FRESH FROM THE PIPELINE

Roflumilast

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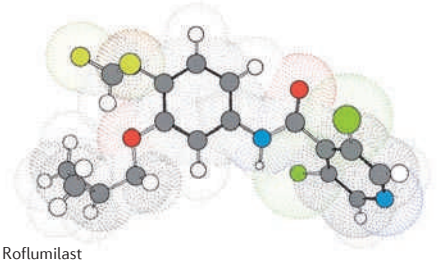
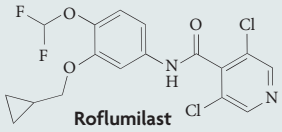


Roflumilast

In July 2010, roflumilast (Daxas; Nycomed) was granted marketing authorization by the European Commission for the maintenance treatment of severe chronic obstructive pulmonary disease, as an add-on to bronchodilator treatment.

Chronic obstructive pulmonary disease (COPD) — a chronic inflammatory disease of the airways and lungs — is a major cause of morbidity and mortality worldwide[1]. The disease, which is characterized by progressive airflow limitation that is not fully reversible, is primarily caused by cigarette smoking, although occupational and environmental pollution might also have a role in some cases[1]. COPD is nearly always associated with complex chronic co-morbidities such as heart failure and metabolic syndrome, which may contribute to its clinical manifestations and progression.

At present, there are no approved drugs that have been shown to slow or halt the progression of COPD. Current pharmacotherapy provides symptomatic relief with bronchodilatory drugs[1,2] — in particular, inhaled β_2-adrenoceptor agonists such as salmeterol (Serevent; GlaxoSmithKline), formoterol (Foradil; Novartis/Astellas) and indacaterol (Onbrez; Novartis), and anticholinergic agents such as tiotropium bromide (Spiriva; Boehringer Ingelheim/Pfizer). Patients with severe disease and a history of exacerbations are typically prescribed inhaled corticosteroids in combination with long-acting β_2-adrenoceptor agonists (LABAs), which can help reduce the frequency of disease exacerbations[1,2] (see Supplementary information S1 (figure)). Theophylline, a weak bronchodilator that has several activities including non-selective inhibition of phosphodiesterase enzymes, has also been used to treat COPD, but its narrow therapeutic window and interactions with other drugs limit its use[3].



Roflumilast

3-(cyclopropylmethoxy)-*N*-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide;
$C_{17}H_{14}Cl_2F_2N_2O_3$; M_r = 403.2

Figure 1 | **Structure of roflumilast.**

Basis of discovery

Phosphodiesterase 4 (PDE4) is one of a family of at least 11 enzymes that catalyse the breakdown of the signalling molecules cyclic AMP and/or cyclic GMP[3]. PDE4 is the main cAMP-metabolizing enzyme in inflammatory and immune cells, and PDE4 inhibitors have a range of anti-inflammatory properties, including inhibition of the release of inflammatory mediators and inhibition of immune-cell activation[3]. Furthermore, PDE4 inhibitors have shown therapeutic effects in animal models of airway inflammation[3]. Several PDE4 inhibitors have therefore been investigated in diseases involving airway inflammation, including COPD and asthma. Roflumilast is the first such agent to receive marketing approval.

Drug properties

Roflumilast (FIG. 1) and its major active metabolite, roflumilast *N*-oxide, are potent and selective PDE4 inhibitors[3–8]. Both compounds suppress the release of inflammatory mediators following *in vitro* stimulation of human immune cells[3,4,8]. Roflumilast showed efficacy in animal models of airway inflammation[3,5,6,8], including chronic exposure to cigarette smoke[6], and reduced the number of sputum neutrophils and eosinophils in patients with COPD[7,8].

Clinical data

The safety and efficacy of roflumilast (500 μg orally once daily) in patients with COPD was investigated in several randomized, double-blind, placebo-controlled trials[8–12].

Two 1-year studies involved 3,091 patients with severe to very severe COPD (post-bronchodilator FEV_1 (forced expiratory volume in 1 second) ≤50% of the predicted value based on gender, age and height controls) associated with chronic cough and sputum (chronic bronchitis), with at least one documented disease exacerbation in the previous year[8,11]. The use of LABAs, or short-acting anticholinergic agents in patients not taking LABAs, as well as 'rescue products' (salbutamol or albuterol) when necessary, was allowed[8,11]. The use of inhaled corticosteroids, tiotropium and theophylline was prohibited[8,11]. The primary end points were the change in pre-bronchodilator FEV_1 and the rate of occurrence of disease exacerbations that were moderate or severe[8,11].

In a pooled analysis of the two studies, roflumilast significantly improved lung function compared with placebo, increasing the mean pre-bronchodilator FEV_1 by 48 ml[8,11]. After 1 year, the rate (per patient per year) of moderate disease exacerbations (requiring intervention with systemic glucocorticosteroids) or severe exacerbations (resulting in hospitalization and/or death) was 1.14 for patients receiving roflumilast and 1.37 for patients receiving placebo — a relative risk reduction of 16.9% (REFS 8,11).

A previous, similar 1-year study involved 1,513 patients with severe COPD (post-bronchodilator FEV_1 ≤50% of the predicted value) but not necessarily associated with a history of chronic bronchitis and of COPD exacerbations[10]. The use of inhaled corticosteroids was permitted, but the use of LABAs and theophylline was prohibited[10]. Roflumilast significantly improved lung function compared with placebo, increasing mean post-bronchodilator FEV_1 by 39 ml, but did not reduce the rate of disease exacerbations[10].

Two 6-month supportive studies involved patients with moderate to severe COPD (non-reversible airway obstruction and a FEV_1 of 40–70% of the predicted value)[8,12]. Roflumilast or placebo was added to continuous treatment with either salmeterol in one study (which involved 933 patients) or tiotropium in the other (which involved 743 patients)[8,12]. Addition of roflumilast improved pre-bronchodilator FEV_1, the primary end point, by 49 ml beyond the bronchodilator effect of salmeterol treatment alone in the first study, and by 80 ml beyond tiotropium treatment alone in the other study[8,12].

Indications

Roflumilast is approved by the European Commission for the maintenance treatment of severe COPD (FEV_1 post-bronchodilator <50% of the predicted value) associated with chronic bronchitis in adult patients with a history of frequent disease exacerbations, as an add-on to bronchodilator treatment[8]. ▸

ANALYSIS | CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Analysing issues for the treatment of COPD are Leonardo M. Fabbri, M.D., Professor of Respiratory Medicine, and Bianca Beghé, M.D., Aggregate Professor, Department of Medical and Surgical Specialties, Section of Respiratory Diseases, University of Modena and Reggio Emilia, Italy.

The management of COPD has improved dramatically in the past 20 years. Inhaled long-acting bronchodilators, particularly LABAs and long-acting anticholinergics, and inhaled corticosteroids, substantially reduce symptoms and disease exacerbations, and improve lung function and quality of life[1]. However, their effects are limited; for example, in patients with severe COPD, lung function may be improved from 30% of the predicted value to a maximum of 40–50% of the predicted value, and the frequency of disease exacerbations may be reduced by a maximum of 30%. Furthermore, these inhaled agents have more marginal and inconsistent effects on the pulmonary and systemic chronic inflammation associated with COPD, and do not affect the chronic co-morbidities of COPD.

The most important unmet need in COPD is for prevention[13]. Once COPD is established, the second most important unmet need is for early diagnosis and interventions[14]. Third, although COPD is known to be heterogeneous, it is managed as a single disease entity, thus missing the opportunity for targeted therapy for specific phenotypes and for proper treatment of co-morbidities[15]. Finally, the limited compliance and adherence of patients with COPD to pharmacotherapies is also an important issue[16].

Although various compounds have been and continue to be investigated for their therapeutic potential in COPD[2], it is likely that the only drug with a novel mechanism of action for COPD to be introduced in the next few years will be roflumilast, an oral PDE4 inhibitor that has recently been granted marketing authorization in the European Union. Several innovative aspects of roflumilast might help address some of the unmet needs of patients with COPD. First, when co-administered with existing medications, roflumilast further reduces symptoms and disease exacerbations[11,12], although only in patients with the most severe symptoms. So, roflumilast will be the first agent targeted to a specific phenotype of COPD — that is, patients with severe airflow limitation associated with chronic cough and sputum and recurrent disease exacerbations.

As COPD exacerbations are associated with progression of disease and may increase mortality, the effect of roflumilast on disease exacerbations is particularly important[17]. Roflumilast reduces pulmonary inflammation[7], and this effect might be additive to that of inhaled corticosteroids. The oral administration route of roflumilast might improve compliance and could result in systemic effects that also influence chronic co-morbidities. However, roflumilast is associated with significant adverse events, including diarrhoea, headache and nausea in some patients[8–12]. Interestingly, roflumilast caused a small loss of weight that, in patients with diabetes, is associated with a decrease in levels of blood glucose and glycosylated haemoglobin[18], suggesting a systemic metabolic effect. However, roflumilast had no effect on systemic inflammatory biomarkers[11,12], such as C-reactive protein, suggesting that more studies are needed to investigate its potential effects on systemic inflammation and co-morbidities.

Box 1 | The market for drugs for chronic obstructive pulmonary disease (COPD)

Analysing the market for drugs for COPD is Uma Yasothan, IMS Health, London, UK.

The global market for drugs for respiratory diseases, primarily asthma and COPD, was valued at US$57 billion in 2009, and is estimated to grow at an average rate of 5% in the next 5 years[19,20]. It is currently dominated by inhaled therapies, with the market leaders being salmeterol in combination with fluticasone (Seretide/Advair; GlaxoSmithKline), and tiotropium bromide (Spiriva; Boehringer Ingelheim/Pfizer), which had 2009 sales of $8.5 billion and $3.9 billion, respectively. Theophylline, an oral drug currently used for COPD, had sales valued at $375 million in the major European markets (France, Germany, Italy, UK and Spain) in 2009 (REF. 19).

Roflumilast (Daxas; Nycomed) has been in clinical development for both asthma and COPD. In July 2010, it was granted marketing authorization in Europe for the maintenance treatment of severe COPD as an add-on to bronchodilator treatment, thereby becoming the first oral drug to be approved for COPD for many years. However, in the United States, the FDA issued a complete response letter in May 2010 to the regulatory application for the use of roflumilast for COPD. Analyst estimates suggest that the initial uptake of roflumilast will be modest, with forecasts for sales in the European Union starting at 7 million euros in 2010 and reaching 150 million euros in 2015 (REF. 21).

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Competing financial interests
L.M.F. and B.B. declare competing financial interests: see web version for details.