Monaldi Arch Chest Dis
2013; 79: 3-4, Suppl., 7-18

REVIEW

The use of roflumilast in COPD: a review

Andrea Zanini[1,2*], Francesca Cherubino[2], Patrizia Pignatti[3], Antonio Spanevello[1,2]

ABSTRACT: ***The use of roflumilast in COPD: a review. A. Zanini, F. Cherubino, P. Pignatti, A. Spanevello.***

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Chronic inflammation and exacerbations play a central role in the progression of the disease. Currently, treatment options for COPD have been shown to improve the progressive decline in lung-function and/or decrease mortality rates. Roflumilast, a phosphodiesterase-4 inhibitor, is an anti-inflammatory drug which has been licensed as an add-on therapy for COPD patients with forced expiratory volume in the first second <50% and frequent exacerbations. Clinical trials have demonstrated that roflumilast improves lung function and reduces exacerbation frequency. Roflumilast has a mechanism of action which allows it to obtain a significant additive effect to current therapeutic options for COPD patients. It is generally well tolerated, although the most common adverse effects include diarrhea, nausea, weight loss, and headache. This review article provides an overview of the positive effects of roflumilast on lung function, exacerbation frequency and glucose metabolism, and its interaction with concomitant inhaled treatments.

Monaldi Arch Chest Dis 2013; 79: 3-4, Suppl., 7-18.

Keywords: Roflumilast, Daxas, COPD, Exacerbations, Lung Function.

[1] Department of Clinical and Experimental Medicine, University of Insubria Varese, Italy.
[2] Operative Unit of Pulmonary Rehabilitation, Salvatore Maugeri Foundation (IRCCS), Tradate (VA), Italy.
[3] Laboratory of Immunology, Autonomous Service of Allergy and Clinical Immunology, Salvatore Maugeri Foundation (IRCCS), Pavia, Italy.

Correspondence: Dr. Andrea Zanini, MD, UO di Pneumologia Riabilitativa, Fondazione Salvatore Maugeri, IRCCS, Via Roncaccio 16, 21049, Tradate, Italia; e-mail: andrea.zanini@fsm.it

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide health problem [1]. It has been calculated that COPD will become the third leading cause of death worldwide by 2030 [2]. There is an increasing demand for new and additional interventions for patients with COPD, and, until now, no existing pharmacological treatment has been shown to reduce disease progression [3]. The primary cause of the disease is cigarette

This work originated from the Operative Unit of Pulmonary Rehabilitation, Salvatore Maugeri Foundation (IRCCS), Via Roncaccio 16, 21049 Tradate, Italy, and has been supported by a grant from Takeda Italia SpA.

** This author received a consultancy fee from Takeda Italia SpA for literature review.*

Editorial assistance was provided by Selene Mogavero, PhD and Colin G Egan, PhD (Primula Multimedia SrL) and was sponsored by Takeda Italia SpA.

smoking, although occupational and environmental pollution may also play a role. COPD can briefly be defined as a chronic inflammatory disease, characterized by slowly progressive airflow limitation and associated chronic inflammatory comorbidities, which affect its severity [1]. Clinical aspects of COPD include progressive dyspnea, impaired exercise tolerance, and, in most patients, cough and sputum, with acute exacerbations [1]. In patients with COPD, exacerbations are significant events leading to accelerated decline in lung function, increased risk of hospitalization, loss of quality of life (QoL), and reduced survival [4].

Treatment of COPD is based on inhaled bronchodilators (BD) such as anti-cholinergics and β2-agonists, and inhaled corticosteroids (ICS). These drugs have been shown to significantly reduce COPD symptoms and exacerbations, with improvement of patient QoL, but, to date, none of the established pharmacological COPD therapies (alone or in combination) have been shown to improve the progressive decline in lung-function typical of the disease or to reduce mortality rates [1, 5-7].

Chronic inflammation is the basis of COPD, and, consequently, anti-inflammatory drugs as selective phosphodiesterase-4 (PDE4) inhibitors represent a valuable opportunity for COPD treatment. In general, pharmacological treatment is centered around the use of short-acting BD for patients in low risk categories and long-acting BD/ICS for higher risk patients. Recently, add-on therapy with the PDE4 inhibitor roflumilast has also been used. In fact, compared to previous guidelines, the recent "Global Initiative for Chronic Obstructive Lung Disease (GOLD)" guidelines for the diagnosis, management and prevention of COPD promotes a more individual tailoring of pharmacological therapy according to symptoms, airflow obstruction, risk of exacerbation and the presence of comorbidities [1]. Patients are then classified according to these three aspects into one of four groups indicated as A, B, C or D. Treatment recommendations are made on the basis of the group into which the patient belongs. In this regard, roflumilast has been introduced as a drug of third choice, whereas it currently is considered as a second-line alternative, for patients allocated to class C and D [1].

In July 2010, the European Commission approved roflumilast (Daxas) for the maintenance treatment of severe COPD, as an add-on treatment for patients with severe airflow obstruction (forced expiratory volume in the first second, FEV_1 <50% predicted after BD test) and frequent exacerbations despite correctly-dosed therapy with a long-acting BD. The US Food and Drug Administration approved roflumilast (Daliresp) in March 2011 "as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations".

The purpose of this review is to outline the unique characteristics of roflumilast, the first specific PDE4 inhibitor to be licensed for the treatment of COPD, focusing on pharmacology, clinical efficacy, and safety.

Pharmacology and drug properties

PDE4 is one of the eleven isoenzymes in the PDE family, with four genes (A, B, C and D) coding for this enzyme and each gene showing a number of splice variants at the N-terminus of the encoded proteins [8]. PDE4 is the main cAMP-metabolizing enzyme present in inflammatory and immune cells, and PDE4 inhibitors have a range of anti-inflammatory properties, including inhibition of inflammatory mediators' release and inhibition of immune-cell activation [9]. The chemical name of roflumilast is N-(3,5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F2N_2O_3$ and its molecular weight is 403.2 g/mol [9]. Following oral dosing, roflumilast is rapidly converted by

cytochrome P450 (CYP) 3A4 and 1A2 to its active metabolite roflumilast N-oxide. This metabolite has similar potency and specificity to the parent compound, and has been estimated to contribute to 90% of the total PDE4 inhibitory activity of roflumilast [10]. Roflumilast functions by increasing cAMP levels mainly in CD8+ lymphocytes, monocytes-macrophages and neutrophils, which are implicated in both the pathogenesis and the ongoing inflammation of COPD, through the selective and competitive inhibition of PDE4 [11]. Increased cAMP levels in these inflammatory cells reduces their activation, thereby attenuating the inflammatory response [11]. Roflumilast treatment is associated with a significant reduction in the numbers of neutrophils and eosinophils in induced sputum from COPD patients, along with a reduction in inflammatory mediators, including soluble interleukin (IL)-8, neutrophil elastase, eosinophils cationic protein and β2-macroglobulin. In addition, roflumilast has been shown to stimulate the release of TNF-α from blood cells [12]. PDE4 is also expressed in airway smooth muscle cells, thus justifying the significant, although modest, increase in FEV_1 [12]. Roflumilast is therefore a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with COPD.

Roflumilast has an 80% oral bioavailability and its absorption is not affected by cigarette smoking or food consumption. Importantly, absorption is not affected by either magnesium hydroxy- or aluminium hydroxy-based antacids. Time-to-peak concentrations are 1.5 and 10 hours and elimination half-lives are 10 and 20 hours, for roflumilast and the N-oxide metabolite, respectively. As previously mentioned, the N-oxide metabolite accounts for approximately 90% of the PDE4 activity and provides reasonable PDE4 inhibition over 24 hours, allowing for once daily oral administration [13]. There are few clinically important drug interactions apart from potential concerns about the co-administration of roflumilast and rifampicin [14]. The administration of rifampicin, an inducer of cytochrome P450, was shown to cause a reduction in total PDE4 inhibitory activity of about 60%. Therefore, the use of strong inducers of cytochrome P450 (e.g. phenobarbital, carbamazepine and phenytoin) may reduce the therapeutic efficacy of roflumilast. On the other hand, clinical interaction studies with CYP3A4 inhibitors cimetidine, erythromycin and ketoconazole have demonstrated an increase in the total PDE4 inhibitory activity of roflumilast. Moreover, fluvoxamine reduces clearance of roflumilast [15]. It is worth noting that there are no interactions with warfarin, digoxin and oral midazolam, as well as with a variety of respiratory medications including salbutamol, formoterol or budesonide [15].

Clinical efficacy and safety

The clinical efficacy of roflumilast has been studied in a series of large placebo-controlled trials, namely: “RECORD” (M2-107), “OPUS” (M2-111), “RATIO” (M2-112), “HERO”(M2-121), “AURA” (M2-124), “HERMES” (M2-125), “EOS” (M2-127) and “HEILOS” (M2-128).

In particular, two identical studies, “AURA” (M2-124) and “HERMES” (M2-125), performed on two different populations, were conducted to address the efficacy of roflumilast in preventing COPD exacerbations [16]. Another primary endpoint was the change in pre-BD FEV_1. In these double-blind, multicenter trials, a total of 3091 patients with severe COPD (FEV_1 less than 50% predicted), a clinical phenotype of chronic bronchitis, and a history of exacerbations, received roflumilast (500 μg once daily; n = 1537) or placebo (n = 1554) for 1 year [16]. The study populations were sufficiently homogenous to allow composite data analysis, and both primary endpoints were reached. The rate of moderate or severe

COPD exacerbations (moderate: requiring systemic corticosteroids, and severe: associated with hospital admission or death) was significantly lower in the roflumilast-treated groups compared to placebo groups (1.14 per patient per year vs. 1.37 per patient per year, respectively; *p<0.0003*), with a 17% reduction [16]. Figure 1 shows how the reduction in exacerbation rates are even greater when stratifying by number of exacerbations in the previous year, since frequent exacerbators (≥2 exacerbations in the previous year) show a reduction of 22.3% when comparing roflumilast to placebo treated patients. Moreover, pre-BD $FEV_1$was significantly higher with roflumilast compared to placebo (+48 ml, *p<0.0001*) [16] (figure 2). Furthermore, the study partially met the secondary endpoints: post-BD FEV_1 and dyspnea measured as Transition Dyspnea Index (TDI) focal score were significantly improved with roflumilast compared to placebo [16]. Mortality rates per year, health status measured as EQ-5D scores, and concentrations of C-reactive proteins, did not differ between treatments [16]. Finally, rates of adverse events (AEs) were higher with roflumilast (67%) than with placebo (62%), as were rates of discontinuation (14% vs. 12%, respectively). It is important to note that the probability of withdrawal due to AEs did not differ from the fourth month of the study onwards. The most common AEs associated with roflumilast included diarrhea, nausea, vomiting and headache. In the roflumilast group, patients lost more weight compared to the placebo group (-2.17 kg in 1 year for each patient). The largest absolute weight loss with roflumilast occurred in obese patients [16]. In conclusion, roflumilast reduced ex-

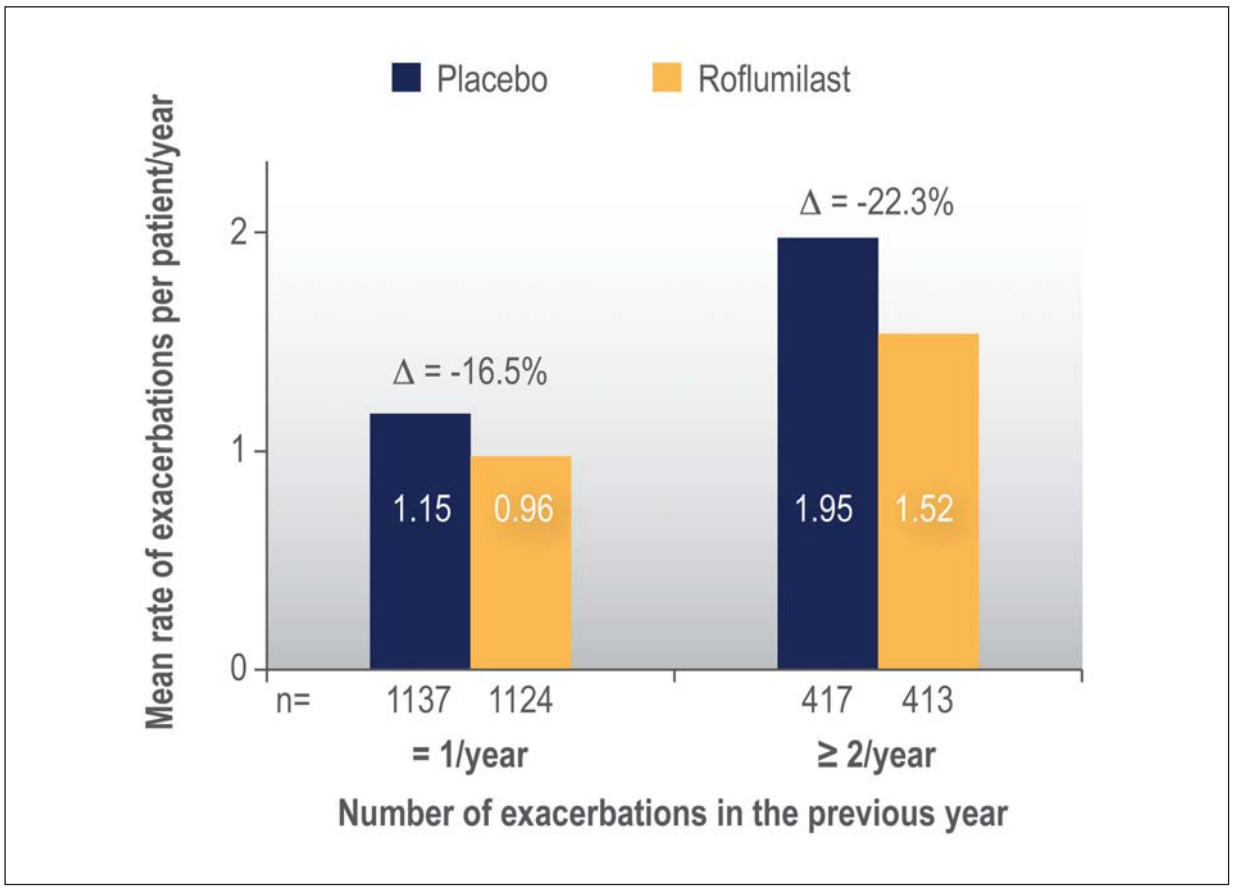

Fig. 1. - Integrated analysis of M2-M124/M2-M125 trials, showing moderate/severe exacerbation rates per year in patients stratified by number of exacerbations in the previous year. Moderate exacerbation: requiring systemic corticosteroids; severe exacerbation: associated with hospital admission or death. Data elaborated from [16].

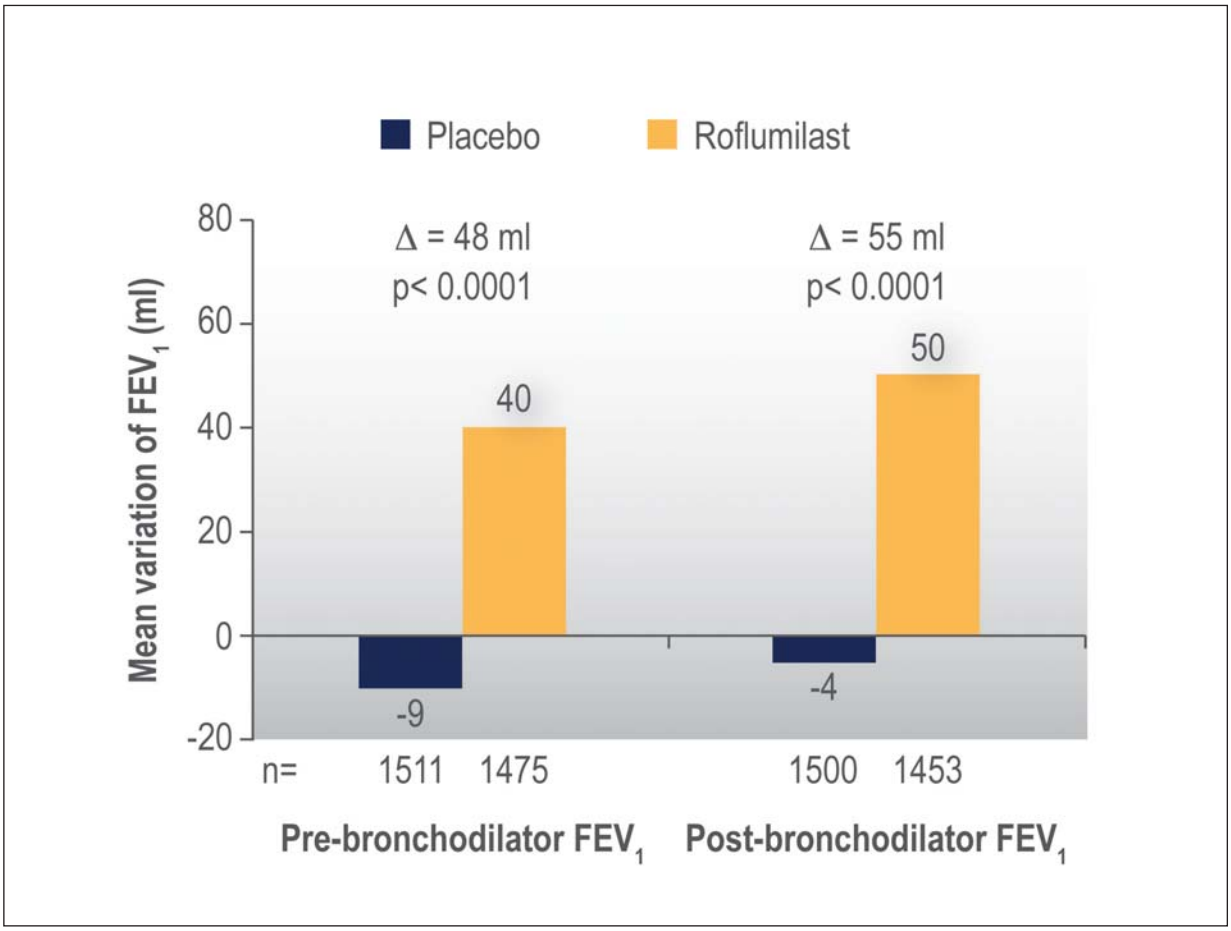

Fig. 2. - Integrated analysis of M2-M124/M2-M125 trials, showing changes in pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 in placebo and roflumilast treated groups. Data extracted from [16].

acerbation frequency and induced consistent and significant improvements in FEV_1, both before and after BD use. These changes were independent of the patient's smoking status or use of concomitant medication, such as inhaled long-acting β_2 agonists (LABAs) [16]. It should be noted that this treatment is not suitable for all patients because of the presence of AEs that usually tend to decrease during treatment [16].

Subsequently, Bateman and colleagues performed a pre-specified, additional, pooled analysis of AURA and HERMES trials, addressing efficacy and safety of roflumilast, used concomitantly with LABAs, to reduce exacerbations, and investigating the influence of exacerbation history on the response to roflumilast [17]. Approximately half of the patients reported concomitant treatment with LABAs at baseline, and 27% had experienced two or more exacerbations in the previous year (i.e., they were frequent exacerbators). The effect of roflumilast was compared between patients with and without LABAs, and the rate of moderate or severe exacerbation was found to be reduced in patients with roflumilast, regardless of concomitant use of LABAs ($p=0.0003$ and $p=0.0011$, respectively) [17]. Of interest was that a significant increase in time to first exacerbation was only seen in the subgroup using LABAs, but not in the subgroup without LABAs ($p=0.035$ and $p=0.300$, respectively) [17]. There were no additional safety concerns regarding the use of roflumilast in addition with a LABA. Finally, previous exacerbation history appeared to be associated with the response to roflumilast [17]. It is also worth highlighting that frequent exacerbators experienced a greater reduction in moderate or se-

vere exacerbations (*p=0.002*) compared to infrequent exacerbators (*p=0.0062*) [17]. These results support the use of roflumilast concomitantly with LABAs in patients with severe COPD and symptoms of chronic bronchitis. The present report reassures clinicians that despite the use of a LABA, roflumilast will still exert its intended effect and further reduce the risk of acute exacerbation.

Two studies, "EOS" (M2-127) and "HELOS" (M2-128), evaluating the effects of adding roflumilast to long-acting BD were reported by Fabbri and colleagues [18]. They performed two randomized, multicenter studies that compared roflumilast (500 µg once daily) with placebo in patients with moderate-to-severe COPD who were also receiving the LABA salmeterol or tiotropium [18]. In these two studies, a total of 1580 patients (mean FEV_1 55% and 56%) were treated for 6 months. Chronic bronchitis was a prerequisite for inclusion only in the "HELOS" (M2-128) study, but 79% of the patients recruited in the "EOS" (M2-127) study had chronic cough and sputum production as well. Compared to placebo, roflumilast improved mean pre-BD FEV_1, primary endpoint, by 49 ml in patients receiving salmeterol and by 80 ml in those treated with tiotropium (*p<0.0001* for each comparison) [18]. Similar improvements in post-BD FEV_1 were noted in both groups. The frequency of exacerbations, the time to first exacerbation and the proportion of patients with exacerbations generally improved with the active-treatment combinations compared to placebo. However, in this regard, roflumilast resulted in the best possible outcomes and most significant improvements when administered with salmeterol [18]. Treatment-related AEs occurred in approximately 3% to 18% of patients, with the highest rate of AEs in the roflumilast/salmeterol group. Diarrhea, nausea, and weight loss (approximately 2 kg) were the most common AEs [18]. The tendency for treatment discontinuation was higher in patients who received roflumilast. This observation was consistent with that of previous studies. In conclusion, Fabbri and colleagues demonstrated that roflumilast may provide additional clinical benefits for patients with moderate-to-severe COPD treated with salmeterol or tiotropium [18].

As COPD is a heterogeneous disease, it is unlikely that all patients will benefit equally from a given therapy. To test this hypothesis, Rennard and colleagues revised the datasets of two previous replicate, randomized, double-blind, placebo-controlled, parallel-group studies ("RATIO" M2-112 study, oral roflumilast 500 µg or placebo once daily for 52 weeks), that were inconclusive regarding exacerbations [19]. The results of the RATIO study were pooled, and a series of post-hoc analyses performed. The results of these analyses are presented in the "OPUS" study (M2-111) [20]. The pooled analysis, evaluating 2686 patients with a mean post-BD FEV_1 of 39% of predicted, demonstrated a 14.3% reduction in the rate of exacerbations (*p=0.026*) [20]. However, the median time to first moderate or severe exacerbation was comparable in the roflumilast and placebo groups (120 and 126 days, respectively). Notably, post-hoc subgroup analyses demonstrated a more pronounced treatment effect of roflumilast in patients with the chronic bronchitis phenotype (26.2% reduction in exacerbation rate vs. placebo, *p=0.001*), in patients with presence of cough (20.9% decrease, *p=0.006*), with presence of sputum (17.8% reduction, *p=0.03*), and in patients with concurrent use of ICS (18.8% decrease, *p=0.014*) [20]. The incidence of AEs was similar with roflumilast and placebo (81.5% vs. 80.1%), but, importantly, roflumilast was not associated with an increase in AEs in the subgroups that experienced a greater reduction in exacerbations [20].

An unexpected finding in patients with COPD and comorbid type 2 diabetes mellitus (T2DM) was that roflumilast reduced fasting blood glucose and hemoglobin A1c (HbA_{1c}) levels [21]. After having observed that there

is a transient and reversible weight decrease with roflumilast therapy, Wouters and colleagues hypothesized that the systemic actions of this drug may impact metabolism [21]. They suggested that this effect could be mediated by the action of roflumilast on cAMP levels, since the small changes in weight would not be expected to have an effect of this magnitude. Conversely, fasting blood glucose levels did not change in COPD patients without comorbid T2DM. These findings suggest that roflumilast may improve glycemic control in patients with co-morbid T2DM [21]. The authors conducted a 12-week, randomized, double-blind, placebo-controlled multicenter study. Patients with newly diagnosed T2DM but without COPD (N=205) were enrolled to evaluate mean change in blood HbA_{1c} levels. Roflumilast was associated with a significantly greater reduction in blood HbA_{1c} levels compared to placebo (*p<0.0001*) in patients with T2DM [21]. Moreover, it should be considered that in previous clinical studies (AURA, HERMES, EOS and HEILOS) in patients with COPD, roflumilast was associated with a weight decrease of about 2 kg [16-18]. Interestingly, in the present study, patients in the roflumilast group had a mean weight decrease of 1.9 kg, but patients in the placebo group also lost weight, with a mean change of 1.2 kg, because of diet and exercise; the difference between treatment groups was not statistically significant (*p=0.0584*). In conclusion, roflumilast lowered glucose levels in patients with newly diagnosed T2DM without COPD, although the drug's precise mechanism of action remains to be elucidated [21]. Further studies will be required to determine how roflumilast affects T2DM control, and whether it can prevent some of its complications.

Another important point in favor of roflumilast is the possibility to shift patients from the more adverse frequent exacerbator state, to the more favorable infrequent exacerbator state. The classification of exacerbator frequency status was based on definitions used in the "Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints" (ECLIPSE) study. The ECLIPSE study showed that the majority of patients defined as frequent exacerbators at the start of the study remained in their respective phenotypic groups after one year of study, supporting the observation that this phenotype is relatively stable over time [22]. Given the link between frequent exacerbations and increased inflammation, Wedzicha and colleagues hypothesized that the anti-inflammatory roflumilast would have a specific effect in patients with the frequent exacerbator phenotype [23]. The analysis showed that, in frequent exacerbators, one year of treatment with roflumilast reduced the risk of remaining a frequent exacerbator by 20% as compared to placebo (*p=0.0148*) (figure 3). In addition, one year treatment with roflumilast in infrequent exacerbators reduced the risk of becoming a frequent exacerbator by 23% (*p=0.0018*) (figure 4). Importantly, this effect was independent of concomitant LABAs or previous ICS treatment and was applicable for both moderate to severe exacerbations and severe exacerbations [23]. The importance of these results are underlined by the fact that, for the first time, the anti-inflammatory effects of roflumilast in reducing exacerbations were associated with a stabilizing effect on COPD. In this regard, it is known that the frequent exacerbator phenotype is associated with an accelerated decline in lung function, reduced physical activity, poorer QoL and an increased risk of mortality. In conclusion, the identification of patients at risk and the prevention of frequent exacerbations represent a logical focus for COPD management.

For a considerable time now, a crucial point in the treatment of COPD has been represented by the frequency of cardiovascular diseases (CVD). The risk of incident cardiac arrhythmia, venous thromboembolic disorders, myocardial infarction (MI) and stroke

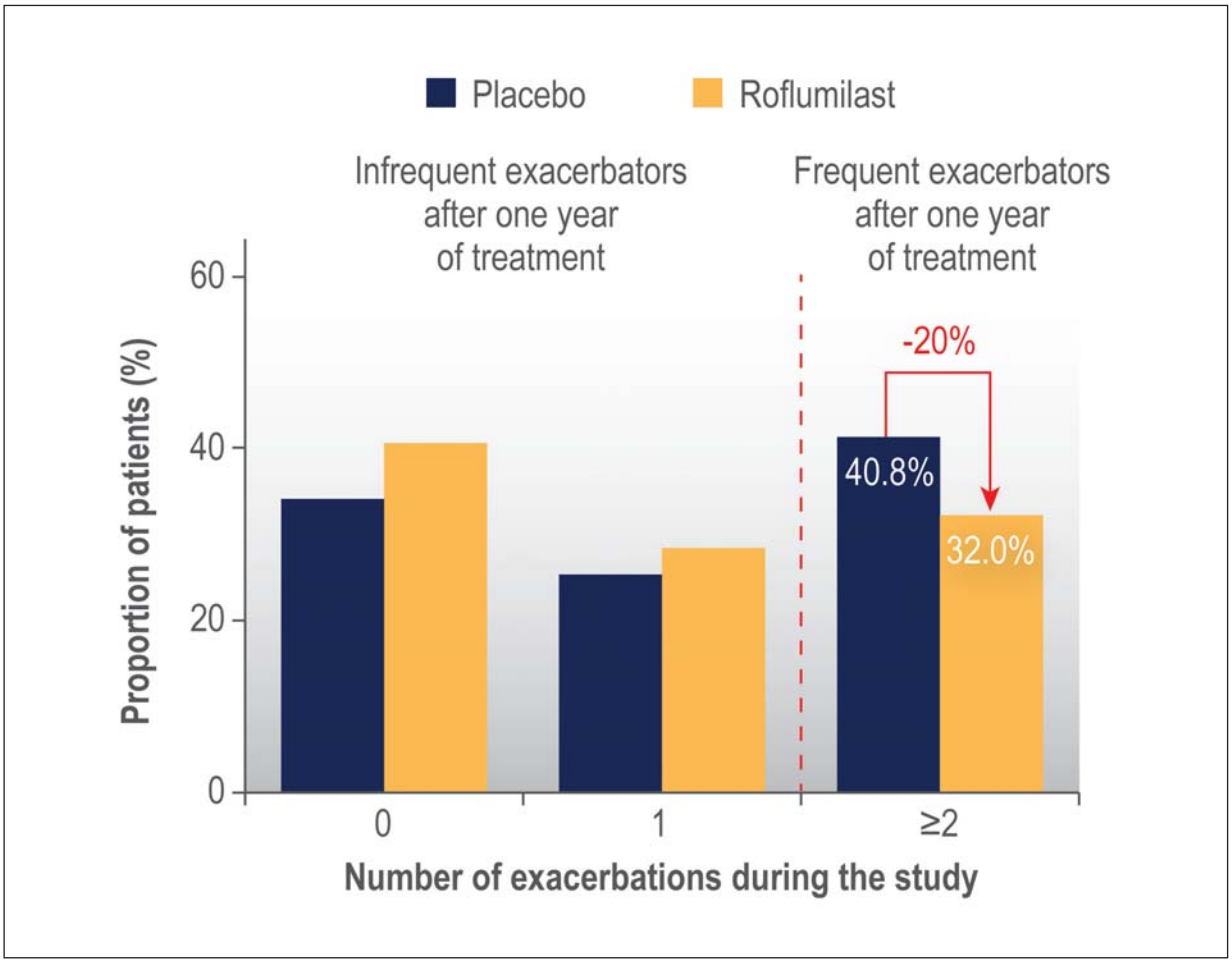

Fig. 3. - Patient exacerbation status after 1 year of treatment with roflumilast in a subgroup of frequent exacerbators at baseline. Roflumilast significantly decreased the risk of remaining a frequent exacerbator (*p=0.0148*). Modified from [23].

are substantially greater in COPD patients than in healthy individuals [24]. Additionally, COPD patients are known to have higher rates of cardiovascular mortality and hospitalizations [25]. Moreover, there is evidence of systemic inflammation in moderate and severe COPD patients, and this fact has been proposed as a link between COPD and systemic comorbidities, such as CVDs [26]. White and colleagues, performed a retrospective assessment of cardiovascular events pooled from the entire clinical database of placebo-controlled roflumilast COPD trials of 12 weeks or longer [27]. A total of 12,054 patients were included in the analysis: 6,563 patients were randomized to roflumilast (250-500 µg total daily dose) and 5,491 to placebo. This new post-hoc data analysis evaluated the effects of roflumilast on cardiovascular safety in moderate to very severe COPD patients and showed a 35% reduction of major adverse cardiac events (MACE, i.e.: non-fatal MI, non-fatal stroke, and cardiovascular death) in patients treated with roflumilast as an add-on therapy when compared to placebo (*p=0.019*) [27]. The analysis, found significant reductions of MACEs in patients treated with roflumilast compared to placebo, independent of age, gender, smoking status, use of concomitant COPD treatments, such as LABAs and ICS, and COPD exacerbations [27]. As a PDE4 inhibitor, roflumilast provides a wide range of anti-inflammatory actions *in vitro* and *in vivo* and has been shown to reduce airway inflammation in COPD as assessed by sputum neu-

trophil and eosinophil counts, an anti-inflammatory benefit that may be associated with the drug's ability to reduce exacerbations of COPD [12, 28]. Thus, it is possible that MACE reduction, seen with roflumilast as an add-on therapy, may be in part related to reductions in the vascular inflammation induced by PDE-4 inhibition [27]. In conclusion, while limited data exist on the potential cardiovascular benefits of new COPD therapies, this analysis of MACE on roflumilast is important as it highlights the absence of a cardiovascular safety indicator when treating patients with COPD. The outcomes of the MACE evaluation indicate the potential additional benefits of roflumilast treatment for COPD patients with cardiovascular comorbidities. In addition to reducing future risk in COPD patients, roflumilast may reduce cardiovascular risk factors by improving glucose homeostasis [21, 27].

At this point a final aspect should be discussed, that is the additive effects of roflumilast when administered on top of monotherapy with either LABA or LAMA, and even when used together with ICS [1]. However, the effects of roflumilast added on top of dual or triple therapy have not been studied in a clinical trial setting. The ongoing REACT (Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment) study has been specifically designed to test the hypothesis that roflumilast can provide additional benefit, when used with these other therapeutic combinations, to reduce exacerbations

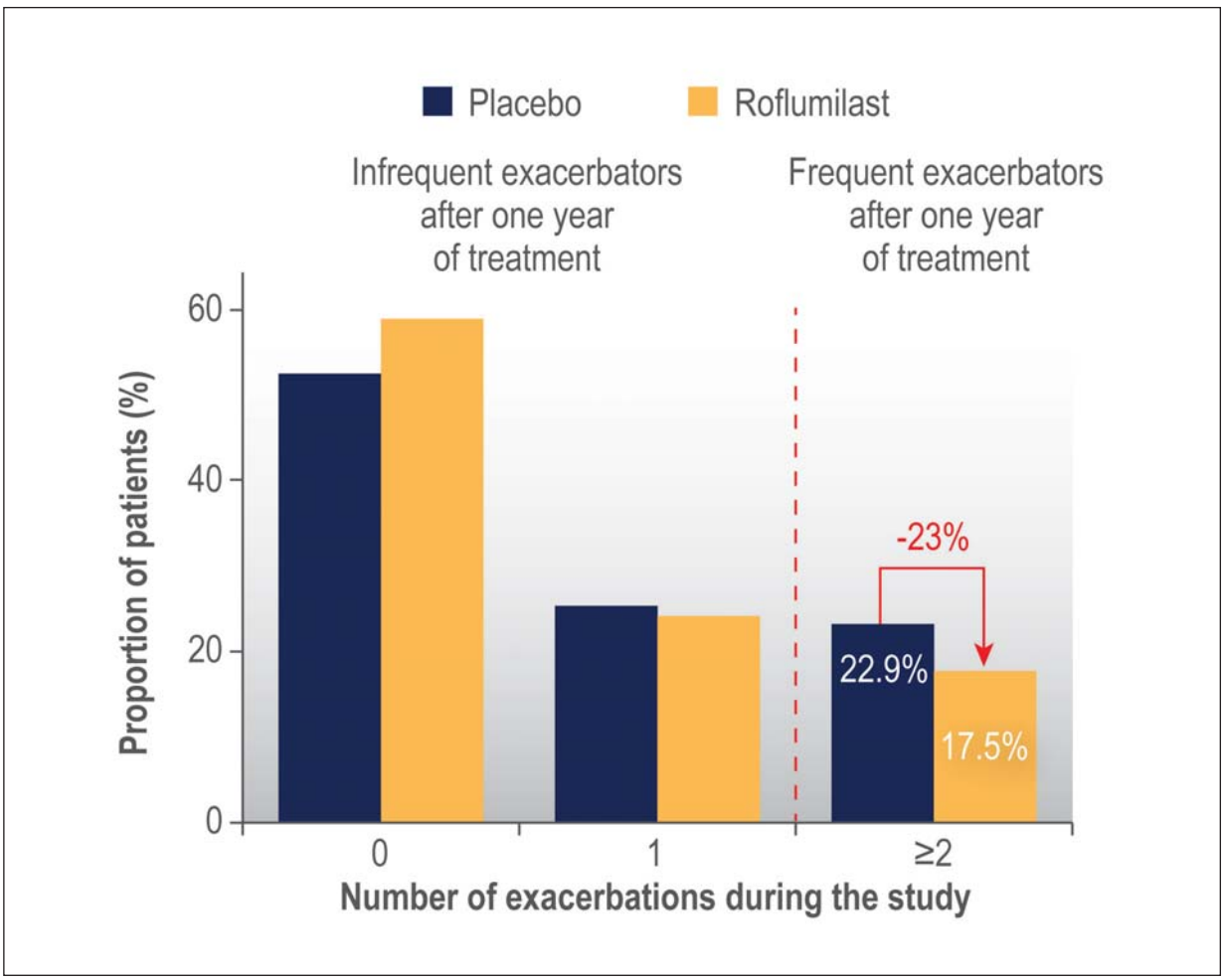

Fig. 4. - Patient exacerbation status after 1 year of treatment with roflumilast in a subgroup of infrequent exacerbators at baseline. Roflumilast significantly decreased the risk of becoming a frequent exacerbator (*p=0.0018*). Modified from [23].

[29]. REACT is a 1-year randomized, double-blind, multicenter, phase III/IV study of roflumilast 500 µg once daily or placebo on top of a fixed ICS/LABA combination. In this study, 1,934 COPD patients with FEV_1 <50% of predicted and a history of frequent exacerbations (at least two in the previous year) will be enrolled [29]. The primary endpoint is the rate of moderate or severe COPD exacerbations. Calverley and colleagues hypothesize that since roflumilast has a different mode of action to BDs and ICS, it may provide additional benefits when added to these treatments in frequent exacerbators. The REACT study will be important to determine the role of roflumilast in COPD management [29].

Conclusions

Roflumilast is the first selective PDE4 inhibitor approved in Europe as an add-on anti-inflammatory therapy in patients with symptomatic severe COPD with frequent exacerbations. This indication is supported mainly by extensive clinical data demonstrating its ability to improve lung function and to reduce exacerbation frequency in this subset of patients. Recently, interesting aspects have emerged, regarding glucose homeostasis and cardiovascular safety. Furthermore, its mechanism of action may allow for a more targeted approach to counteract the inflammatory processes in COPD, compared to other treatments. It is likely that additional studies examining the systemic anti-inflammatory effects would further support the efficacy of roflumilast for COPD. To conclude, roflumilast is the newest anti-inflammatory therapy which can be used in COPD and can significantly affect disease progression.

Riassunto

La broncopneumopatia cronica ostruttiva (BPCO) è una delle principali cause di morbilità e mortalità in tutto il mondo. L'infiammazione cronica e le riacutizzazioni giocano un ruolo centrale nella progressione della malattia. Attualmente le opzioni di trattamento per la BPCO hanno dimostrato di migliorare il progressivo declino della funzionalità polmonare e di ridurre la mortalità. Roflumilast, un inibitore della fosfodiesterasi-4, è un farmaco anti-infiammatorio che ha ottenuto l'indicazione come terapia aggiuntiva per i pazienti con BPCO con volume espiratorio forzato nel primo secondo inferiore al 50% e frequenti riacutizzazioni. Studi clinici hanno dimostrato che roflumilast migliora la funzionalità polmonare e riduce la frequenza di riacutizzazioni. Roflumilast ha un meccanismo di azione che consente di ottenere un significativo effetto additivo alle attuali opzioni terapeutiche per pazienti con BPCO. È generalmente ben tollerato, anche se gli effetti collaterali più comuni comprendono diarrea, nausea, perdita di peso e mal di testa. Questo articolo redazionale fornisce una panoramica degli effetti positivi di roflumilast sulla funzionalità polmonare, frequenza di esacerbazioni e sul metabolismo del glucosio, così come la sua interazione con terapie inalatorie concomitanti.

Parole chiave: Roflumilast, Daxas, BPCO, Riacutizzazioni, Funzionalità polmonare.

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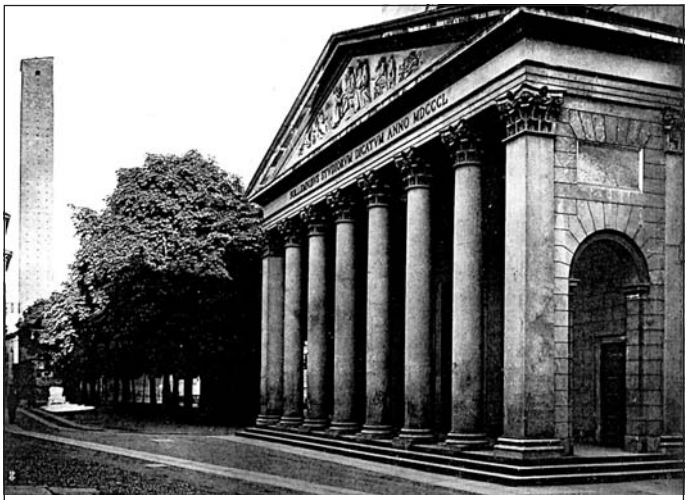

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