Roflumilast for the treatment of chronic obstructive pulmonary disorder

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Evaluation of: **Rabe KF, Bateman ED, O'Donnell D Witte S, Bredenbroker D, Bethke TD. Roflumilast – an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 366 (9485), 563–571 (2005)** [1].

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by progressive, irreversible airway obstruction and respiratory symptoms, aggravating during exacerbation and with disease progression. Available therapies for treatment of stable COPD include bronchodilators and inhaled corticosteroids, which only relieve symptoms, prevent exacerbations, potentially improve health-related quality of life and slow disease progression. Novel anti-inflammatory therapies, such as phosphodiesterase-4 inhibitors, are currently under development for the treatment of COPD, and among them, roflumilast has demonstrated promising efficacy and safety in several clinical trials, including the Phase III study discussed herein.

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease which results in progressive airway obstruction and is usually triggered by smoking, and less commonly, by other causative factors. It is characterized clinically by the presence of symptoms such as dyspnea, cough and sputum production, which aggravate during exacerbations and with disease progression. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) outlines diagnostic, therapeutic and preventive guidelines for COPD [101]. According to GOLD, management of stable COPD is complex and depends on the severity stage, that is, on the presence of symptoms and the degree of lung function impairment (airway obstruction), and is aimed at relieving symptoms, preventing and treating exacerbations, improving health-related quality of life (HRQoL – health status), reducing mortality and preventing disease progression [101].

Pharmacological agents available for the treatment of stable COPD include β2-agonists, anticholinergics, inhaled corticosteroids (ICSs) and methylxantines. None of these are capable of reversing airway obstruction, but instead work by slowing disease progression. ICSs failed to show the same effectiveness in asthma [101].

Phosphodiesterase (PDE)4 inhibitors represent an evolving class of anti-inflammatory compounds which could be potentially used in the treatment of COPD. This study assessed the safety and efficacy of roflumilast, a PDE4 inhibitor, in the treatment of COPD.

Keywords: COPD, efficacy, roflumilast, safety

Methods & results

The authors carried out a Phase III, multicenter, double-blind, randomized, placebo-controlled study in stable COPD patients who received placebo, roflumilast 250 µg, or roflumilast 500 µg orally once-daily over 24 weeks. Medications concomitantly allowed included salbutamol (rescue medication), short-acting anticholinergics (constantly) and oral corticosteroids (short course, for exacerbations occuring during the active phase of treatment).

Primary efficacy outcomes included postbronchodilator forced expiratory volume in 1 sec (FEV1) and HRQoL as the total score of Saint George's Respiratory Questionnaire (SGRQ) analyzed as changes from baseline to the end point (last observation carried forward) and secondary efficacy outcomes were prebronchodilator FEV1, postbronchodilator forced vital capacity (FVC), postbronchodilator FEV6, postbronchodilator forced expiratory flow between 25 and 75% of the vital capacity ($FEF_{25–75}$), and number of COPD exacerbations analyzed similar to the primary outcomes. Adverse events were assessed over the study. The intention-to-treat analysis included 1411 COPD patients (n = 280) randomized to receive placebo (n = 576), roflumilast 250 µg (n = 555) and 500 µg.

Both roflumilast doses increased postbronchodilator FEV1 over the study period as compared with baseline ($p < 0.05$), and with placebo ($p < 0.03$), the improvement being significant after the first 4 weeks of treatment, whereas in

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placebo group, postbronchodilator FEV1 declined significantly over the study period. Roflumilast 250 µg improved FEV1 from baseline by 74 ml compared with placebo, whereas an improvement with roflumilast 500 µg of 97 ml ($p < 0.0001$) was observed. *Post hoc* analysis in COPD severity subgroups yielded that both roflumilast doses increased FEV1 significantly from baseline compared with placebo ($p = 0.0001$ for 250 µg and $p < 0.0001$ for 500 µg) in moderate COPD, whereas roflumilast 500 µg only, increased FEV1 significantly from baseline compared with placebo ($p = 0.0010$) in severe COPD.

HRQoL improved significantly (i.e., SGRQ total score reduced) in all treatment groups and placebo compared with baseline (-3.4 units $p < 0.0001$ for roflumilast 250 µg, -3.5 units $p < 0.0001$ for roflumilast 500 µg and -1.8 units $p = 0.02$ for placebo). All component scores (symptoms, activity, impact) were significantly improved when compared with baseline, the most significant effect being found in symptom scores (-3.6 units with placebo, -6 units with roflumilast 250 µg, -4.6 units with roflumilast 500 µg). However none of these improvements were significant when compared with placebo.

Both roflumilast doses improved prebronchodilator FEV1 independently from baseline, whereas in the placebo group this measure declined. Prebronchodilator FEV1 improvement at 24 weeks compared with placebo was 64 ml ($p = 0.0006$) for roflumilast 250 µg and 88 ml ($p < 0.0001$) for roflumilast 500 µg. Dose-dependent improvements were reported for both pre- and postbronchodilator FEV1. For all other secondary pulmonary 'functional' outcomes (FEV6, $FEF_{25–75}$ and FVC) a similar pattern of improvement was reported.

COPD exacerbations over the study period were more frequent in the placebo group and roflumilast 250 µg groups than in the roflumilast 500 µg group ($p = 0.0114$). Roflumilast treatment also reduced the mean exacerbation number/patient compared with placebo (1.13 in placebo group; 1.03 in roflumilast 250 µg and 0.75 in roflumilast 500 µg, $p = 0.0029$) mainly due to the reduction in the number of mild exacerbations (42% reduction of the number of mild exacerbations in roflumilast 500 µg compared with placebo).

The most common adverse events were moderate and severe COPD exacerbations as well as nasopharyngitis. Adverse events considered to be related to study medication were reported in 4% of placebo, 8% of roflumilast 250 µg and 17% of roflumilast 500 µg patients. Diarrhea was the most common medication-related adverse event, followed by nausea and headache. The most common adverse event leading to withdrawal was COPD exacerbation which was also the most serious adverse event found throughout the study.

Discussion

The current study shows that, compared with placebo and allowed inhaled medication, roflumilast improved lung function and reduced exacerbation numbers in COPD patients. Pre- and postbronchodilator FEV1 and FVC, SGRQ subcomponent and total scores improved significantly in both roflumilast groups compared with baseline values, whereas in the placebo group these variables deteriorated. The incidence of adverse events increased with dosage and diarrhea. Nausea and headache were the most common side effects.

Pharmacological agents with anti-inflammatory activity, such as ICSs, had a different impact on the above-mentioned outcome variables, whereas methylxantines and other PDE4 inhibitors (cilomilast) had similar therapeutic effects.

Inhaled corticosteroids in COPD

In a meta-analysis of the studies assessing the effect of ICSs on lung function in 3715 COPD patients, it was found that they reduced the FEV1 decline rate by 7.7 ml/year (95% confidence interval [CI]: 1.3–14.2; $p = 0.02$), this effect being greater at higher corticosteroid doses (9.9 ml/year; 95% CI: 2.3–17.5, $p = 0.01$) [2].

The impact of ICSs on HRQoL, however, is still unclear. Fluticasone propionate 500 µg twice-daily, for example, did not show any HRQoL (SGRQ) significant improvement compared with placebo when given after an oral corticosteroid run-in therapy, but did impact significantly on HRQoL deterioration on a long-term basis [3–5]. However, when administered without any similar run-in therapy, it did improve HRQoL [6].

Conversely, budesonide 400 µg twice-daily produced improvements in HRQoL when given after run-in oral prednisolone, an effect augmented as in the case of fluticasone propionate by the addition of a long-acting β2 agonist (LABAs, formoterol, salmeterol respectively) [6–8].

ICSs reduced exacerbation number and severity in COPD patients when given either alone or in combination with LABAs, which probably contributed to the delay in HRQoL observed in one study [5–7,9].

Theophylline

Theophylline is a nonselective PDE inhibitor with bronchodilator activity, which has been in use for both asthma and COPD for many years [10]. Although inhaled bronchodilators such as anticholinergics or β2 agonists are preferred to theophylline in the treatment of stable COPD, the latter is recommended for use in more severe patients in order to augment the bronchodilator effect of the former and for restoring the reduced corticosteroid sensitivity [11,12].

Theophylline has been shown to improve lung function, exercise capacity and HRQoL in COPD [13]. However the narrow therapeutic index and potentially serious drug interactions limit its widespread use.

Cilomilast

Cilomilast is another PDE4 inhibitor currently in development for the treatment of COPD. A 6-week Phase II, randomized, dose-ranging study found that cilomilast 15 mg twice-daily increased trough postbronchodilator FEV1 by 0.10 l, but no significant impact on HRQoL (SGRQ) as compared with placebo was found [14].

In a 6-month, randomized, Phase III study, cilomilast 15 mg twice-daily improved trough FEV1 by 80 ml, reduced the risk of exacerbation by 39% and significantly improved HRQoL (SGRQ) [15–17]. Gastrointestinal adverse events (diarrhea, nausea, abdominal pain) were more commonly found in patients receiving cilomilast, but were mild-to-moderate in intensity [18].

Expert commentary

The current study demonstrated that in COPD patients, roflumilast at either 250 or 500 µg daily significantly improved lung function in moderate COPD patients, whereas only the highest doses had this effect in severe COPD patients. Roflumilast at either dose reduced the exacerbation rate and number of exacerbations per patient but had no significant impact on HRQoL as compared with placebo. No *post hoc* subgroup (severity) analysis similar to that on lung function has been performed for exacerbation number and HRQoL. Therefore, based on the current data it cannot be inferred which is/are the COPD severity subclasses that would benefit most from this therapy.

Despite these, roflumilast could become, in the near future, an effective anti-inflammatory therapy for COPD.

Highlights

- Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease of the airways in which current anti-inflammatory therapies, such as inhaled corticosteroids (ICSs) and methylxantines, have modest efficacy.
- In COPD, inhaled corticosteroids reduce the number and severity of exacerbations, and slowed lung function decline; however, their impact on health-related quality of life (HRQoL) is unclear.
- Newer, potential anti-inflammatory agents are represented by phosphodiesterase 4 inhibitors, such as cilomilast and roflumilast.
- Roflumilast demonstrated its efficacy in improving lung function and reducing the number of exacerbations. It's therapeutic impact on HRQoL and the COPD severity subset, that would benefit most from such a therapy, remains to be clarified.

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