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Roflumilast added to triple therapy in patients with severe COPD: A real life study

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ABSTRACT

Background: Roflumilast is used in severe chronic obstructive pulmonary disease (COPD) patients with frequent exacerbations. However, limited information is available on its impact in a "real-life" population that may be receiving triple therapy.
Objective: This study aimed to evaluate the effectiveness and safety of roflumilast in COPD patients already receiving triple therapy (long-acting β-agonist/inhaled corticosteroids and long-acting muscarinic antagonist).
Methods: Prospective registry that included COPD patients who were prescribed roflumilast added to triple therapy. The yearly rate of all COPD exacerbations before and after roflumilast and side effects related to the drug were registered.
Results: Among 55 patients prescribed 500 mg of roflumilast. Only 50.9% ($n = 28$) completed 1 year of therapy (roflumilast group). A reduction of all exacerbations with roflumilast was observed (2.75 ± 0.29 vs. 3.57 ± 0.26; $P = 0.022$), with a particular benefit in patients with $\geq$4 exacerbations prior to initiating therapy (3.55 ± 0.51 vs. 5.00 ± 0.30; $P = 0.034$). Side effects (mainly gastrointestinal) and treatment discontinuation occurred in 69.1% and 49.1% of the overall population, respectively.
Conclusions: Roflumilast, when added to triple therapy, reduces exacerbations in a "real-life" population of severe COPD patients with frequent exacerbations. However, side effects are more common and lead more frequently to discontinuation of therapy than has been reported in trials.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence and has become one of the leading causes of morbidity and mortality worldwide [1]. It is well-known that exacerbations of COPD are associated with an accelerated decline in lung function, worse quality of life, increased hospital admission and mortality rates, and a greater utilization of health care resources [2–4]. Notably, many patients with COPD continue to suffer frequent exacerbations despite being treated with maximum recommended therapy, which consists of a triple pharmacological therapy: inhaled corticosteroids (ICS), long-acting β-agonist (LABA) and long-acting muscarinic antagonist (LAMA) and non-pharmacological treatment: vaccination, pulmonary rehabilitation, educational skills and tobacco cessation therapy. In these patients, therefore, treatment strategies and interventions to prevent and reduce exacerbations deserve particular attention.

Roflumilast, a new oral selective phosphodiesterase-4 (PDE-4) inhibitor, has been introduced for the treatment of severe COPD patients with symptoms of chronic bronchitis and a history of frequent exacerbations [5–10]. However, most of the available information on the efficacy and safety of roflumilast is from randomized clinical trials, which may not accurately reflect its effectiveness in real-life populations with higher burden of

Abreviations: AECOPD, acute exacerbation of COPD; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; PDE-4, phosphodiesterase-4.

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comorbidities. In particular, a concern has been raised regarding adverse effects which lead to the discontinuation of treatment [5–7,11]. Furthermore, there is limited data on the effects of adding roflumilast to the treatment of patients already on triple therapy, which is a common clinical practice [11,12]. The present study aims to evaluate the effectiveness and safety of roflumilast during the first year of treatment in a real life population of severe COPD patients with chronic bronchitis and a history of frequent exacerbations who are already receiving standard of care therapy.

2. Methods

2.1. Study design and population

This observational prospective study was performed in a cohort of 278 patients with severe COPD regularly attended in a specific integrated care program from two university centres (Bellvitge University Hospital and Sabadell Hospital). The care program consists in: 1) scheduled visits (every 3 ± 1 months), 2) unscheduled visits (for acute exacerbations), 3) medical call centre, 4) educational skills, annual vaccination, adherence of medication and general care plan. The clinical guidelines recommends the use of roflumilast for those patients not adequately controlled by long-acting bronchodilators and having: a) symptoms of chronic bronchitis; b) a forced expiratory volume in 1 s less than 50% of predicted; and c) history of frequent exacerbations [13].

All consecutive patients of this cohort who were prescribed roflumilast ($n = 55$) according to current guidelines between February 2011 and May 2012 were included in the analysis. They had chronic bronchitis and frequent exacerbations of COPD ($\geq$2 in the previous year) despite regular treatment (at least 1 year) with triple therapy (LABA/ICS + LAMA). The registry of exacerbations suffered in the previous year and the 1-year clinical follow-up was performed by interviewing the patients at scheduled and unscheduled visits and by revising electronic medical reports. Before including a patient in the specific integrated care program for COPD, all subjects were thoroughly evaluated including the use of a thoracic computerized tomography, so the presence of significant bronchiectasis were ruled out. This study was approved by the local Institutional Ethics Committee.

2.2. Endpoints, assessment of outcomes and definitions

The effectiveness endpoint was the rate of all COPD exacerbations (per patient per year) before and after roflumilast treatment in patients who completed 1 year of follow-up. Secondary endpoints included comparisons in absolute and relative rates for: a) moderate and severe exacerbations and b) number of hospital admissions (considering that a given patient could have more than one hospitalization during a single episode of severe exacerbation). The change in exacerbation category during the year of follow-up was also described (e.g. “frequent exacerbator” changes category to “infrequent exacerbator” after one year of treatment). Furthermore, additional comparisons for the rate of COPD exacerbations in one year of follow-up were performed between patients under roflumilast treatment and those subjects with an early abandonment of roflumilast therapy (less than 12 weeks of treatment).

An exacerbation was defined as any respiratory clinical event characterized by a worsening in symptoms that is beyond normal daily variations, which requires a change in the baseline medications of the patient [13]. Exacerbations were classified as mild (worse symptoms requiring more reliever treatment), moderate (outpatient treatment requiring antibiotics and/or oral corticosteroids) and severe (requiring hospital admission).

Safety assessment included all sides effects observed with roflumilast therapy whether they lead to drug withdrawal or not. A side effect was defined as any severe adverse event (dead or pneumonia) or minor undesired effect related to the treatment, reported by the patient or noticed by the treating physician. Tolerability analyses included the rates of treatment withdrawal and the identification of clinical factors associated to withdrawal comparing the clinical variables from the patients which tolerated roflumilast therapy to those who withdrew from treatment. According to the tolerability of treatment, patients were classified in three groups: 1) roflumilast group: one year of completed treatment; 2) early withdrawal group: subjects who did not tolerate roflumilast due to side effects and withdrew treatment after less than 12 weeks; and 3) late withdrawal group: patients who withdrew from treatment after 12 weeks but in less than 1 year (Fig. 1).

2.3. Statistical analyses

For baseline characteristics, continuous variables are summarized by mean ± standard deviation or by median and interquartile range whether a normal distribution was assumed or not (Kolmogorov–Smirnov test), respectively. Comparisons of two continuous variables were performed with Student's *t*-test or Mann–Whitney's *U* test where appropriate; while an analysis of variance (ANOVA) or Kruskal–Wallis test was used to compare more than two groups. Categorical variables are expressed as frequencies and percentages and were tested by means of the chi-square test or Fisher's exact test according to application conditions.

To evaluate the primary endpoint and all other intragroup analyses, a repeated measures ANOVA model was used. Unadjusted and adjusted analyses were performed using ANOVA or ANCOVA, respectively. The number of exacerbations during the previous year and variables that might be considered clinically relevant such as smoking habit, oral corticosteroids, azithromycin, inhaled antibiotics, and statins were considered as covariates. A general linear model (GLM) was used to evaluate comparisons in the rate of exacerbations between roflumilast and early withdrawal group. Results are reported as least squares mean (LSM) ± standard error of the mean (SEM) for the above detailed GLM analyses.

Safety analyses were performed descriptively. Besides, in order to identify independent factors associated with treatment tolerability, a logistic regression model (backward stepwise method) was performed, including all variables deemed of clinical relevance or unbalanced between groups ($P < 0.20$). A two-tailed P value <0.05 was considered statistically significant for all the analyses performed. Statistical analyses were performed using PASW Statistics v18.0 software (SPSS Inc., Chicago, IL).

3. Results

Between February 2011 and May 2012, roflumilast was prescribed for 55 COPD patients (all of them current of former smokers) with frequent exacerbations at the two hospitals participating in this registry. Among these, 28 subjects (50.9%) completed 52 weeks of treatment (roflumilast group), 11 patients (20%) discontinued the treatment before 12 weeks (early withdrawal group) and 16 patients (29.0%) discontinued roflumilast between 12 and 52 weeks (late withdrawal group). Patient disposition is shown in Fig. 1. Baseline characteristics of the overall study population and groups are summarized in Table 1. Overall, baseline variables were well balanced between groups. None of the subjects in the present study were being administered theophylline and only one subject (in the Roflumilast group) was having mucolytic therapy with *n*-acetylcysteine.