Roflumilast: a novel phosphodiesterase 4 inhibitor for the treatment of inflammatory airways disease

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Isoenzyme phosphodiesterase 4 inhibitors are novel therapeutic agents in late clinical development for the treatment of chronic obstructive pulmonary disease and asthma, both diseases with significant unmet treatment needs. Roflumilast is one such isoenzyme phosphodiesterase 4 inhibitor that is undergoing Phase III clinical development. It is an orally active compound that owes part of its efficacy and long duration of action to its primary metabolite roflumilast N-oxide. Preclinical and clinical studies have indicated that its probable mechanism of action is anti-inflammatory, although it may also have the ability to relax airway smooth muscle. Its relatively low incidence of class-associated gastrointestinal events and long duration of action may account for its improved therapeutic profile over other agents in its class.

Keywords: anti-inflammatory, asthma, chronic obstructive pulmonary disease, phosphodiesterase, roflumilast

Inflammatory airways diseases, including asthma and chronic obstructive pulmonary disease (COPD), are currently two of the most prevalent diseases worldwide and the incidence of both conditions is on the increase. In 2000, it was estimated that 2.74 million people died of COPD and that by 2020, COPD will be the sixth leading cause of death worldwide. In industrialized countries, this represents the fastest growing cause of mortality [1,2]. It is also evident that the economic burden of COPD will rise exponentially as the prevalence of COPD increases, owing to an aging population. With respect to asthma, it has been estimated that at least 150 million people suffer from the condition worldwide, with the disease contributing to approximately 180,000 deaths annually. Again, the incidence of this disease is rising, although the precise reasons behind the explosion in diagnosed cases of asthma remain to be determined.

There is an urgent need for the development of new therapies to aid the management of COPD as there are no existing treatments that can modify disease progression. β_2-agonists, such as salbutamol and salmeterol, and muscarinic antagonists, such as tiotropium bromide, which provide symptomatic relief, are the current drugs of choice [1]. Long-acting β_2-agonists are used alone or increasingly in combination with inhaled glucocorticosteroids and combination therapy is now considered 'gold standard' therapy for the treatment of asthma, although there is little evidence to suggest that glucocorticosteroids are effective in the majority of patients with COPD [1]. Another drug regularly prescribed for COPD is theophylline, which is a nonspecific phosphodiesterase (PDE) inhibitor with proven anti-inflammatory and bronchodilator activity [1]. In addition, sodium cromoglycate and the orally active cysteinyl-leukotriene receptor antagonist montelukast are regularly prescribed for asthma [3]. Nonetheless, there remain a significant number of unmet medical needs in the treatment of asthma and COPD, which will be discussed.

Unmet needs with current drugs in the treatment of COPD

COPD is generally poorly managed because there are no drugs that can modify disease progression and the current drugs only provide, at best, symptomatic relief and/or reduced exacerbations of the disease. Furthermore, many of the drugs used are administered via inhalation and the success of these compounds depends on the ease of use of the delivery devices, of which there are many and which are likely to increase further with the introduction of generic versions of β_2-agonists and inhaled glucocorticosteroids in the not too distant future. This is particularly relevant in patients with COPD, who are generally elderly and may have impaired coordination skills that limit the effectiveness of these devices. In addition, to obtain optimal benefit from these devices, patients need ongoing training and education, which is both time consuming and expensive. Consequently, for the effective management of

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COPD, there is an urgent need for the development of orally active disease-modifying drugs, and several studies have revealed a patient preference for oral therapy, even if the drugs have side effects [4]. Dosing regime is also important as evidence shows that once-daily dosing increases compliance in all patient groups.

Unmet needs with current drugs in the treatment of asthma

The major goal of asthma management is to minimize exacerbations of the disease while maintaining good lung function and, although the use of inhaled glucocorticosteroids and bronchodilators have revolutionized treatment of this disease, there are still many patients who achieve poor disease management with the available drugs. These include patients whose underlying inflammation is not controlled by the use of inhaled glucocorticosteroids and young children and the elderly who have trouble using inhalation devices. Consequently, compounds that are orally active, efficacious, tolerable and improve compliance would all be desirable in the management of asthma.

A number of compounds are in development that have the potential to address some of these unmet needs in the treatment of airways disease. One of the most promising new class of drugs undergoing clinical development for the treatment of airways diseases are the PDE4 inhibitors.

Phosphodiesterase 4 inhibitors

There are now known to be 11 families of enzymes called phosphodiesterases that hydrolyze the cyclic nucleotides cyclic AMP (cAMP) and/or cyclic GMP (cGMP), to their inactive monophosphates, 5′-AMP and 5′-GMP, respectively [5]. Physiologically, elevation of cAMP has been shown to be broadly anti-inflammatory, mediate smooth muscle relaxation and modulate sensory nerve activity in the lung. Consequently, inhibition of certain PDE isoenzymes has been targeted as a novel treatment for inflammatory disease. Attention has focused on the PDE4 isoenzyme, which is predominant in inflammatory cells since the discovery that experimentally, a number PDE4 inhibitors have profound anti-inflammatory effects [6]. Furthermore, by selectively targeting PDE4, it has been anticipated that the clinical efficacy of the nonselective PDE inhibitor theophylline (a drug that has been used in the treatment of airways disease for many years) can be improved in tandem with the loss of many of the unacceptable side effects of this drug. As a consequence of these early studies, several isoenzyme-selective PDE4 inhibitors are in clinical development, including roflumilast (Daxas®), which is being developed by Nycomed (formally Altana).

Introduction to roflumilast

Roflumilast is an isoenzyme-selective PDE4 inhibitor with an inhibitory concentration 50% (IC_{50}) of 0.8 nM against the PDE4 enzyme and represents a novel class of drug for the treatment of inflammatory airways disease. Thus far, roflumilast has progressed furthest in clinical studies of all the PDE4 inhibitors in development. It has been formulated as a once-daily oral tablet and is rapidly absorbed and metabolized to its primary metabolite roflumilast N-oxide, which is only two- to threefold less potent than roflumilast itself, but has a prolonged half-life (~15 h) following ingestion of a 500-µg tablet of roflumilast [7,8]. As a result, this metabolite is highly likely to be a major contributor to the pharmacological efficacy of roflumilast [8].

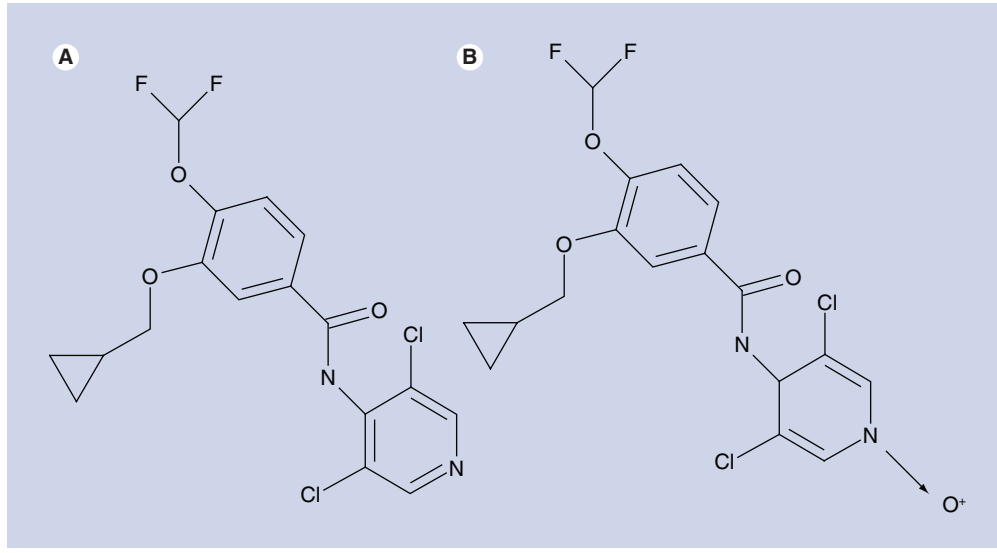
Chemistry

Roflumilast, (3-cyclopropylmethoxy-4-difluromethoxy-N-[3,5-di-chloropyrid-4-yl]-benzamide; molecular weight 403.2) is a benzamide derivative [7]. The primary metabolite of roflumilast, known as roflumilast N-oxide, results from N-oxidation of the dichloro-pyridyl moiety. The structure of both these compounds is shown in **Figure 1**.

Pharmacokinetic & pharmacodynamic properties of roflumilast

The pharmacokinetic characteristics of roflumilast after oral (500 µg) and intravenous (150 µg) administration were investigated in a randomized, two-period, crossover study of 12 healthy male volunteers. From these studies, it was determined that the absolute bioavailability of orally administrated roflumilast is 79% [9]. Maximum plasma concentrations (C_{max}) of roflumilast peak approximately 3 h after administration and then decline rapidly. Plasma levels of roflumilast N-oxide peak approximately 6 h after administration and remain elevated for up to 24 h. Consequently, the extent of exposure, assessed as area under the curve (AUC), is 12-fold higher for roflumilast N-oxide than roflumilast [9]. This exposure and prolonged

Figure 1. Chemical structures of (A) roflumilast and (B) roflumilast N-oxide.



duration of action of roflumilast N-oxide is believed to allow once-daily administration of roflumilast.

There were no significant difference in pharmacokinetic parameters in morning or evening administration of roflumilast [10]. Upon comparison of the pharmacokinetics in young and middle-aged subjects, apart from an increased C_{max} in middle-aged subjects, reflecting a higher rate of absorption, there was no major difference between the two populations [11]. Food intake [8], smoking [12], salbutamol [13], budesonide [14] and warfarin [15] do not significantly alter the pharmacodynamics of roflumilast. In addition, roflumilast has, thus far, not been shown to adversely influence cardiovascular function, unlike the nonselective PDE inhibitor theophylline [16]. It has been approximated that 70% of orally administered roflumilast is eliminated via the kidneys and therefore the effect of roflumilast in patients with severe renal impairment has also been evaluated. Patients with severe renal impairment were assessed with matched pairs of healthy subjects. Subjects were given roflumilast 500 µg once daily in an open-label study and pharmacokinetic parameters were measured, as well as creatinine clearance as an assessment of renal impairment. Although the plasma concentrations of both roflumilast and its active metabolite roflumilast N-oxide were slightly lower in patients with renal failure than healthy subjects, this was not statistically significant and therefore no dose adjustment of roflumilast is required in patients with kidney problems [17]. These data demonstrate that roflumilast appears to be safe and efficacious in all patient groups.

Preclinical data

A wide range of preclinical studies have been undertaken with roflumilast, investigating both its bronchodilator and anti-inflammatory mechanism of actions. In cellular assays, roflumilast, alongside other PDE4 inhibitors, has been shown to suppress cytokine synthesis [18], lymphocyte proliferation [7], protease release [19], airway smooth muscle proliferation [20] and leukocyte adhesion to endothelial cells [19]. Furthermore, particularly pertinent to asthma, PDE4 inhibitors have been shown to reduce eosinophil survival and inhibit eosinophil chemotaxis [21]. In addition, both roflumilast and roflumilast N-oxide can suppress electrical field stimulation-induced, nonadrenergic, noncholinergic contraction of isolated guinea pig bronchus, implicating a potential role for roflumilast in modulating sensory nerve activity in the lung. The effect of roflumilast has also been examined in a wide range of classical *in vivo* models and has been shown to inhibit both spasmogen and antigen-induced bronchoconstriction in allergic guinea pigs, rats and mice; although, in guinea pigs, roflumilast was far more potent at inhibiting allergen rather than histamine-induced bronchoconstriction, suggesting that this drug may be inhibiting mast cell degranulation rather than

directly causing smooth muscle relaxation [22–24]. In addition, roflumilast reduced eosinophil and neutrophil accumulation in allergen-challenged Brown Norway rats, a model for the late asthmatic response, and tumor necrosis factor (TNF)-α release in a rat model of lipopolysaccharide (LPS)-induced pulmonary neutrophilia [23]. In models of chronic remodeling of the airways, roflumilast has also been shown to suppress development of emphysema-like morphology in mice exposed to chronic cigarette smoke [25] and in a chronic remodeling murine model of inflammation, induced by ovalbumin, roflumilast-suppressed subepithelial collagen deposition, epithelial thickening and reduced inflammatory cell accumulation [26]. These data suggest that, in animal models, roflumilast possesses significant anti-inflammatory activity and remodeling with some capacity to influence airway smooth muscle tone.

Clinical profile

A wide variety of Phase II and III clinical studies have now been undertaken with roflumilast and its active metabolite roflumilast N-oxide in patients with asthma, COPD and allergic rhinitis. These studies are now discussed in more detail.

Asthma

Dose-ranging studies (100–500 µg) were conducted in asthmatic patients (total 690 patients, forced expiratory volume $[FEV]_1$ 50–85% of predicted) taking no concomitant medication except the β_2-agonist salbutamol. Patients were assessed by FEV_1, morning and evening peak expiratory flow (PEF), lack of efficacy and incidence of adverse events. After a run-in period of 1–3 weeks, roflumilast (100, 250 or 500 µg) was administered once-daily for 12 weeks. In these studies, there was a dose-dependent improvement in FEV_1 and PEF with clinically significant improvements observed at the highest two doses, 250 and 500 µg, respectively ($p < 0.0001$). The improvements in lung function parameters observed with the 500 µg were significantly superior to those seen with the 100-µg dose ($p = 0.0017$). Furthermore, a dose-dependent reduction in the dropout rate, as a result of lack of efficacy, was also observed [27]. Significantly, roflumilast demonstrated an early onset of action with significant improvements in morning PEF noted just 24 h after the first dose, although the underlying mechanisms behind this remain unclear [28]. In another Phase II study, the effect of roflumilast was examined on the allergen-induced early and late asthmatic responses of 23 asthmatics (FEV_1 ≥70% predicted, aged 18–50 years) in a double-blind, placebo-controlled, three-period, cross-over study. None of these patients were taking any other asthma medication, except bronchodilators for symptomatic relief. Each patient was treated with placebo or roflumilast (250 or 500 µg) for 7–10 days, followed by a 2–5-week washout period. On the last day of each treatment period, allergen provocation was undertaken. In this design, all patients received placebo and both doses of roflumilast. Patients were assessed by spirometry prior to, and at standard time points after, allergen or methacholine provocation. Roflumilast (250 and 500 µg) was found to suppress both the early asthmatic response (EAR) and late asthmatic response (LAR), although this was far more pronounced with respect to LAR (43 vs 28%, roflumilast 500 µg vs placebo) [29], suggesting that roflumilast has an anti-inflammatory mechanism of action. In support of this, in another double-blind, placebo-controlled study ($n = 15$, FEV_1 50–90% predicted) that directly assessed the bronchodilator actions of roflumilast (1000 and 500 µg once daily), roflumilast, in direct contrast to salbutamol, was found to have no direct bronchodilator activity, supporting the notion that the predominant mechanism of action of roflumilast in improving lung function is as an anti-inflammatory agent [30]. This is further evident from a double-blind, placebo-controlled study of 421 patients with asthma (FEV_1 50–85% predicted, aged 12–70 years) in which the effects of roflumilast (500 µg once daily) were directly compared with the inhaled glucocorticosteroid beclomethasone dipropionate (200 µg twice daily). After a 1–3-week run-in period in which patients were solely administered placebo compounds, patients were either administered a roflumilast tablet once daily and given placebo via an MDI or beclomethasone dipropionate twice daily via an MDI and a placebo tablet for a further 12 weeks. Both drugs significantly improved lung function (FEV_1, forced vital capacity [FVC] and morning PEF) and, although the improvements were superior in the patients taking beclomethasone diproprionate, this was not significant. In addition, both drugs reduced the need for rescue medicine to a comparable degree [31].

Studies have also been conducted in patients who experience exercise-induced asthma. In a randomized, placebo-controlled, double-blind,

two-period, crossover study, patients either received roflumilast for 28 days, followed by a 14-day washout period before being administered placebo for a further 28 days, or this was reversed with patients receiving placebo prior to roflumilast. Roflumilast 500 µg caused a significant reduction (28%) in FEV_1 after exercise by day 28. Furthermore, *ex vivo* studies demonstrated a significant reduction in TNF-α release, following stimulation with LPS, from peripheral blood mononuclear cells of patients treated with roflumilast [32]. This suggests that roflumilast may be exerting an anti-inflammatory effect in these patients. Further exploration of this is necessary.

In studies to assess the long-term efficacy of roflumilast, patients (n = 456) who had previously been administered roflumilast (100, 250 and 500 µg) in a 12-week dose-ranging study were enrolled for a further 40 weeks in an open-label follow-up trial. All patients received 500 µg once daily. Patients who were given 500 µg for the first 12 weeks maintained their improvement in lung function over the further 40 weeks of the study. Patients who had previously taken the lower doses of roflumilast significantly improved FEV_1 over the course of the study. Collectively, these studies have demonstrated that roflumilast (500 µg) can significantly improve lung function in asthmatics, which is most likely to be via an anti-inflammatory mechanism of action. [33]

COPD

A large body of clinical trial data has now been collected on the effects of roflumilast in patients with COPD.

The first major trial of roflumilast in patients with COPD was undertaken to assess the safety and efficacy of this drug in patients with mild-to-moderate COPD. In a randomized, double-blind, placebo-controlled study, COPD patients (n = 516, postbronchodilator FEV_1 35–75%) were all given placebo for 2 weeks, followed by a further 26 weeks of either placebo, 250 or 500 µg once daily. The efficacy of roflumilast in this study was assessed with post-bronchodilator FEV_1, FVC, $FEF_{25–75,}$ morning PEF and exacerbation rate. Roflumilast dose dependently improved FEV_1, $FEF_{25–75}$, FVC and morning PEF. There was also a 48% reduction in exacerbations, relative to placebo, in the group taking 500 µg [34]. In a wider study of 1411 patients with mild-to-moderate COPD (post-bronchodilator FEV_1 30–80%) receiving roflumilast (250 or 500 µg) or placebo for 24 weeks, there was a statistically significant, dose-dependent ($p < 0.0001$) improvement in FEV_1, whereas a significant fall in FEV_1 was observed in the placebo-treated group. Furthermore, roflumilast significantly reduced the exacerbation rate of patients with COPD. When compared with placebo, the patients treated with roflumilast (500 µg) experienced 34% fewer exacerbations. The patients evaluation of their health-related quality of life was assessed using the St George's Respiratory Questionnaire (SGRQ) and a positive change in this score was greatest in the group treated with roflumilast 500 µg (3.51 unit decrease vs 1.79 unit decrease in the placebo group). These data demonstrate that as well as lung function improvements, roflumilast improved quality of life in COPD patients [35].

In another randomized, double-blind, placebo-controlled trial (n = 581), patients received either roflumilast or placebo for 24 weeks or roflumilast for 12 weeks followed by placebo for the remaining 12 weeks. Roflumilast significantly improved FEV_1 compared with placebo ($p = 0.0003$). In patients administered continuous roflumilast, these improvements were maintained throughout the 24 weeks of study. In the patients where roflumilast was withdrawn after 12 weeks, FEV_1 slowly declined, but remained above placebo levels, supporting a likely anti-inflammatory mechanism of action. In a third study of 1513 severe/very severe COPD patients, there was a significant improvement in FEV_1. Total moderate and severe exacerbations were 7% less with roflumilast treatment than placebo, which was not statistically significant. However, upon secondary analysis of patients with stage 4 COPD, moderate/severe exacerbations, were significantly lower with roflumilast 18% ($p = 0.0147$). This suggests roflumilast may be of greatest use in patients with more severe COPD [101].

To further examine whether roflumilast was having an anti-inflammatory effect in patients with COPD, 38 patients (mean post bronchodilator FEV_1 61% expected) were treated with roflumilast 500 µg once daily for 4 weeks. Sputum samples were collected before and after 2 and 4 weeks of treatment and assessed for cell counts, interleukin (IL)-8 and neutrophil elastase levels. Roflumilast significantly reduced the number of neutrophils (38%) and eosinophils (50%) present in the sputum. Furthermore, a

concomitant reduction in NE (30.6%) and IL-8 levels was observed [36]. These data provide further evidence that roflumilast has an anti-inflammatory effect, which may contribute to its efficacy in patients with COPD.

Allergic rhinitis

A small-scale study has also investigated the potential of roflumilast in patients with allergic rhinitis. In a randomized, double-blind, placebo-controlled trial undertaken during the allergen-free season, 25 patients received either roflumilast for 9 days, undertook a 14-day washout period and then took placebo for 9 days, or vice versa. During treatment intranasal, allergen provocation was undertaken daily, 2 h after drug administration, rhinal airflow was assessed by anterior rhinomanometry and subjective symptoms (including itching and rhinorrhea) were also measured. Roflumilast 500 µg consistently improved rhinal airflow throughout the 9 days of treatment and, on day 9, their was significant improvement over placebo [37]. These data demonstrate the potential of roflumilast in treating allergic rhinitis and may provide an alternative oral treatment for this disease.

Safety & tolerability

The adverse side effects (mainly gastrointestinal [GI] intolerance) of first-generation PDE4 inhibitors, such as rolipram, prevented further clinical development of these drugs. There is little doubt that drugs of this class have the potential to be highly effective, yet their use has been constrained by the class-limiting side effects of GI disturbances, nausea and sometimes vomiting. Thus, the predominant aim when developing novel PDE4 inhibitors is to generate efficacious compounds while reducing the side effects associated with these drugs.

Roflumilast 500 µg once daily is associated with a low frequency of drug-related GI adverse events. Examination of the data from the major clinical trials in asthmatic and COPD patients reported the frequency of these drug-related adverse effects to be approximately 6%, with the most commonly reported events being headache (3%), diarrhea (1%) and nausea (1%). In a study of 456 asthmatic patients receiving roflumilast 500 µg once daily for 40 weeks, the most common adverse events reported were associated with the respiratory system and were deemed unrelated to drug treatment. Nonetheless, 6% of patients exhibited side effects that were likely to relate to roflumilast treatment. These side effects were reportedly mild-to-moderate in intensity and transient in nature. In this study, 6% of patients discontinued the trial owing to adverse effects, but less than 3% were due to roflumilast. A total of 16 patients in the study reported serious adverse events, but none of these were deemed to be drug related. Other laboratory parameters assessed included vital signs and electrocardiogram (ECG). However, no clinically relevant changes occurred with these [33]. In addition, a long-term safety study has been conducted in patients with COPD. Patients received placebo, or roflumilast 250 or 500 µg in a placebo-controlled, double-blind trial for 26 weeks. Following this, 397 patients continued on an open-label extension, taking roflumilast for a further 26 weeks of the study. There was no significant difference in the incidence of adverse effects between the placebo control and drug-treatment group (49% during the first 26 weeks, 41% thereafter). More than 90% of these adverse drug events were deemed to be unrelated to drug treatment, although this still suggests that nearly 10% of adverse events were a result of roflumilast treatment. However, the majority of these events were mild to moderate in intensity and transient in nature. During the open-label extension, ten patients (2.5%) experienced adverse side effects that were definitely related to roflumilast and three of these patients dropped out of the study. Nevertheless, this represents a small fraction of the total patients on roflumilast and demonstrates that, although there are still incidences of class-associated side effects, in general, administration of roflumilast for up to 52 weeks is safe and well tolerated.

Long-term safety studies

The clinical effects of the long-term administration of roflumilast have yet to be determined, given that it has only been administered in humans for up to 52 weeks. However, in both rats and cynomolgus monkeys, long-term administration of high doses of other PDE4 inhibitors has elicited arteriopathy in the mesenteric bed. Arteriopathy is a condition associated with arterial necrosis and recruitment of inflammatory cells and has been observed in rats after treatment with large doses of many vasodilators, including PDE3 and PDE4 inhibitors, adenosine agonists, endothelin receptor antagonists and potassium channel openers [38]. This suggests that the hemodynamic properties of vasodilators rather than any cytotoxic effects of these drugs *per se* are causing

this condition. Nevertheless, the mechanisms by which these agents induce arteriopathy in rats remain to be established, as does whether rats are more susceptible to this condition that other species. However, 3 months treatment of rising, high doses of the PDE4 inhibitor SCH351591 (12, 24 and 48 mg/kg) to cynomolgus monkeys also induced inflammation of the arterioles in many organs and tissues, including the mesentery, gall bladder, esophagus, heart kidneys and stomach. Three animals were also sacrificed due to inflammation of the colon [39]. These data suggest that arteriopathy resulting from PDE4 inhibitors is not peculiar to the rat and can also be observed in nonhuman primates, previously thought resistant to such toxicity. However, no such changes have been reported with roflumilast.

These effects observed in preclinical studies are not anticipated to be observed in clinical trials as the dose used in humans is likely to be a fraction of that used in human studies. Furthermore, theophylline, which has been used to treat asthma and COPD for over half a century, can also induce arteriopathy in rats, with no evidence of this occurring in humans. Nonetheless, there remains the concern that PDE4 inhibitors may induce mesenteric inflammation in patients with asthma and COPD, particularly as GI disturbances are the predominant adverse effect observed with these drugs. Thus, the US FDA have highlighted arteriopathy as a significant safety issue with the use of PDE4 inhibitors and markers of this condition must be rigorously monitored in clinical trials and postmarketing surveillance. However, patients administered another PDE4, cilomilast, were monitored closely for mesenteric vasculopathy and a number of patients who experienced GI disturbances and positive fecal occult blood test underwent colonoscopy and no evidence of arteriopathy in any patient was observed [102]. Another potential consequence of chronic treatment with PDE4 inhibitors is immunosuppression, given the data demonstrating an anti-inflammatory mechanism of action of these drugs. This has yet to be observed in patients treated with roflumilast, although it is clearly something to be monitored in postmarketing surveillance.

Conclusion

The clinical data arising from studies with roflumilast should be interpreted with cautious optimism. Roflumilast, unlike other PDE4 inhibitors examined in clinical studies, appears to be both efficacious and well tolerated, with a relatively low incidence of mild-to-moderate, transient side effects. Nevertheless, these adverse effects are dose limiting and, thus, the full potential of roflumilast in humans may not be realized. Interpreting the data from these trials has also not been without its difficulties as, until recently, very few studies concerning this drug had been published as full articles in peer-reviewed journals. The long-term beneficial treatment effects associated with roflumilast are probably linked to the pharmacokinetic and pharmacodynamic properties of roflumilast. Roflumilast is converted to its primary active metabolite roflumilast N-oxide, which is only twofold less potent than the parent compound itself, thereby producing a prolonged half-life of 15 h. As a result, roflumilast has the added advantage over other PDE4 inhibitors, such as cilomilast, in development as it only has to be administered once daily, thus reducing compliance problems encountered with repetitious dosing. For the first time, roflumilast appears to be an orally active anti-inflammatory agent efficacious in both patients with asthma and COPD. In both conditions, roflumilast significantly improves FEV_1 peak flow and encouragingly appears equally as effective as low doses of beclomethasone diproprionate in a limited trial in asthmatics [31]. In addition, in COPD patients, exacerbations of the disease appear to be reduced [35]. Nevertheless, there remain key questions to be answered concerning the potential prescribing of roflumilast. For example, it is yet to be determined whether roflumilast will be prescribed alone or in combination with glucocorticosteroids, perhaps to enable the dose of both these drugs to be reduced. In addition, it needs to clearly established which asthma patient groups would derive most benefit from treatment with roflumilast and to facilitate further studies directly comparing roflumilast with glucocorticosteroids and combination therapies. Furthermore, to persuade clinicians to prescribe roflumilast, the differences between theophylline and PDE4 inhibitors need to be highlighted and indeed comparator trials with theophylline are required. However, it is evident from studies conducted already that, in contrast to theophylline, roflumilast is not a significant bronchodilator and is predominantly modulating inflammation. Any bronchodilator effects seen with PDE4 inhibitors in COPD may be attributed to the attenuation in

airways inflammation, as has been observed with cilomilast [40]. Additionally, the narrow therapeutic index and troublesome drug interactions that restrict the prescribing of theophylline are not seen with roflumilast.

Future perspective

There are many clinical trials being undertaken with new classes of drugs for airways disease, including novel leukotriene antagonists, chemokine inhibitors, signal transduction pathway inhibitors, antioxidants and proteinase inhibitors [41]. With this, and the promise that PDE4 inhibitors present, the next 5 years will be an exciting time in this field. Within this time, it is hoped that roflumilast will be licensed for the treatment of asthma and COPD by both the FDA and European Medicines Agency (EMEA) and start to have a significant therapeutic role. If this is the case, it can be anticipated that prescriptions will be given to a large number of patients, thus allowing the investigation of whether PDE4 inhibitors can achieve long-term disease control as well as improve the quality of life in both asthmatics and COPD patients. Over 5 years, a more conclusive comparison between oral PDE4 inhibitors and inhaled glucocorticosteroids can also be drawn, alongside distinguishing the actions of PDE4 inhibitors from those of older nonselective PDE inhibitors, such as theophylline. Furthermore, some notion on the benefits of any possible synergistic effects of PDE4 inhibitors and other respiratory drugs can begin to be investigated. It will also become apparent whether side effects associated with roflumilast will constrain use and compliance of the drug. In addition, it is also highly probable that other drugs of the same class will begin to appear on the market. If this is the case, there is likely to be real competition for market share, especially if any newer drugs appear to be better tolerated.

Executive summary

- Inhaled glucocorticosteroids are the recommended first therapy for treating the underlying inflammation in both asthma and chronic obstructive pulmonary disease (COPD). Nevertheless, the place of inhaled corticosteroids in the treatment of patients with COPD is controversial and, since they are administered via inhalation, problems with delivery and compliance occur with many patient groups.
- Roflumilast is a phosphodiesterase 4 inhibitor with potent anti-inflammatory properties currently under development for the treatment of asthma and COPD.
- Roflumilast is formulated as an oral, once-daily medication, which is converted to its primary metabolite roflumilast N-oxide, which contributes to its long duration of action.
- Roflumilast has demonstrated efficacy in patients with both COPD and asthma with minimal side effects and has the potential to be the first disease-modifying agent for COPD.

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