Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Chronic obstructive pulmonary disease: the effect of roflumilast on exacerbations in people with severe disease – the REACT study

In a double-blind randomised controlled trial, roflumilast reduced the relative rate of moderate to severe exacerbations in people with chronic obstructive pulmonary disease (COPD) who were also taking inhaled corticosteroid/long acting beta-2 agonist combination therapy by 13.2% over 1 year compared with placebo. This reduction was not statistically or clinically significant based on the primary analysis in the intention-to-treat population. Secondary outcomes relating to severe exacerbations were statistically and clinically significantly reduced with roflumilast. Currently, roflumilast is only recommended by NICE for people with COPD who are taking part in a clinical trial.

Overview and current advice

Roflumilast (Daxas) is an oral phosphodiesterase-4 inhibitor with an associated anti-inflammatory action. NICE technology appraisal guidance on roflumilast for the management of severe chronic obstructive pulmonary disease (published in 2012) recommended roflumilast only as part of a clinical trial for adults with severe COPD and a history of frequent exacerbations, as an add-on to bronchodilator treatment. The guidance also recommended that a study should be conducted to generate robust evidence about the benefits of roflumilast as an add-on to long acting muscarinic antagonists (LAMA) plus long acting beta-2 agonists (LABA) plus inhaled corticosteroids (ICS) or LAMA plus LABA for those people who are intolerant to ICS. A decision regarding the updated status of the NICE technology appraisal guidance will be made in Autumn 2015.

The NICE guideline on chronic obstructive pulmonary disease (published in 2010) makes recommendations on the sequence of inhaled therapies and other treatments for managing stable COPD, but does not include roflumilast. The NICE pathway on COPD brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A large, multicentre study (REACT) investigated the effectiveness of roflumilast in people with severe COPD (n=1945) over 1 year\(^1\). In this double-blind, parallel group randomised controlled trial (RCT),
people were recruited from 203 centres (outpatient clinics, hospitals, specialist pulmonologists and family doctors) in 21 countries. Participants were 40 years or older (mean age 65 years, 75% male) with a smoking history of at least 20 pack years and severe airflow limitation (forced expiratory volume in 1 second [FEV\textsubscript{1}] of 50% or less and FEV\textsubscript{1}/forced vital capacity [FVC] ratio less than 0.70). Participants had a history of at least 2 exacerbations in the previous year, symptoms of chronic bronchitis and were on a stable dose of ICS/LABA combination therapy prior to study entry; 70% were also using a LAMA. Baseline characteristics were balanced across both groups.

Following a 4-week run in period, people were randomised to either once daily oral roflumilast 500 microgram (n=973) or placebo (n=972) for 52 weeks, alongside their usual ICS/LABA combination inhaler and inhaled tiotropium if they were already taking this. Ten people did not receive any drug treatment after randomisation, therefore the intention-to-treat population was n=1935. Allocation was concealed. In the case of exacerbations occurring through the course of the study, pre-defined rescue therapy was allowed at the physician’s discretion including 40 mg prednisolone daily for 7 to 14 days and appropriate antibiotics. A salbutamol inhaler was also permitted.

The primary outcome was the rate of moderate to severe COPD exacerbations per person per year. Pre-defined criteria for moderate exacerbations were those requiring treatment with systemic corticosteroids (with or without antibiotics) and severe exacerbations were those requiring hospital admission, or which led to death, or both. Secondary outcomes included change in lung function (change from baseline in FEV\textsubscript{1}) and the rate of severe exacerbations per person per year. Any adverse events were also recorded. The primary end point was analysed using Poisson regression modelling, with a pre-defined sensitivity analysis using negative binomial regression modelling.

In the intention-to-treat population, there was a 13.2% relative risk reduction in the rate of moderate to severe exacerbations with roflumilast compared with placebo, which was not statistically significant in the primary Poisson regression analysis (rate ratio [RR] 0.868, 95% confidence interval [CI] 0.753 to 1.002, p=0.0529). This reduction was statistically significant in the negative binomial regression analysis (RR 0.858, 95% CI 0.740 to 0.995, p=0.0424). In the per-protocol population, using Poisson regression analysis, the reduction in the rate of moderate to severe exacerbations with roflumilast compared with placebo was statistically significant (RR 0.806, 95% CI 0.688 to 0.943, p=0.0070).

For secondary outcomes, using pre-defined alternative definitions for exacerbations and further sensitivity analysis in the intention-to-treat population, compared with placebo, there was a statistically significant 24.3% relative risk reduction in severe events with roflumilast (RR 0.757, 95% CI 0.601 to 0.952, p=0.0175) and 23.9% relative risk reduction in exacerbations requiring hospital admission (RR 0.761, 95% CI 0.604 to 0.960, p=0.0209). Treatment difference for changes from baseline in lung function for the roflumilast group compared with the placebo group were statistically significant (treatment difference for post-bronchodilator FEV\textsubscript{1} +56ml, 95% CI 38 to 73 ml, p<0.0001). Discontinuations were 28% in the roflumilast group compared with 20% in the placebo group, and more people withdrew in the roflumilast group compared with the placebo group in the first 12 weeks after randomisation.

Adverse events were reported by 67% of the roflumilast group and 59% of the placebo group, with serious adverse events reported by 26% and 30% respectively. More people withdrew because of adverse events in the roflumilast group (11% compared with 5%). The most frequently reported adverse events were COPD exacerbations (15% with roflumilast compared with 19% with placebo), diarrhoea (10% compared with 4% respectively), weight loss (9% compared with 3% respectively) and nausea (6% compared with 2% respectively). Mortality rates were the same in both groups (2%); as were major adverse cardiovascular events (2% in both groups). There was no increase in the incidence of pneumonia with roflumilast.
The authors highlight a number of limitations with the study. They state that the observed exacerbation rate was 25% lower than anticipated which may have influenced the results. In addition, the mortality rate was lower than reported previously in similar populations even though there was a high incidence of hospitalisations, which is an established risk factor for mortality. Not all participants were followed up until the end of the study and the authors identify that this could have led to an underestimation of the true mortality risk.

**Commentary**

**Commentary provided by Dr Kevin Gruffydd-Jones, BM BCH, FRCGP, General Practitioner, Box, Wiltshire, NICE COPD Guideline Development Group Member**

This is a well conducted large multinational, industry sponsored, randomised controlled study of roflumilast versus placebo in people with moderate to severe airflow limitation over 1 year. The inclusion criteria reflect a specific group of people who had 2 or more exacerbations of COPD in the previous year and who had been stable on inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) therapy (70% of participants were on triple therapy with a long-acting anti muscarinic agent). Importantly the study participants were of a “chronic bronchitis” phenotype and the results are not applicable to all people with severe COPD. The modest reduction in moderate to severe exacerbations could be accounted for by an overall low rate of exacerbations in both groups. The significant reduction in hospital admissions of 23.9% (albeit a secondary outcome) in the active group is more compelling.

The side effects of diarrhoea and weight loss may limit use of the drug in a group of people already with significant co-morbidities such as low body mass index (BMI). However, this study, combined with previous studies of the drug do suggest a place for roflumilast in people with severe airflow limitation with a “chronic bronchitic, exacerbator” phenotype. The international Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (updated 2015) already suggest a role for roflumilast in this group of people and, as noted above, NICE will make a decision regarding the updated status of its technology appraisal guidance in Autumn 2015.

**Study sponsorship**

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**References**


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