Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic obstructive pulmonary disease (COPD) is associated with cough, sputum production or dyspnoea and a reduction in lung function, quality of life and life expectancy. Apart from smoking cessation, there are no other treatments that slow lung function decline. Roflumilast and cilomilast are oral phosphodiesterase 4 (PDE_4) inhibitors proposed to reduce the airway inflammation and bronchoconstriction seen in COPD.

Objectives

To evaluate the efficacy and safety of oral PDE_4 inhibitors in the management of stable COPD.

Search methods

We identified randomised controlled trials (RCTs) from the Cochrane Airways Group Specialised Register of trials (date of last search June 2013). We found other trials from web-based clinical trial registers.

Selection criteria

We included RCTs if they compared oral PDE_4 inhibitors with placebo in people with COPD. We allowed co-administration of standard COPD therapy.

Data collection and analysis

One review author extracted data and a second review author checked the data, before entry into The Cochrane Collaboration software program (RevMan version 5.2). We reported pooled data as mean differences (MD), standardised mean differences (SMD) or odds ratios (OR).

Main results

Twenty-nine separate RCTs studying roflumilast (15 trials, 12,654 patients) or cilomilast (14 trials, 6457 patients) met the inclusion criteria, with a duration between six weeks and one year. These included people across international study centres with moderate to very severe COPD (GOLD grades II-IV), with a mean age of 64 years.

Treatment with a PDE_4 inhibitor was associated with a significant improvement in forced expiratory volume in one second (FEV_1) over the trial period compared with placebo (MD 45.60 mL; 95% confidence interval (CI) 39.45 to 51.75, 22 trials with 15,670 participants,

moderate quality evidence due to moderate levels of heterogeneity and risk of reporting bias). There were small improvements in quality of life (St George's Respiratory Questionnaire MD -1.04; 95% CI -1.66 to -0.41, 10 trials with 7618 participants, moderate quality evidence due to moderate levels of heterogeneity and risk of reporting bias) and COPD-related symptoms, but no change in exercise tolerance. Treatment with a PDE_4 inhibitor was associated with a reduced likelihood of COPD exacerbation (OR 0.77; 95% CI 0.71 to 0.83, high quality evidence). For every 100 people treated with PDE_4 inhibitors, six more remained exacerbation-free during the study period compared with placebo (number needed to treat for an additional beneficial effect (NNTB) 20; 95% CI 16 to 27). More participants in the treatment groups experienced non-serious adverse events compared with controls, particularly gastrointestinal symptoms and headache. Roflumilast in particular was associated with weight loss during the trial period and an increase in insomnia and depressive mood symptoms. Participants treated with PDE_4 inhibitors were also more likely to withdraw from the trials because of adverse effects; on average 24% in the treatment groups withdrew compared with 19% in the control groups.

Authors' conclusions

In people with COPD, PDE_4 inhibitors offered benefit over placebo in improving lung function and reducing the likelihood of exacerbations; however, they had little impact on quality of life or symptoms. Gastrointestinal adverse effects and weight loss were common, and safety data submitted to the US Food and Drug Administration (FDA) have raised concerns over psychiatric adverse events with roflumilast. The optimum place of PDE_4 inhibitors in COPD management therefore remains to be defined. Longer-term trials are needed to determine whether or not PDE_4 inhibitors modify FEV_1 decline, hospitalisation or mortality in COPD.

PLAIN LANGUAGE SUMMARY

In people with chronic obstructive pulmonary disease (COPD), what are the benefits and risks of phosphodiesterase 4 inhibitors?

Background of the review

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition caused by damage from harmful chemicals that are breathed in. This condition is predominantly seen in people who smoke tobacco. Chemicals in cigarettes set up a cascade of inflammatory reactions, which on one hand damage the structures in the lung responsible for the exchange of oxygen into the bloodstream, but also increase mucus production in the airways. These two processes leads to intermittent symptoms of breathlessness and decreased capacity to perform day to day tasks. In addition, people with COPD are at greater risk of developing exacerbations ('flare ups') which become more frequent and severe over time. People vary in terms of how they are affected by COPD. This is in part related to the severity of the disease but also to differences in response to medicines, an individual's fitness and coexistent conditions. The only way to prevent further lung damage in most people is to stop smoking. General approaches such as exercise, nutrition and vaccinations against influenza and pneumococcal infections are important in maintaining health.

Medicines prescribed to manage COPD generally aim to improve symptoms, reduce exacerbations or both. In the early stages, bronchodilator medicines are helpful because these relax the small muscles in the airway allowing more air to move freely in and out of the lungs. Some long-acting agents may reduce exacerbations. Steroid-containing inhalers may be added specifically to target inflammation in the lungs and thus modestly reduce the number of exacerbations.

Phosphodiesterase 4 (PDE_4) inhibitors are a relatively new class of medicines that have been marketed to improve COPD. They have both bronchodilator and anti-inflammatory effects. Moreover, the two currently available medicines, roflumilast and cilomilast, are taken as a tablet. Our review collated and analysed existing trials to define the benefits and risks of PDE_4 inhibitors in COPD.

What did we look at?

We found 29 trials on 12,654 adults, completed up to June 2013. This consisted mainly of trials in people with moderate to severe disease who discontinued other regular COPD medications. However, there were three trials that allowed continuation of inhaled corticosteroids and two that continued long-acting bronchodilators. The trials ranged from 6 to 52 weeks duration and the average age of participants was 64 years. The trials were all sponsored by the manufacturers of PDE_4 inhibitors.

What did we find out?

Compared with placebo, these medicines provide a small improvement in lung function measurements and reduce the likelihood of an exacerbation of COPD. Based on these results, we would expect that out of 100 people who took PDE_4 inhibitors every day for a year, 24 would experience at least one exacerbation which is six fewer than others who did not receive these medicines.

However, people reported that these medicines only provided a small effect on levels of breathlessness and quality of life. On the other hand, around 5% to 10% of people in trials who received roflumilast or cilomilast reported side effects such as diarrhoea, nausea and vomiting. There was also a two- to three-fold increase in the risk of sleep or mood disturbance, although overall the total number of reported incidents was still small. There was no effect on rates of hospitalisation and deaths. Trial duration and COPD severity did not influence the size of the effects. Furthermore, there was a suggestion of an additive benefit on top of inhaled corticosteroids or bronchodilators, but the number of studies that reported this was small.

Quality of the evidence

The studies were generally well designed, as people did not know if they were receiving this new treatment or a placebo medicine. Overall we rated the evidence as being of moderate to high quality.

It is of concern that results seen in trials published in journals by pharmaceutical companies showed a greater benefit of these medicines than those which were unpublished. The psychiatric adverse effects data remain unpublished. Longer-term trials are necessary to get a more accurate estimate of the benefits and safety of these medicines over time, including whether they slow COPD disease progression.