_1. [2,3] There was also no difference in mortality between the roflumilast group and the placebo group in the trial by Martinez et al. [3] These findings suggest the benefit of roflumilast is likely limited to improvement in COPD exacerbation frequency alone.

Level of evidence: A

Answer: Yes

Conclusion

Exacerbations are an important complication of COPD, because they lead to decline in lung function as well as increased cost through medication use and hospitalization. Current research argues that roflumilast has a statistically significant impact on preventing exacerbations. Longer investigations need to be done to determine cost-effectiveness and effect on mortality.

References

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