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REVIEW

Phosphodiesterase Inhibitors: Present and Future

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ABSTRACT

Phosphodiesterase (PDE) inhibitors act on specific phosphodiesterase enzymes (fundamentally 3, 4 and 5), which are characterized by their expression in different organs. Currently, their use is approved for the treatment of chronic obstructive pulmonary disease (COPD), erectile dysfunction, pulmonary arterial hypertension, psoriasis, psoriatic arthritis and atopic dermatitis. Although the experiences with most have been negative, phosphodiesterase inhibitors (especially type 4) have shown positive results, as they are able to provide additional benefits in patients who are not adequately controlled with bronchodilators, either with or without inhaled corticosteroids. To date, roflumilast is the only drug that has met these expectations in the treatment of a specific COPD phenotype (COPD associated with chronic bronchitis). Work is currently underway to develop more selective inhibitors that, by modulating PDE in specific tissues and cells, can improve the therapeutic effect in a specific organ with fewer side effects.

Keywords: Asthma. COPD. Inhibitors. Roflumilast.

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PHARMACOLOGY AND INDICATIONS OF PDE INHIBITORS

Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are intracellular second messenger molecules degraded and inactivated by the enzyme phosphodiesterase (PDE). Phosphodiesterase inhibitors exert their effects on specific phosphodiesterase enzymes (PDE-3, PDE-4, PDE-5), thereby preventing cGMP or cAMP degradation. The result is an increase in their intracellular concentrations, which, through the activation of protein kinase A, increases protein phosphorylation, which in turn induces the inhibition of chemotaxis, cellular inflammatory infiltration, a decrease in the release of inflammatory and cytotoxic mediators and, by reducing inflammation, relaxation in the bronchial smooth muscle (Fig. 1).

In humans, 21 PDE genes have been identified that express more than 100 separate isoforms, which are grouped into 11 families. The most important are PDE-3, PDE-4 and PDE-5 (Table 1). PDE-4, which is the most relevant at the respiratory level, is probably the most complex, and 4 genes (A, B, C and D) encode this enzyme[1-3].

PDE-3 inhibitors

The effects exerted by PDE-3 inhibitors increase cAMP levels in the myocardium, peripheral vasculature and platelets. This causes positive inotropic effects by increasing ionized calcium in the myocardium and vasodilation of the peripheral vessels, while preventing platelet aggregation. Due to this mechanism of action, its main indication is in decompensated heart failure and peripheral arterial disease.

Cilostazol is a PDE-3 inhibitor that reversibly inhibits platelet aggregation and is therefore indicated for the treatment of intermittent claudication due to peripheral arterial disease. Milrinone and amrinone also inhibit PDE-3 enzymes, but their action is primarily at the cardiac level. By increasing cAMP levels in the myocardium, they cause a positive inotropic effect and can therefore be used in the short term for decompensated heart failure, as prolonged treatment can precipitate ventricular arrhythmias. The classic dipyridamole is also a PDE-3 inhibitor, but its action on the enzyme is relatively weak. It is used for postoperative prophylaxis of thrombosis and as a diagnostic tool in stress tests. Anagrelide is another drug that decreases platelet counts and platelet aggregation by inhibiting PDE-3. Although its mechanism of action is not exactly known, this drug lowers platelet counts, thereby preventing thrombotic complications in myeloproliferative disorders, such as essential thrombocytopenia, polycythemia vera, and chronic myeloid leukemia[4].

PDE-4 inhibitors

Although their development was initially focused on pulmonary pathology, these agents are also useful in the treatment of psoriatic arthritis and atopic dermatitis. In these cases, PDE-4 inhibition results in an intracellular increase in cAMP levels, modulating the expression of inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-23, IL-17, IL-2, IL-4, IL-5) and interferon gamma. cAMP

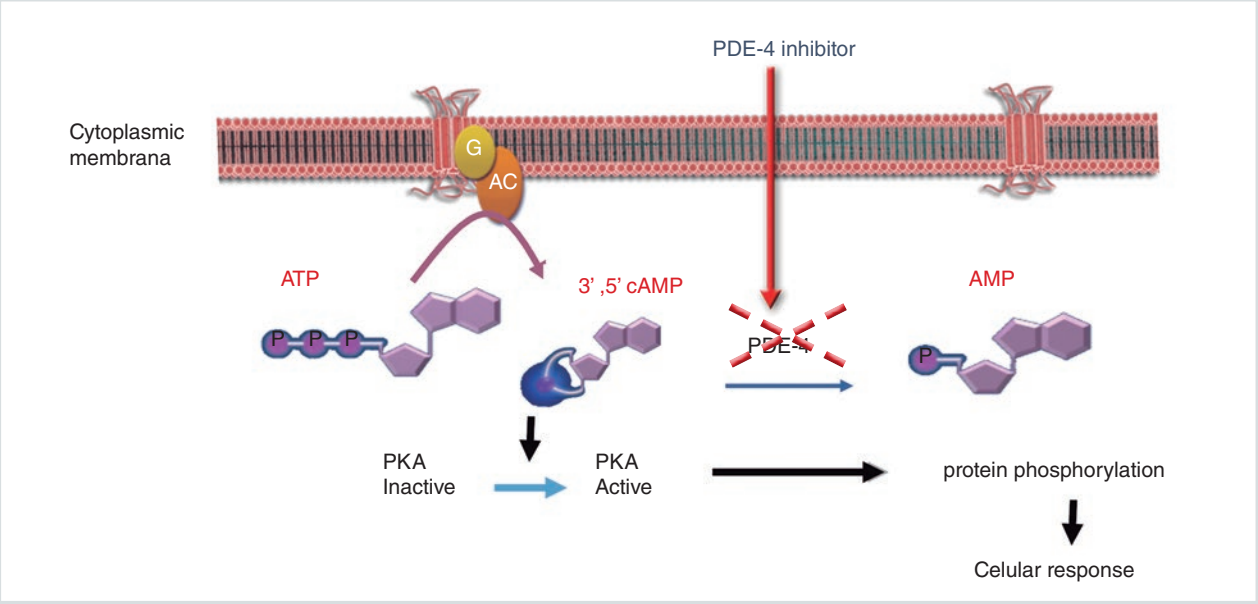

Figure 1. Inhibition of PDE avoids cAMP and cGMP degradation, acting on structural and inflammatory cells by means of protein kinase A (see text).
cAMPA: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; PDE: phosphodiesterase; PKA: Protein Kinase A.

Table 1. Main phosphodiesterase (PDE) inhibitors approved for clinical use

Non-selective PDE inhibitors	theophylline, caffeine, ibudilast
PDE-3 inhibitors	cilostazol, dipyridamole, milrinone and amrinone
PDE-4 inhibitors	roflumilast, apremilast, crisaborole
PDE-5 inhibitors	sildenafil, tadalafil, vardenafil and avanafil

also regulates the levels of certain anti-inflammatory cytokines, such as IL-10.

Crisaborole is a PDE-4 inhibitor indicated for atopic dermatitis[5]. Apremilast, administered alone or in combination, is indicated for the treatment of active psoriatic arthritis in adult patients who have either had inadequate response or intolerance to prior treatment with a disease-modifying antirheumatic drug[6].

However, the most important drug at the pulmonary level, and to a certain extent one of the main precursors of PDE inhibitors in clinical practice, is roflumilast.

Roflumilast is a selective PDE-4 inhibitor with multiple anti-inflammatory qualities that specifically act on the inflammatory mechanisms that predominate in chronic obstructive pulmonary disease (COPD), although in recent years the number of potential indications has increased progressively (Fig. 2).

The high potency and selectivity of roflumilast for competitive inhibition of PDE-4 is due to its being 700 times more selective for the inhibition of PDE-4 than for any other PDE isoenzyme. Roflumilast does not demonstrate PDE-4 subtype selectivity, with the exception of PDE-4C, which is inhibited with somewhat

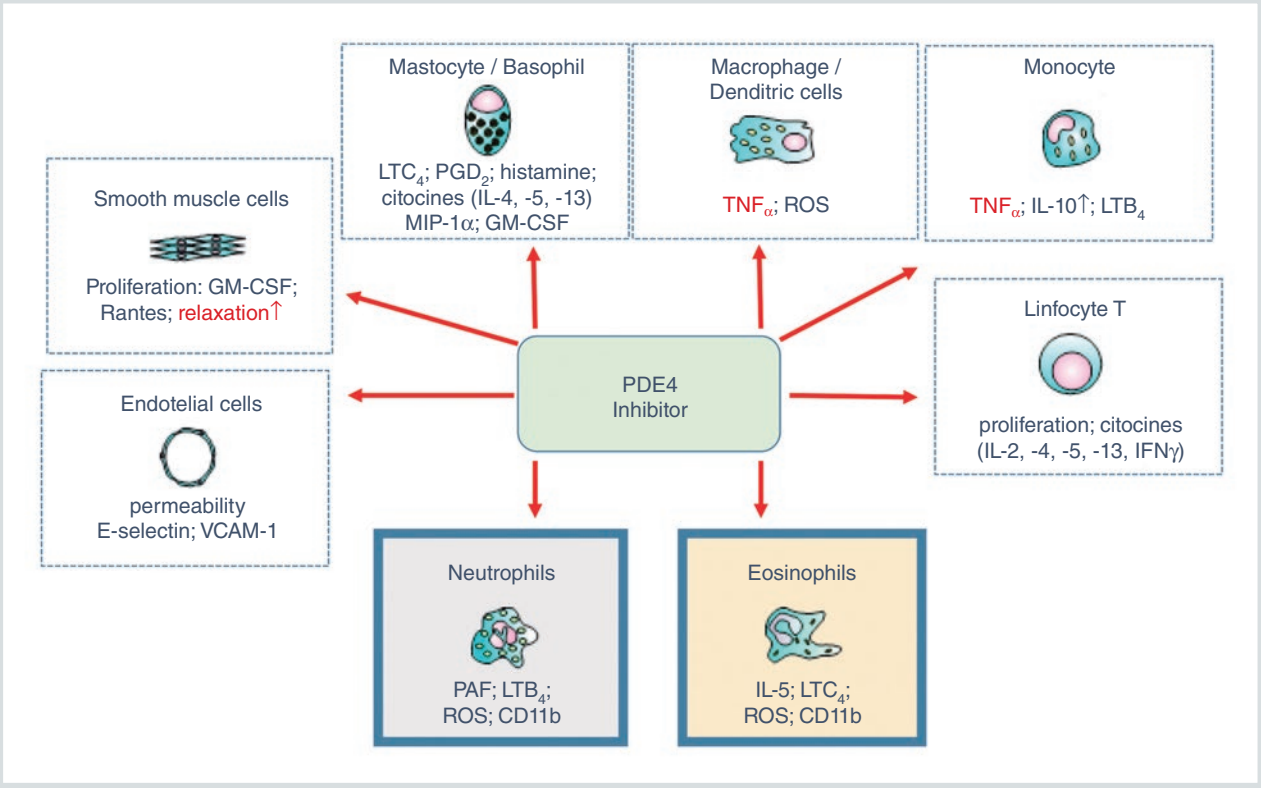

Figure 2. Effects of PDE-4 inhibition on pulmonary inflammatory and immunocompetent cells.
IL: interleukin; LT: leukotriene; MIP-1 α: macrophage inflammatory protein 1 alpha; PDE: phosphodiesterase; PAF: platelet-activating factor; ROS: reactive oxygen species; TNF-α: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule-1.

less potency[7]. The main effect of roflumilast in COPD and asthma is as an anti-inflammatory drug. COPD is characterized by chronic inflammation dominated by neutrophils, macrophages, and CD8 (cytotoxic) lymphocytes, primarily in the small airways and lung parenchyma. This inflammatory process involves destructive and aberrant repair processes, perhaps mediated by proteases and oxygen-free radicals released by inflammatory cells. Most cells involved in COPD contain predominantly the PDE-4 isoenzyme. These cells are attracted to the airways by mediators, such as interleukin (IL)-8 or leukotriene B4 (LTB4), which are produced by alveolar macrophages in airway inflammation. In various *in vitro* and *in vivo* studies with human cells implicated in the pathogenesis of COPD, roflumilast and its active metabolite roflumilast N-oxide suppressed the release of various mediators, such as LTB_4, tumor necrosis factor alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), granzyme B, IL 2, IL 4, IL 5 and IL 13. In addition, roflumilast induces the inhibition of emphysema formation and airway remodeling as well as a reduction in mucus production. Regarding neutrophilic inflammation, the potential of

roflumilast to alleviate airway neutrophil accumulation in COPD was explored in a double-blind, placebo-controlled study. At the end of the treatment period, induced sputum neutrophils had decreased by 35% with roflumilast compared to placebo. In contrast, a previous study reported that neither oral nor inhaled glucocorticoids reduced the number of neutrophils in the induced sputum of COPD patients. Another parameter reduced by roflumilast is α2-macroglobulin, which is considered a marker of microvascular leakage. A complete analysis on this topic is beyond the scope of this review, but other more specific articles provide further discussion[7-9].

PDE-5 inhibitors

The endothelial cells of the corpus cavernosum of the penis release nitric oxide, which initiates the enzyme guanylate cyclase, favoring the synthesis of cGMP. Prevention of cGMP degradation prolongs erection and is therefore used therapeutically to treat erectile dysfunction. PDE-5 inhibitors also cause pulmonary vasodilation and may therefore be useful in treating pulmonary arterial hypertension, as this may be related to impaired release of nitric oxide from the pulmonary vasculature, resulting in decreased levels of cGMP.

Among the phosphodiesterase inhibitors, sildenafil is the most widely known agent that acts on PDE-5. It was approved by the Food and Drug Administration (FDA) in 1998 for erectile dysfunction and in 2005 to treat pulmonary arterial hypertension in adults. Vardenafil and avanafil are other PDE-5 inhibitors, also approved for erectile dysfunction. Tadalafil is a PDE-5 inhibitor approved to treat benign prostatic hyperplasia and erectile dysfunction. As both conditions can coincide later in life, tadalafil can be used as monotherapy to treat both conditions[10-12].

Non-selective PDE inhibitors

Theophylline is a non-specific phosphodiesterase inhibitor that has been widely used to treat COPD, although its mechanism of action is not completely understood[13]. Another non-selective inhibitor, pentoxifylline, is believed to act by non-selective inhibition of phosphodiesterase enzymes, like theophylline. It has been reported to improve blood flow and perfusion in the extremities by increasing red blood cell flexibility while also reducing blood viscosity, cell proliferation, and inflammation. Due to this mechanism, pentoxifylline is used therapeutically in peripheral arterial disease in patients suffering from pain caused by intermittent claudication[14].

Ibudilast is a non-selective inhibitor of PDE-3, PDE-4, PDE-10, and PDE-11, which reduces the production of nitric oxide, proinflammatory chemokines, LTB4, and toll-like receptor 4. Due to its bronchodilator and anti-inflammatory effects, ibudilast has been used in Japan to treat bronchial asthma and, because it crosses the blood-brain barrier, in complications after stroke[1,15].

Caffeine exerts an effect on phosphodiesterase enzymes through non-selective inhibition of PDE-1, PDE-4, and PDE-5, which promotes cAMP accumulation. Caffeine also inhibits adenosine and gamma-aminobutyric acid (GABA) receptors and increases intracellular calcium release. Clinically, it improves and enhances

cognition and memory, while reducing fatigue and drowsiness[16]. Caffeine citrate has been used to treat apnea of prematurity.

PHOSPHODIESTERASE INHIBITORS IN RESPIRATORY PATHOLOGY

Phosphodiesterase inhibitors in bronchial asthma

In most patients, bronchial asthma can be satisfactorily controlled with a combination of bronchodilators and inhaled corticosteroids. When this is not sufficient, newly developed drugs focus on the inhibition of T2 inflammation. Despite the great advances made with these treatments, there is a group of asthmatic patients, especially those with a non-T2 profile, whose therapeutic needs are currently not covered.

Based on the fact that several inflammatory and structural cells involved in the pathogenesis of asthma express PDE-4, the usefulness of PDE inhibitors, especially roflumilast, in this disease has been evaluated. In fact, the first lines of clinical research with roflumilast were in asthma.

There is a solid experimental base that supports the potential of PDE inhibitors in bronchial asthma. PDE-4 is expressed in the effector cells involved in allergic reactions, including eosinophils, basophils, and mast cells. In purified human eosinophils, PDE-4 inhibition reduces chemotaxis and synthesis of leukotriene C4 induced by the platelet-activating factor, attenuates eotaxin-induced eosinophil expression, and inhibits superoxide anion production by the eosinophils induced by zymosan. They also reduce IL-3-induced, IgE-dependent histamine production as well as the release of cytokines T2, IL-4, and IL-13 by the basophils[17,18].

The first published clinical trials investigating the effect of selective PDE-4 inhibitors in asthma and COPD were conducted 20 years ago. A randomized, double-blind, placebo-controlled crossover trial studied the effect of seven days of treatment with an oral dose of a PDE-4 inhibitor (BAY19-8004). This study reported no significant bronchodilation, but an anti-inflammatory signal was observed with decreased sputum levels of eosinophil cationic protein[19-20]. In 2006, Bateman et al.[21] analyzed the efficacy of three doses of roflumilast in a 12-week randomized, double-blind, parallel-group clinical trial of 693 patients with mild-moderate asthma. Roflumilast once daily at doses of 100, 250, and 500 mcg demonstrated an increase in forced expiratory volume in one second (FEV_1) of 260, 320, and 400 mL, respectively[21]. Improvements in FEV_1, forced vital capacity (FVC), peak expiratory flow (PEF), and rescue medication use have been confirmed in other clinical trials[22,23].

In a systematic review and meta-analysis of 17 placebo-controlled studies, roflumilast (500 µg) and MK-0359 significantly increased FEV_1 and PEF compared to a placebo, attenuated asthma symptoms, and reduced the use of rescue medications, inflammatory markers such as TNF-α and severe asthma exacerbations[24]. In this same review, PDE-4 inhibitors improved bronchial hyperresponsiveness to different allergen provocations but did not attenuate the response in the methacholine test. A better evaluation based on the phenotype/endotype could potentially provide more precise information. In fact, especially favorable

responses have been described in obese patients with asthma[25].

In addition to classic placebo-controlled studies, roflumilast has been evaluated as an added treatment used in association with existing asthma therapies. When it was administered along with inhaled corticosteroid therapy, roflumilast provided additional statistically significant improvements in FEV_1[23]. The authors concluded that roflumilast provides anti-inflammatory benefits when given as a complementary treatment with inhaled corticosteroids. In another controlled study, roflumilast (500 mcg) associated with montelukast (10 mg/day) versus montelukast alone, used in conjunction with inhaled corticosteroids and a long-acting beta-2 agonist, demonstrated a significant improvement in FEV_1 of 100 mL[26].

Despite these favorable data in asthma, no large phase III clinical trials have been conducted, possibly due to the side effects observed in patients with COPD and the availability of very effective treatments in asthma, such as inhaled corticosteroids and biological treatments in patients with T2 profile. However, roflumilast has shown functional and clinical improvements as well as fewer exacerbations, so it is necessary to expand our knowledge about PDE inhibitors in patients not controlled with current treatments. Asthmatic patients with obesity or with a non-T2 profile may possibly be the main candidates to assess said treatment.

Phosphodiesterase inhibitors in COPD

Although studies demonstrate the efficacy of roflumilast in bronchial asthma, the clinical development and authorization of this molecule have focused on COPD, specifically for patients with clinical criteria for chronic bronchitis, with or without associated emphysema.

Patients with COPD and chronic bronchitis (cough and sputum production) have a higher risk of exacerbations. Consequently, it is interesting to pay special attention to this type of patient since chronic cough and sputum production are caused by inflammation of the airways, and this may be especially sensitive to the use of anti-inflammatory drugs like roflumilast[27].

Currently, the first option in the maintenance treatment of COPD is long-acting bronchodilator drugs, which include long-acting β2-agonists (LABA) and long-acting muscarinic antagonists (LAMA). Both have significantly improved the clinical management of symptomatic patients, while also reducing the number of exacerbations. Furthermore, the relevance of the inflammatory component of the airways cannot be forgotten, at least in certain patients with COPD, which may be associated with a worse evolutionary course of the disease. Therefore, in patients with a history of exacerbations, it is common to use a fixed combination of inhaled corticosteroids (IC) (anti-inflammatory) associated with bronchodilator treatment, frequently in triple therapy.

However, many patients with severe COPD and associated chronic bronchitis remain symptomatic and suffer repeated exacerbations, despite being treated with different combinations of these drugs. It is therefore necessary for new therapies to provide an additional effect to the usual treatment, especially within in the context of an evident unmet medical need. Roflumilast has pharmacological properties and a

mechanism of action that are clearly different from IC and bronchodilators, so its use should be assessed in patients whose symptoms are not controlled with other treatments.

Scientific evidence with roflumilast prior to its commercialization

The clinical development program began with dose-finding and proof-of-concept studies, followed by a larger 6-month study (M2-107). In these studies, the efficacy of roflumilast improved lung function (FEV_1) and quality of life as measured by the St. George Respiratory Questionnaire (SGRQ).

In addition, the M2-107 study provided the first evidence of the effect of roflumilast on COPD exacerbations, with a 34% reduction in the total rate of exacerbations (mild, moderate and severe) in the roflumilast group compared to placebo.

The next step in clinical development was to undertake studies specifically designed to show the effect of roflumilast on moderate and severe exacerbations. Studies M2-111 and M2-112, which have identical designs, tried to show this effect including more severe patients (post-bronchodilator $FEV_1 \leq 50\%$) and a longer follow-up (52 weeks). Roflumilast treatment significantly improved lung function compared to placebo, and in both studies the rate of moderate/severe exacerbations was numerically lower in the roflumilast group than in the placebo group. This difference was not statistically significant, although it did reach statistical significance in the pooled analysis. A possible explanation for this result was the low incidence of exacerbations in these studies. Most notably, however, a subgroup analysis of this pooled evaluation found that the decrease in exacerbations was especially pronounced in patients with associated chronic bronchitis (26%, $p = 0.001$). This finding led to the hypothesis that this population could especially benefit from the effect of roflumilast, making it the first drug proposed for development in a specific COPD phenotype, thus opening the doors to personalized disease treatment[28].

With this information, the studies included in the so-called 'enhanced' roflumilast program tried to confirm the efficacy of roflumilast in the phenotype of COPD patients with associated chronic bronchitis. This program included two phase III studies in patients with a history of exacerbations and severe or very severe COPD associated with chronic bronchitis. Additionally, there were two other studies that assessed the efficacy of roflumilast when used in association with salmeterol and tiotropium.

The results of the main variables were consistent, showing a statistically significant reduction in moderate or severe exacerbations in the roflumilast groups versus placebo. Roflumilast produced an increase in pre-bronchodilator FEV_1. The difference, which was evident starting at week 4, increased in week 8 and has been maintained since then throughout the treatment. In the M2-124/125 pooled analysis, the reduction in exacerbations achieved with roflumilast was 16.9% in the overall analysis of all patients. The drop was 20.7% in patients taking concomitant LABA and 14.6% in patients not taking LABA. This clinical benefit was maintained in studies with salmeterol and tiotropium[29,30].

A large percentage of patients in severe and very severe stages of COPD are also treated

with IC. Both roflumilast and IC are anti-inflammatory drugs, although their mechanisms of action are different. In fact, the typical neutrophilic inflammation of COPD is relatively insensitive to high doses of oral or inhaled corticosteroids. In contrast, *in vitro* and *in vivo* studies have shown the effects of roflumilast on neutrophils as well as on macrophages and CD8+ lymphocytes. Based on their differing modes of action, the anticipated added effect of roflumilast on IC was confirmed by the results obtained with roflumilast in the subgroups of patients treated with IC in previous studies[28]. In these studies, about 60% of patients were prescribed concomitant IC (≤ 2000 µg beclomethasone or equivalent). The efficacy of roflumilast in terms of exacerbations and FEV_1 was independent of IC treatment. In the subpopulation treated with IC, roflumilast showed a reduction in moderate or severe exacerbations of 19% versus placebo and a difference in pre-FEV_1 of 53 mL. When the analysis was limited to patients with chronic bronchitis, the reduction in exacerbations reached 30% ($p = 0.0012$). These results demonstrate that roflumilast can provide a clinically relevant effect in patients already being treated with IC.

The safety of roflumilast was evaluated in a large number of patients, although in real life the percentage of adverse effects has been higher than observed in premarketing clinical trials. Diarrhea was the most frequently reported adverse event, followed by weight loss and nausea. Weight loss was observed within the first six months of treatment, but it did not progress significantly afterwards and was later resolved in most patients when the treatment was interrupted. The profile of roflumilast was not modified according to the concomitant treatment that the patient was taking for COPD.

Studies with roflumilast after commercialization

Since roflumilast came onto the market, the two main clinical studies have evaluated its efficacy in patients treated with bronchodilators and IC. To date, no studies have been conducted to directly compare roflumilast with IC, either with or without concomitant bronchodilator therapy.

The clinical argument for the use of roflumilast is that it would be effective in patients with severe COPD who are at risk of exacerbations and whose disease is not adequately controlled with an IC used in association with a LABA or with triple therapy. The objective of the Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy (REACT) study was to assess the effect of roflumilast as adjuvant therapy in patients receiving recommended inhaled therapy who were at risk of COPD exacerbations[31]. The REACT study was a one-year, double-blind, parallel-group, placebo-controlled, multicenter study conducted in patients with severe COPD and associated chronic bronchitis, who had a history of frequent exacerbations and were receiving fixed-dose combination therapy with a LABA and an IC or triple therapy with LAMA/LABA/IC at the maximum approved doses. Roflumilast produced a statistically significant improvement in lung function, with a 56 mL increase in post-bronchodilator FEV_1 compared to placebo. In the total study population, the rate of moderate or severe exacerbations dropped by 14.2%. Roflumilast reduced the rate of severe exacerbations by 24.3% and the rate of hospitalizations by 23.9%. In patients receiving triple therapy, roflumilast significantly reduced

the rate of severe exacerbations by 23.3%, indicating that patients with severe COPD may experience a greater benefit if roflumilast is added to their treatment regimen.

To accept the positive impact of a medication, a standard requirement is for the results of a study to be replicated in a second clinical trial, with a similar methodology but in a different geographical setting. The REACT study was evaluated by the European Medicines Agency. The Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy) (RE[2]SPOND study)[32] responds to the previous criterion, and the methodology is very similar to the REACT study, but it was evaluated by the US FDA. The rate of moderate or severe COPD exacerbations per patient and year (primary endpoint) was numerically lower with roflumilast versus placebo (8.5%), but this difference was not statistically significant (p = 0.16). However, roflumilast did improve lung function, and in a *post hoc* analysis it significantly reduced the rate of moderate or severe exacerbations in participants with a history of more than three exacerbations and/or one or more hospitalizations in the previous year. The improvement in pre-dose FEV_1 favored roflumilast (0.053 L: 95% confidence interval [CI], 0.040 – 0.066).

Safety and tolerance of roflumilast

Although the efficacy of roflumilast in patients with COPD and chronic bronchitis has been widely demonstrated, the main limitation for its use in daily practice has been the high incidence of side effects. There are clinical experiences that have described a better tolerance when the treatment is administered every 48 hours during the first weeks. Moreover, in dose-finding studies, the rate of adverse effects was clearly lower at 250 mg. Based on this information, the Standard COPD Treatment to Treat Severe COPD (OPTIMIZE) study[33]) was designed to evaluate the withdrawal rate (for any reason) among patients who were taking roflumilast at a dose of 500 mcg/day from the beginning compared to those who took 250 mcg/day or 500 mcg/48 h for a month before increasing to this dose. Subsequently, all patients continued with 500 mcg for eight weeks. A total of 1321 patients were randomized, with baseline characteristics similar to previous studies with roflumilast. The main conclusion of this study was that the chances of premature treatment discontinuation are 34% lower when roflumilast is started at 250 mcg for four weeks before increasing the dose to 500 mcg. The improvement in lung function over the 12-week treatment period was clinically relevant (approximately 100 mL), with minimal differences between the three treatment groups. The OPTIMIZE study demonstrates that a reduced roflumilast dose of 250 mcg once daily for four weeks, before escalation to the maintenance dose of 500 mcg, improves tolerance and reduces treatment interruption. Thus, this option may be recommended to introduce this medication in candidate patients. The 250-mcg dose can even be maintained if the clinical response is favorable, but side effects appear after the dose is increased to 500 mcg.

POTENTIAL BENEFITS OF DUAL PDE INHIBITORS IN ASTHMA AND COPD

Although the best results to date have been obtained with roflumilast (which acts primarily on PDE-4), PDE-3 is the predominant isoenzyme

in the airway smooth muscle. Its inhibition produces relaxation, and PDE-3 inhibitors have been shown to induce bronchodilation in patients with asthma. Preclinical studies suggest that co-inhibition of PDE-3 and PDE-4 synergistically suppresses airway smooth muscle contraction. This observation has been confirmed using a dual PDE-3 and PDE-4 inhibitor (ensifentrine), which is capable of inducing significant bronchial relaxation *in vitro*, providing rapid and sustained bronchodilation in patients with asthma or COPD. However, PDE-3 is also involved in the regulation of vascular smooth muscle and in cardiac muscle function, so its inhibition has the potential to cause adverse events, particularly cardiovascular. These extrapulmonary effects have limited the development of these drugs. To date, none have been approved for the treatment of asthma or COPD.

Inhaled PDE inhibitors

The use of PDE-4 inhibitors has been limited due to systemic side effects. As with bronchodilators and corticosteroids, inhaled administration of PDE4 inhibitors could greatly increase the therapeutic index of a drug. Unfortunately, almost all PDE inhibitors evaluated by this route have failed in clinical trials. CHF 6001 is currently the only PDE-4 inhibitor with promising results in phase II clinical trials in asthma[34].

CONCLUSIONS

Phosphodiesterase (PDE) inhibitors act on specific phosphodiesterase enzymes characterized by their expression in different organs. Currently, their use is approved for the treatment of several diseases. For many, in which its effectiveness has been proved, the main limitation has been the high incidence of side effects. Work is currently underway to develop more selective inhibitors that, by modulating PDE in specific tissues and cells, can improve the therapeutic effect in a specific organ with fewer side effects.

DISCLOSURES

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