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KEY PAPER EVALUATION

Roflumilast in patients with advanced chronic obstructive pulmonary disease: towards a better-targeted use

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ABSTRACT

Introduction: For patients with chronic obstructive pulmonary disease (COPD), one of the main goals in its management is to reduce the number of disease exacerbations. Roflumilast is an anti-inflammatory compound used in patients with advanced COPD and chronic bronchitis in order to fulfill this objective. However, this is not always easily achieved due to the heterogeneity of the population. Clinical trial data can allow more in-depth analysis in order to identify predictors for maximal efficacy in different patient populations.

Areas covered: A post hoc pooled data analysis derived from two large-scale randomized controlled trials helped to better define the disease subsets in which roflumilast would exert the maximal therapeutic effect. These are represented by patients with prior hospitalizations for COPD exacerbations and by patients with higher values for eosinophil blood count. This analysis is the focus of our key paper evaluation.

Expert opinion: This pooled data analysis suggests that a phenotype/endotype guided therapy has the potential to be impactful on overall survival by reducing the number of exacerbations and increase the life span of patients.

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Chronic bronchitis; COPD; exacerbations; eosinophil; roflumilast; prognosis

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent condition of the airways characterized by bothering symptoms such as breathlessness, cough and sputum and by their exacerbations that are usually triggered by lower respiratory tract infections which can further worsen the health status and sometimes be lethal. The existing management guidelines generally recommend inhalatory therapies (bronchodilators, inhaled corticosteroids) as mainstay, their indication alone or in combination being mainly made based on the disease stage [1]. Some other medications such as roflumilast can be added based on specific criteria (see below). Among the goals of such an approach the reduction of exacerbations and in particular of hospitalizations is essential. However, often, the pharmacological management has to be further tailored taking into account some particular markers of efficacy. Such markers are identified as a result of secondary analyses (post hoc) in clinical trials. They are very valuable because they can help with a more targeted therapy in COPD. This is the case of the markers of efficacy identified as a result of a pooled data analysis from two clinical trials investigating roflumilast in COPD and this is the focus of our key paper evaluation [2].

2. Methods and results

This was a pooled analysis of efficacy and safety derived from two larger-scale randomized trials, the REACT study and the RESPOND study [2]. The REACT study was a phase III-IV 52 week year multicenter placebo-controlled trial evaluating the efficacy and safety of roflumilast 500 µg added to a fixed dose of inhaled long-acting β2 agonists/corticosteroid combination (with or without an inhaled long-acting muscarinic (LAMA) agent) on severe to very severe COPD patients who had a chronic bronchitis phenotype and at least two exacerbations during the previous year [3,4].

The RESPOND study was a 52-week phase IV randomized placebo-controlled study with a similar design and study population [4,5].

The primary endpoint was the same and was represented by the rate of moderate or severe COPD exacerbations per patient and per year (MSE), whereas the secondary endpoints included severe exacerbations rate, the number of MSE requiring antibiotics and the change from baseline in trough FEV1.

In the first study roflumilast was found to reduce the MSE rate versus placebo although with borderline statistical significance (13.2 lower with roflumilast $p = 0.052$), whereas in the second study roflumilast did not improve significantly the primary endpoint versus placebo but was found to have a

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significant therapeutic effect in a post hoc analysis performed in patients nowadays labeled as being 'frequent exacerbators (>3 exacerbations/year)'.

The need to better characterize the COPD phenotypes in which roflumilast would be the most efficient triggered the pooled data analysis according to relevant pre-specified criteria such as blood eosinophil count (overall <150 cells/µl versus ≥150 cells/µl; or <150 cells/µl versus 150-<300 cells/µl versus ≥300 cells/µl) or the exacerbations number in the previous year (2 versus >2) and the number of hospitalizations for COPD exacerbations in the previous year (0 versus ≥1).

The pooled intention to treat population (used for efficacy, respectively, for safety analyses) included 4287 patients (2147 receiving roflumilast and 2140 receiving placebo). Most of the patients analyzed in both groups had severe COPD (64%), and received inhalatory LAMA at baseline (56.9%). A proportion of 32% of patients had at least 1 hospitalization during the previous year and 19.5% of the patients had a baseline blood eosinophil count of ≥300 cells/µl. The study population subsets obtained with the categorizing criteria were comparable in terms of main baseline variables except for the prior hospitalization subset which included more current smokers, more LAMA users and a higher number of patients with at least 2 exacerbations over the previous year than no hospitalizations subset.

Overall roflumilast therapy was associated with a significant improvement of the primary endpoint (12.3 reduction of the MSE rate, 1.01 versus 1.16 with placebo, $p = 0.0008$). The maximum therapeutic effect on the primary endpoint was reported in patients with at least one COPD hospitalization and with blood eosinophil count of ≥150 cells/µl (34.5 MSE rate reduction with roflumilast versus placebo, RR = 0.65, $p = 0.0003$). In patients with at least one hospitalization ($n = 1386$), a 25.6% MSE rate reduction versus placebo (rate ratio (RR) 0.74, $p = 0.0005$) was found, whereas in patients without prior hospitalization no significant MSE decrease versus placebo was reported. In patients with more than 2 exacerbations during the previous year roflumilast reduced the MSE rate by 20.5% versus placebo (RR = 0.79, $p = 0.01$), with no significant reduction compared to placebo in patients with 2 exacerbations. Patients with ≥150 cells/µl experienced a 19.1% reduction in MSE rate (RR = 0.81, $p = 0.002$) whereas those with ≥300 cells/µl had a RR for MSE rate of 0.77 ($p = 0.02$).

The severe exacerbation (SE) rate was significantly reduced in patients hospitalized for a COPD exacerbation during the previous year (29.7%, RR = 0.7, $p = 0.003$),in patients with >2 exacerbations(29.8, RR = 0.7, $p = 0.004$) and in patients with ≥150 cells/µl (22.4%, RR = 0.78, $p = 0.03$).

Safety analysis identified adverse events (AEs) in 67.7% patients receiving roflumilast and 62.1% of patients receiving placebo. The most commonly reported AEs included COPD exacerbation, diarrhoea, pneumonia and weight loss. Diarrhea, weight loss, headache, and nausea were the AEs most commonly reported in roflumilast group. The incidence of serious AEs was 20.0% in roflumilast group and 20.9% in the placebo group. The mortality rates over study period were comparable (2.1% in roflumilast, respectively, 2% in placebo group).

3. Significance of the results

This analysis demonstrates that roflumilast, when added to inhalatory therapies used in patients with advanced COPD is able to reduce the disease-related morbidity i.e. the number of moderate/severe exacerbations. However, the fact that the efficacy of this compound was not constant across the initial samples of patients but showed superior efficacy in certain patients raised the need to better define this population with maximal therapeutic benefit. The findings previously discussed suggested that frequently hospitalized COPD patients (i.e. patients with at least one hospitalization for COPD exacerbation over the last year) and with increased blood eosinophil count might benefit the most from such a therapy.

4. Conclusions

The results of this pooled analysis support the phenotype/endotype-based therapeutic approach in COPD patients. Currently the proposed algorithm takes into account the severity of the airways obstruction and of dyspnea, the health status impairment and the risk of subsequent exacerbations [1].

In these algorithms, roflumilast is indicated in addition to inhaled combined regimen LABA+ICS+LAMA in COPD patients with chronic bronchitis, FEV1 <50% and frequent exacerbations.

5. Expert opinion

In COPD, the therapeutic indication of roflumilast is built upon that formulated by the European Medicines Agency in the European Union and by the Food and Drug Association in the USA recommending roflumilast in COPD patients with similar FEV1, chronic bronchitis and who have frequent exacerbations while on bronchodilator therapy [6].

The further refinement of this initial therapeutic indication is based on the findings from analyses such as the one discussed in this draft which attempted to better characterize the populations' subsets in whom exacerbation rate reduction was higher than that in the overall population.

Such population subsets can be defined in clinical practice according to phenotype (chronic bronchitis, frequent exacerbators) and endotype features (increased blood eosinophilia). A phenotype/endotype approach based on previously demonstrated clinical efficacy would have the potential to improve the prognostic of the disease on a long-term basis, given that with each 'spared' exacerbation the trajectory of the disease towards end-stage is lowered and hence survival is improved.

The impact of roflumilast on survival in COPD patients was not evaluated so far. Previous studies demonstrated that inhaled LABA +ICS combinations were able to reduce mortality rate and to improve health status in large cohorts of COPD patients with less impaired airways obstruction (GOLD stage II) [7]. Given the fact that roflumilast is intended for patients with more severe disease, the improvement of the survival rate as a result of the reduction of exacerbations (and of severe exacerbation in particular) rate, would be an even stronger indicator of efficacy on long-term basis.

The fact that the degree of eosinophilia was proportionally associated with a more important reduction of exacerbations rate raises two issues: one is related to the use of blood

eosinophilia as a biomarker of efficacy of roflumilast in COPD, beyond the number of the subsequent exacerbations, whereas the other one is related to the potential suitability of this compound in patients with asthma-COPD overlap syndrome (ACOS) . The above-discussed analysis reported that in patients with the most severe blood eosinophilia (>300 cells/μl), roflumilast had the highest effect on the reduction of the moderate/severe exacerbations. It is not known if this therapeutic effect was associated with a reduction of the eosinophil count and if this latter variable if 'kept' under a certain threshold level would be associated with exacerbation-free disease.

Phosphodiesterase-4 inhibitors and roflumilast, in particular, were previously evaluated in asthma and their rather inconstant efficacy was probably the cause for compounds inability to progress to later phase clinical studies. However, there are reports of improvement of lung function, especially when roflumilast was given as an add-on therapy for inhaled corticosteroids [8]. The analysis of the pooled data was not done based on the eosinophil count so that in this setting it was not clear if this biomarker can be used to predict the efficacy of the compound. A recently published short-term study performed in COPD patients with various degrees of airways inflammation (i.e. including GOLD stage II and III patients) demonstrated that 16 week therapy with roflumilast was able to reduce eosinophil count in the airways, suggesting an increased efficacy in COPD with more prominent involvement of this cell at bronchial level [9].

However, the ACO phenotype recently recognized in COPD and more and more frequently identified as a subset with both clinical and therapeutic peculiarities, was not considered as a potential beneficiary from roflumilast therapy. This would be an interesting hypothesis to be verified and the discussed results support its testing.

Therefore, post-hoc analysis of this kind can be very useful in better shaping the pharmacological therapy in COPD patients and as outlined above such a phenotype- endotype oriented approach can have the potential to improve the life span in patients with advanced COPD.

Furthermore, all the most recent data demonstrating a more significant therapeutic effect on eosinophilic inflammation of the airways reopens the case for further evaluation of this compound in asthma endotypes in which this is the most prominent pathogenic feature.

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Declaration of interest

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