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Roflumilast – a phosphodiesterase-4 inhibitor licensed for add-on therapy in severe COPD

Anne B. Taegtmeyer[a], *Jörg D. Leuppi*[b], *Gerd A. Kullak-Ublick*[a]

[a] Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Switzerland
[b] Clinic of Internal Medicine, University Hospital Basel, Switzerland

Summary

Roflumilast is a selective phosphodiesterase 4 inhibitor which has been licensed in the European Union since 2010 and in Switzerland since November 2011 as an add-on treatment for patients with chronic obstructive pulmonary disease (COPD) in GOLD (Global Initiative for Chronic Obstructive Lung Disease) stages 3 and 4 (FEV_1 <50% predicted after bronchodilatation) and frequent exacerbations despite correctly-dosed therapy with a long-acting bronchodilator. Roflumilast is designed to target both the systemic and pulmonary inflammation associated with COPD. In this review roflumilast's chemistry, pharmacodynamics, pharmacokinetics, clinical efficacy, safety and tolerability and the current ongoing clinical trials involving roflumilast are outlined. Information has been sourced from the Swiss and US product information monographs, peer-reviewed published literature (identified from a PubMed MEDLINE search 1966 – March 2012 using the term "roflumilast"), the COPD GOLD international guidelines for the management of COPD (Revised 2011) and an independent analysis of phase 3 clinical trial data by FDA staff physicians. Clinical efficacy in terms of a modest gain in FEV_1% and a reduction in exacerbation rate has been demonstrated in phase 3 clinical trials and roflumilast has been recently incorporated into international treatment guidelines. However data examining roflumilast as add-on therapy to long-acting bronchodilators and ICS (standard therapy) is currently awaited and phase 4 post-marketing studies are required to determine the incidence and severity of adverse events and the long-term beneficial effects of roflumilast as a maintenance therapy for COPD in every-day clinical practice.

Key words: *COPD; chronic bronchitis; phosphodiesterase-4 inhibitor; add-on therapy; roflumilast*

Introduction

The burden of the chronic obstructive pulmonary disease (COPD) is increasing worldwide (www.goldcopd.com). The prevalence in Switzerland, for instance, has been estimated to be 2–7% of the population depending on age and gender [1] and as many as twenty-eight per cent of current smokers suffer from COPD [2]. In 2004 COPD was the fourth leading cause of death world-wide [3].

COPD is characterised by irreversible chronic airflow limitation that usually leads to a progressive decline in lung function over time. The development of COPD is associated with both chronic airway and systemic inflammation [4, 5]. Effective treatment of COPD is based on a combination of smoking cessation, physical activity and pharmacological agents. The aim of pharmacotherapy is to reduce symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance [6]. Pharmacological treatment centres essentially around short-acting bronchodilators for patients in low risk categories through long-acting bronchodilators and inhaled corticosteroids to most recently, add-on therapy with the phosphodiesterase-4 (PDE4) inhibitor roflumilast [6]. Theophylline, a non-specific phosphodiesterase inhibitor, is also licensed for the treatment of COPD, however its usefulness in clinical practice is restricted by adverse effects, limited efficacy and its potential for drug interactions. Its use has therefore declined in recent years [7]. Roflumilast has been called a "designer" theophylline by some [8].

However, none of the established pharmacological treatments for COPD, either alone or in combination, have been shown to ameliorate the progressive decline in lung-function or to decrease mortality [9, 10]. There is therefore a great need for new agents such as roflumilast which may show disease-modifiying effects. A further recent development in the management of COPD has been the more individualised approach to pharmacological treatment through more accurate phenotyping [6], which promotes the need for more accurate phenotyping methods [11].

Compared to previous guidelines, the recent global guidelines for the management of COPD promote a more individual tailoring of pharmacological therapy according to symptoms (classified as "less" and "more"), air-flow limitation (classified as "mild", "moderate", "severe" and "very severe", GOLD stages 1–4 respectively), risk of exacerbation (classified as "low": ≤1 exacerbation per year and "high": ≥2 exacerbations per year) and the presence

of co-morbidities. Patients are then grouped according to these three aspects into one of four groups labelled A, B, C or D. Treatment recommendations are made on the basis of the group into which the patient falls [6]. Whether this new approach will improve guideline-conformity among treating physicians, however, remains to be seen [12].

Roflumilast and its main metabolite roflumilast N-oxide are selective PDE4 inhibitors which act to decrease immune and inflammatory cell activation [13, 14]. Roflumilast was developed, patented and marketed by Nycomed GmbH (Germany) and was licensed in the European Union in July 2010 and in Switzerland in November 2011 as an add-on treatment for patients with GOLD stages 3 and 4 (FEV_1 <50% predicted after bronchodilatation) and frequent exacerbations despite correctly-dosed therapy with a long-acting bronchodilator. Roflumilast is marketed in Switzerland by Nycomed Pharma AG (Dübendorf, Switzerland) under the name Daxas®. In the United States of America, roflumilast was granted Food and Drug Administration [15] approval in February 2011 and is marketed by Forest Pharmaceuticals Inc. (St. Louis) as Daliresp®. Roflumilast is licensed in the USA "as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations" [16]. Chronic bronchitis is defined as the presence of cough and sputum production for at least 3 months in each of 2 consecutive years [6]. According to the current GOLD COPD guidelines, roflumilast should be considered as add-on therapy to inhaled corticosteroids (ICS) and long-acting beta2 agonist (LABA) in combination or with a long-acting anticholinergic alone for patients with more symptoms, high risk of exacerbation and severe or very severe airflow limitation ("group D" patients) [6]. For patients with less symptoms but otherwise the same characteristics ("group C" patients), roflumilast is recommended as an alternative choice to standard first-line therapy with ICS and LABA or LAMA. Roflumilast is the first and only PDE4 inhibitor currently licensed for use in humans and the current licensed indication is tightly specified [17], however further applications, such as in the treatment of asthma, are being investigated [18, 19]. The licensed dose is 500 µg in tablet form orally once daily with or without food.

In this review we outline roflumilast's chemistry, pharmacodynamics, pharmacokinetics, clinical efficacy, safety and tolerability and the current ongoing clinical trials. Information has been sourced from the Swiss and US product information monographs, peer-reviewed published literature (identified from a PubMed MEDLINE search 1966 – March 2012 using the term "roflumilast"), the COPD GOLD international guidelines for the management of COPD (Revised 2011) [6] and the independent analysis of phase 3 clinical trial data by FDA staff physicians [15].

Chemistry

The chemical name of roflumilast is N-(3, 5-dichloropyridin-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide. Its empirical formula is $C_{17}H_{14}Cl_2F_2N_2O_3$ and its molecular weight is 403.2 g/mol [16].

Pharmacodynamics

Roflumilast's mechanism of action is to increase cAMP levels in eosinophils, monocytes and neutrophils through selective, competitive inhibition of PDE4. This is achieved by the failure of PDE4, when inhibited, to inactivate cAMP [20]. Increased cAMP levels in these inflammatory cells reduces their activation, thereby attenuating the inflammatory response [14]. PDE4 is also expressed in airway smooth muscle cells, however an acute bronchodilatory effect of PDE4 inhibition has not been confirmed [21]. This fact is explicitly outlined in the product information which warns against the use of roflumilast for the relief of acute bronchospasm [16, 22]. Roflumilast is therefore a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease. The pre-clinical pharmacology of roflumilast has recently been brought together in an extensive review by Hatzelmann and colleagues [13]. A previously trialled PDE4 inhibitor cilomilast showed extensive gastrointestinal side effects (primarily nausea and vomiting) mediated by inhibition of the PDE4 subtype D, for which roflumilast shows a lower affinity [8]. The anti-inflammatory effects of PDE4-inhibitors appear to be mediated by inhibition of the PDE4B subtype, for which roflumilast has a higher affinity than cilomilast [8].

In a randomised, double-blind, placebo-controlled, crossover study to assess the anti-inflammatory potential of roflumilast in moderate-to-severe COPD patients (n = 38) significant reductions in absolute numbers of sputum eosinophils (–50%, p <0.001), neutrophils (–35.5%, p = 0.002) and lymphocytes (–34.8%, p = 0.022) were found [23]. However, a non-significant reduction in the percentage of neutrophils making up the total sputum cell-count was found. Other inflammatory markers in sputum or plasma (studied as secondary endpoints) also showed significant reductions in roflumilast-treated subjects and both pre- and post-bronchodilator FEV_1 increased (79.5 and 68.7ml respectively, p <0.001 and p <0.018). The authors concluded that the improvement in lung function seen was likely due in part to roflumilast's anti-inflammatory effects.

The product information for Daliresp® further references a study by Hohlfeld and colleagues in 37 healthy volunteers who received 28 days of roflumilast 500 µg once daily or placebo in a randomised, double-blind manner [16, 24]. A baseline bronchoalveolar lavage was then performed and the volunteers underwent segmental pulmonary endotoxin challenge with lipopolysaccharide followed by repeat bronchoscopy and segmental lavage 24 hours later. Subjects who had been pre-treated with roflumilast showed reduced total cell-, neutrophil- and eosinophil- influx compared to placebo (statistically significant differences of 36%, 39% and 74% respectively).

Pharmacokinetics

After oral dosing, roflumilast is rapidly and almost entirely absorbed with maximum plasma concentrations being reached within approximately one hour (range 0.5–2 hours) in healthy volunteers [16, 25]. The absolute bioavailability

following oral administration is 79% [26]. After systemic uptake, roflumilast is extensively bound to plasma proteins (99%) and distributed with a volume of distribution of approximately 2.9 L/kg [27]. Roflumilast is metabolised by both phase I (cytochrome P450 – CYP) and phase II (conjugation) reactions. *In vitro* studies and clinical drug interaction studies have shown that roflumilast is primarily metabolised via CYP 3A4 and 1A2 to roflumilast N-oxide. In humans, roflumilast N-oxide is the most important metabolite. The plasma area under the time-concentration curve for roflumilast N-oxide is 10-fold greater than for roflumilast (table 1). So, despite being 3-fold less potent than roflumilast in terms of PDE4 inhibition (measured by total inhibitory PDE4 activity – tPDE4i), roflumilast N-oxide is thought to account for the majority of the pharmacological effects seen [27]. Roflumilast and roflumilast N-oxide show dose-proportional, linear pharmacokinetic properties, whereby doubling the dose results in a doubling of peak concentrations and AUCs for both substances [25].

Roflumilast N-oxide is metabolised by CYP3A4 and 2C19 or glucuronidated to inactive metabolites [7]. Extensive *in vitro* studies using human hepatic microsomes did not show any inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4/5 or 4A9/11 by roflumilast or roflumilast N-oxide at therapeutic concentrations. A weak induction of CYP 2B6 activity was shown for roflumilast [22]. Inactive roflumilast metabolites are excreted to a large extent in the urine (70% of a radioactively labelled oral or intravenous roflumilast dose administered to human subjects was recovered in the urine and 20% in faeces) [22].

Pharmacokinetic parameters of roflumilast and roflumilast N-oxide are summarised in table 1.

Drug-drug interactions

Being substrates for CYP 3A4, 1A2 and 2C19, the pharmacokinetics (and therefore efficacy and toxicity) of roflumilast and roflumilast N-oxide are subject to a number of drug-drug interactions. Due to the formation of the active metabolite roflumilast N-oxide by CYP3A4, the effect of CYP3A4 inhibition or induction is not straight-forward to predict. Pharmacokinetic drug-drug interaction studies are therefore best interpreted in light of changes in tPDE4i – a measure of the total PDE4 inhibitory activity – as this reflects the overall pharmacodynamic effect of inhibiting or inducing roflumilast and roflumilast N-oxide's metabolism. The derivation of the parameter tPDE4i is beyond the scope of this review, but can be found in the current product information for Daxas® [22] or in a recent book chapter by Tenor and colleagues [27].

While there are no contraindicated drug-drug combinations with roflumilast, the product information draws special attention to the interactions with inhibitors of CYP 3A4 or dual inhibitors of CYP3A4 and 1A2 (erythromycin, ketoconazole, fluvoxamine, enoxacin – a fluoroquinolone not licensed in Switzerland – and cimetidine) which "will increase roflumilast systemic exposure and may result in increased adverse reactions. The risk of such a concurrent use should be weighed carefully against benefit" [16]. Similarly the use of strong CYP inducers (e.g., rifampicin, phenobarbital, cabamazepine and phenytoin) is not recommended [16]. Data from drug-drug interaction studies with CYP inhibitors and inducers are shown in table 2. A study of the effects of cigarette smoke on roflumilast pharmacokinetics showed no interaction [28]. Interaction studies with warfarin, inhaled budesonide, oral montelukast, inhaled salbutamol, inhaled formoterol, oral theophylline and an antacid containing magnesium hydroxide and aluminium hydroxide similarly showed no significant changes in roflumilast pharmacokinetics [28]. Midazolam (a CYP3A4 substrate) and digoxin (a P-glycoprotein substrate) showed no alteration in their pharmacokinetic characteristics when co-administered with roflumilast in steady state indicating that roflumilast itself does not affect the activity of CYP3A4 or P-glycoprotein [29, 30]. Sildenafil, a PDE5-inhibitor and weak CYP 1A2, 2C19 and 3A4 inhibitor does not interact significantly with roflumilast and no dose-adjustments are necessary [16].

Special populations (hepatic impairment, renal impairment, pregnancy, children and adolescents, elderly, gender, race, smoking)

Being metabolised in the liver, the pharmacokinetics of roflumilast are affected by liver disease. A study of patients with mild hepatic impairment (n = 8 patients with Child-Pugh A cirrhosis) showed a 51% increase in the roflumilast AUC and a 24% increase in the roflumilast N-oxide AUC when compared with sex, age and body-weight matched healthy controls who also received roflumilast 250 µg for 14 days (n = 8). For patients with moderate hepatic impairment (n = 8 with Child-Pugh B cirrhosis), AUC for roflumilast and roflumilast N-oxide were 92% and 41% higher than for the healthy controls respectively [31]. Roflumilast is therefore contraindicated in patients with Child-Pugh B

Table 1: Pharmacokinetic data for roflumilast and roflumilast N-oxide.

Parameter	Roflumilast	Roflumilast N-oxide	Reference
Bioavailability	~80%	–	[26]
Protein binding	99%	97%	[25]
Volume of distribution (L/kg)	2.9		[22]
Peak concentration range (µg/l)	5.3–8.3	8.8–13.1	[7]
Median time to peak concentration (h)*	1 (range 0.5–2)	8 (4–13)	[22]
Mean half-life (h)	17	30	[22]
Clearance (l/h)**	9.6		[22]
$AUC_{0-\infty}$ range (mg*h/l)	31–61	350–646	[7]
Time until steady state (days)	4	6	[22]

* in fasting state
** following a short intravenous infusion

or C hepatic impairment and caution is advised with patients with Child-Pugh A hepatic impairment [22].

Severe renal impairment (creatinine clearance <30 ml/min) was found to be associated with minor decreases in the AUC of roflumilast and roflumilast N-oxide when compared with healthy controls who were also administered roflumilast 500 µg once daily [32]. There were no significant differences in safety and tolerability between the two groups (n = 12 for each). The product information does not advise dosage adjustment for patients with renal impairment. Although not yet studied, the high protein binding of roflumilast and roflumilast N-oxide (table 1) are likely to preclude roflumilast from effective removal by haemodialysis.

The use of roflumilast in pregnancy and breast-feeding is not licensed in Switzerland. Furthermore, women of childbearing age should use a reliable method of contraception. In the US product information, roflumilast is categorised as FDA "Pregnancy Category C" which is defined as follows: "Either studies in animals have revealed adverse effects on the fetus [teratogenic or embryocidal or other] and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus." [33]. Roflumilast is not licensed for breast-feeding women. Roflumilast has been shown to cross the placenta and to enter breast milk in animal studies.

Roflumilast is not currently licensed for use in children and adolescents. However, if the licensed indication for roflumilast is to be extended to the treatment of asthma in the future, pharmacokinetic data in children and adolescents are required. To date a single study examining the pharmacokinetics, safety and tolerability of roflumilast single 100 µg or 250 µg doses in a cross-over open-label design in 13 children (age 6–7) and 12 adolescents (age 11–16) has been published [34]. The authors conclude that the exposure of roflumilast in children appears to be similar to that seen in adults and that roflumilast was well tolerated. However, further studies are required to assess the pharmacokinetics and pharmacodynamics of roflumilast following single and multiple doses in children with asthma.

Studies comparing the pharmacokinetics of roflumilast and roflumilast N-oxide in persons > and <65 years of age, in men and women, in Caucasians, African Americans, Hispanics and Japanese as well as in smokers and non-smokers concluded that no dosage adjustments are necessary in these groups [16].

Clinical efficacy

The clinical efficacy of roflumilast in the treatment of moderate to severe COPD has been studied in a series of large placebo-controlled trials called "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) (table 3). Primary end points were mainly changes in lung function, rates of exacerbation and health-related quality of life. The US product information cites data from two dose-finding studies (one of which M2-107), four 1-year placebo-controlled trials (M2-111, M2-112, M2-124 and M2-125) and two 6-month trials examining the effect of roflumilast as add-on therapy to long-acting bronchodilators (M2-127 and M2-128) [16] while the Swiss product information cites data from M2-124, M2-125, M2-127 and M2-128 [22].

As shown in table 3, all studies consistently showed statistical improvement in pre- and/or post-bronchodilator FEV1, however there was inconsistency in the effect of roflumilast on exacerbation rate and quality of life. Drug-related undesired effects were recorded in all studies.

In interpreting these findings, the FDA Medical review states the following: "The difference in study designs and use of concomitant medications used to treat COPD make inter-study comparisons difficult. It should be noted that in no study was the efficacy of roflumilast evaluated compared to what has become standard of care treatment for patients with severe COPD, concomitant use of a LABA, LAMA, and an inhaled corticosteroid" [15].

Bateman and colleagues have recently performed a pre-specified, additional, pooled analysis of M2-124 and M2-125 looking at the efficacy and safety of roflumilast used concomitantly with long-acting beta agonists (LABA) to reduce exacerbations and the influence of exacerbation history on the response to roflumilast. The effect of roflumilast was compared in patients using and not using LABA and exacerbation rate was found to be reduced irrespective of concomitant LABA use. A significant increase in time to first exacerbation, however, was only seen as a whole for patients concomitantly treated with roflumilast and LABA. There were no additional safety concerns regarding the use of roflumilast in conjunction with a LABA. Previous exacerbation history appeared to be associated with the response to roflumilast with frequent exacerbators (≥2 exacerbations in preceding year) experiencing a greater reduction in moderate or severe exacerbations (rate ratio 0.78, 95% CI 0.66–0.91, p = 0.002) than infrequent exacerbators (rate ratio 0.835, 95% CI 0.73–0.95, p = 0.0062) [35].

Table 2: Summary of cytochrome P450-related drug-drug interaction studies.

Drug (affected CYP)	Conditions*	Total PDE4 inhibitory activity	Reference
Erythromycin (3A4 inhibitor)	Single dose roflumilast, erythromycin in steady state	+9%	[40]
Ketoconazole (3A4 inhibitor)	Single dose roflumilast, ketoconazole in steady state	+9%	[41]
Eonxacin (1A2 inhibitor)	Single dose roflumilast, enoxacin in steady state	+25%	[42]
Cimetidine (1A2, 2C19, 3A4 inhibitor)	Single-dose roflumilast, cimetidine in steady state	+48%	[43]
Fluvoxamine (1A2, 2C19, 3A4 inhibitor)	Single dose roflumilast, fluvoxamine in steady state	+59%	[44]
Rifampicin (2C19 and 3A4 inducer)	Single dose roflumilast, rifampicin in steady state	–58%	[45]

* Roflumilast dose always 500 µg.
** Ideally roflumilast will not be given in this context.

Table 3: Phase 3 randomised, double-blind, placebo controlled multi-centre clinical trials of roflumilast in moderate to severe COPD.

Study names	Patients, mean post-bronchodilator FEV1 % predicted	Treatments	Duration (study years)	Primary end points	Primary end point reached?	Secondary end points	Secondary end point reached?
RECORD M2 – 107 [36]	1,411, 54%	ROF 250 µg ROF 500 µg PB Plus SABA and/or SAAC as required	6 months (2002–2003)	A. Change in post-bronchodilator FEV1* B. Change in SGRQ	A. Yes: 250 µg + 74 ml, 500 µg + 97 ml (p <0.0001) B. No	A. Pre-bronchodilator FEV_1* B. Mean number of exacerbations per patient**	A. Yes: 250 µg + 64 ml (p = 0.0006), 500 µg +88 ml (p <0.0001) B. Placebo 1.13, 250 µg 1.03 500 µg 0.75
OPUS M2-111 Not published but data made available to FDA [15]	1,176, ≤50% Smoking history of ≥10 pack years	ROF 500 µg PB Plus SABA as required and continued ICS (% unknown)	12 months (2003–2005)	A. Change in pre-bronchodilator FEV1* B. Rate of moderate or severe exacerbations per patient per year	A. Yes: + 36 ml (p = 0.003) B. No: exacerbation rate ratio 0.865 (p = ns)	A. Change in post bronchodilator FEV_1 B. Number of moderate or severe exacerbations per patient per year in different subgroups (FEV_1 <30%, with chronic bronchitis ± emphysema, cough score >1 or >2, h/o moderate or severe COPD exacerbations	A. Yes + 38 ml (p = 0.0002) B. Yes for patients with mean sputum score >2 (rate ratio ROF/PB 0.615, p = 0.03) and for patients with mean cough score ≥2 (rate ratio ROF/PB 0.615, p = 0.03).
RATIO M2-112 [46]	1,513, 41%	ROF 500 µg PB Plus SABA as required and in 65% continued ICS	12 months (2003–2004)	A. Change in post-bronchodilator FEV_1* B. Number of moderate or severe exacerbations per patient per year§	A. Yes + 39 ml (p = 0.001) B. No	A. Improvement in SGRQ B. Pre-bronchodilator FEV_1* C. Exacerbations according to GOLD stage	A. No B. Yes + 36 ml (p <0.002) C. GOLD Stage IV exacerbation rate reduced, rate ratio ROF/PB 0.639 (p = 0.024)
RATIO and OPUS pooled analysis [17]	2,686, all ≤50%	ROF 500 µg PB Plus SABA as required and continued ICS (61% ROF and 60% PB)	12 months (2003–2005)			Rate of moderate or severe exacerbations per patient per year**	Exacerbation rate ratio ROF/PB 0.897 (p = 0.026)
HERO M2-121 Not published but data made available to FDA [15]	Unknown, ≤65%	ROF 500 µg PB	6 months	A. Change in post-bronchodilator FEV_1* B. FRC (functional residual capacity)	To our knowledge not publicly available		
AURA M2-124 [38]	1,523, 38% with at least 1 exacerbation requiring systemic corticosteroids and/or hospitalisation within the last year	ROF 500 µg PB Plus LABA and/or SABA and/or SAAC as required	12 months (2006–2008)	A. Change in pre-bronchodilator FEV1* B. Rate of moderate or severe acute exacerbations**	A. Yes + 39 ml (p = 0.0003) B. Yes: exacerbation rate ratio 0.85 (p = 0.03)	A. Change in post-bronchodilator FEV_1* B. Time to death from any cause C. C-reactive protein concentration D. Transition Dyspnea Index focal score	A. Yes + 49 ml (p <0.0001) B. No C. No D. Yes: difference 0.2 (p = 0.04)
HERMES M2-125 [38]	1,568, 35% with at least 1 exacerbation requiring systemic corticosteroids and/or hospitalisation within the last year	ROF 500 µg PB Plus LABA and/or SABA and/or SAAC as required	12 months (2006–2008)	A. Change in pre-bronchodilator FEV_1* B. Rate of moderate or severe acute exacerbations**	A. Yes + 58 ml (p <0.0001) B. Yes: exacerbation rate ratio 0.82 (p = 0.004)	A. Change in post-bronchodilator FEV_1* B. Time to death from any cause C. C-reactive protein concentration D. Transition Dyspnea Index focal score	A. Yes + 61 ml (p <0.0001) B. No C. No D. Yes: difference 0.3 (p = 0.006)
EOS M2-127 [47]	933, 55%	ROF 500 µg PB Plus Salmeterol	6 months (2006–2008)	A. Change in pre-bronchodilator FEV_1*	A. Yes + 49 ml (p <0.0001)	A. Post-bronchodilator FEV_1 B. Post-bronchodilator FVC* C. Transition dyspnea index score D. Shortness of breath questionnaire E. Use of short acting bronchodilators F. Exacerbation rates (all types)	A. Yes + 60ml (p <0.0001) B. Yes + 58 ml (p 0.003) C, D, E, F No

HELIOS M2-128 [47]	743, 56% plus presence of chronic cough and frequent use of short acting bronchodilators	ROF 500 µg PB Plus Tiotropium	6 months (2006–2008)	A. Change in pre-bronchodilator FEV1*	A. Yes + 80 ml (p <0.0001)	A. Post-bronchodilator FEV_1 B. Post-bronchodilator FVC* C. Transition dyspnea index score D. Shortness of breath questionnaire E. Use of short-acting bronchodilators F. Exacerbation rates (all types)	A. Yes + 81 ml (p <0.0001) B. Yes + 101 ml (p = 0.0004) C. Yes: Difference 0.4 (p = 0.003) D. Yes: Difference –2.6 (p = 0.005) E. Yes: Difference –0.51 (p = 0.0004) F. No

* value is the difference between placebo and treatment changes in spirometry parameters from baseline
** moderate exacerbations = treatment with systemic corticosteroids, severe exacerbations = exacerbation requiring hospitalisation and/or leading to death
§ Moderate exacerbations = symptomatic deteriorations treated with systemic corticosteroids and/or antibiotics, severe exacerbations = those requiring hospitalisation.
FEV_1 = forced expiratory volume in 1 second, PB = placebo, ROF = roflumilast, SAAC = short-acting anticholinergic, SABA = short-acting beta-2 agonist, SGRQ = St George's respiratory questionnaire.

Safety and tolerability

The FDA has published data from a pooled analysis of COPD studies obtained from 14 placebo-controlled Phase 2 and 3 studies which comprise the so called "COPD safety pool". This pool includes approximately 12000 patients with COPD of which more than half received roflumilast. With regard to dose and duration of exposure, 5766 (88%) received the proposed, once daily regimen of 500 µg oral roflumilast, 797 (12%) received roflumilast 250 µg. Among those who received 500 µg roflumilast, 1,232 were treated for at least one year, 1,081 for 6 months to less than 1 year, 2,081 for 3 to less than 6 month and 1,370 for less than 3 months. The median duration of exposure with 500 µg roflumilast was 167 days [15]. The most common adverse effect of roflumilast is diarrhoea (10.1% in the groups treated with roflumilast 500 µg/d compared with 2.6% in the placebo arms) (table 4). Other adverse events are also shown in table 4. Adverse events were found to occur mainly within the first weeks of therapy and resolved during continued treatment [27].

A few key areas in the safety and tolerability of roflumilast which require special attention have emerged: gastrointestinal effects, weight loss, psychiatric disturbance (including suicide) and possible carcinogenesis [15]. These adverse effects are uncommon to existing COPD therapies and patients require close monitoring, particularly during the early phases of treatment with roflumilast.

Gastrointestinal adverse events

Gastrointestinal adverse events are an established class effect of PDE4 inhibitors. Vomiting has only rarely been seen with roflumilast (≤1%) [36]; the main events are diarrhoea

Table 4: Adverse event frequency: analysis of pooled data [15, 28]. All adverse events occurring at a frequency ≥2% in patients treated with roflumilast are listed.

Adverse event	**Placebo (n = 5491)**	**Roflumilast 500 µg (n = 5,766)**
All adverse events (%)	3,447 (62.8)	3,873 (67.2)
Patients with serious adverse events (%)	782 (14.2)	781 (13.5)
Deaths (%)	86 (1.6)	84 (1.5)
Adverse events with suggested causality as judged by investigator	294 (5.4)	1,003 (17.4)
Study discontinued due to adverse events	503 (9.2)	824 (14.3)
Infections and infestations	1,508 (27.5)	1,492 (25.9)
Nasopharyngitis	346 (6.3)	364 (6.3)
Bronchitis	192 (3.5)	177 (3.1)
Upper respiratory tract infection	234 (4.3)	219 (3.8)
Pneumonia	110 (2)	104 (1.8)
Influenza	132 (2.4)	145 (2.5)
Gastrointestinal disorders		
Diarrhoea	143 (2.6)	585 (10.1)
Nausea	79 (1.4)	297 (5.2)
Investigations		
Weight decreased	101 (1.8)	394 (6.8)
Respiratory, thoracic and mediastinal disorders		
COPD	1,271 (23.1)	1,142 (19.8)
Dyspnoea	120 (2.2)	84 (1.5)
Musculoskeletal and connective tissue disorders		
Back pain	117 (2.1)	176 (3.1)
Nervous system disorders		
Headache	110 (2.0)	266 (4.6)
Dizziness	65 (1.2)	139 (2.4)
Metabolism and nutrition disorders		
Decreased appetite	22 (0.4)	125 (2.2)
Psychiatric disorders		
Insomnia	50 (0.9)	148 (2.6)
Vascular disorders		
Hypertension	136 (2.5)	95 (1.6)

and nausea – a likely consequence of which being decreased appetite (table 4).

Weight loss

Weight loss is an adverse event not previously associated with PDE4 inhibitors. It is a relevant event as lower body mass is associated with a poorer prognosis in COPD patients [37]. In M2-124 and M2-125, the mean weight change was a reduction of 2.09 kg (SD 3.98) in the roflumilast-treated arm after 1 year and an increase of 0.08 kg (3.48) in the placebo arm. The largest absolute weight loss with roflumilast was seen in obese patients (BMI >30). The change in weight in the roflumilast arm occurred during the first 6 months of treatment and showed an association with the presence of gastrointestinal symptoms and headache [38], however this is unlikely to account entirely for the weight loss seen. A direct lipolytic effect of roflumilast has been proposed [28].

The Swiss product information makes further note of the reversibility of weight loss on stopping roflumilast – in M2-124 and M2-125 patients attained their baseline weight 3 months after stopping roflumilast. Doctors should keep a close eye on their patients' weight and patients should be encouraged to weigh themselves every two weeks.

Psychiatric effects

Insomnia is the most common psychiatric adverse event reported (2.6% in the pooled safety data – table 4). Other reported effects are anxiety states and depression. The US product information notes three cases of suicide-related adverse reactions (one completed suicide) while receiving roflumilast in clinical trials compared to one patient with suicidal ideation who received placebo. The Swiss product information mentions rare cases of suicidal ideation under roflumilast and, like the American product information warns against its use in patients with a past history of suicidal ideation resulting from depression [16, 22]. Data reported by the FDA show 3 completed and 2 attempted suicides among roflumilast-treated and none among placebo-treated study participants [15]. Causality was however not commented upon [15]. Post-marketing data for roflumilast is limited and being a new drug, subject to reporting bias. Nonetheless, in 2011, 16 cases of suicidal ideation, 3 cases of attempted suicide and 2 cases of completed suicide were reported to the Uppsala Monitoring Centre World Health Organization collaborating Centre for International Drug Monitoring (VigiBaseTM Services. www.umc-products.com Date last accessed 13. March 2012, search terms "Roflumilast" and "Psychiatric disorders"). To date in 2012, 4 cases of suicidal ideation, 1 case of attempted suicide and 1 case of completed suicide have been reported to the same organisation. Causality assessments are not given so the relationship between these events and roflumilast cannot be commented upon and would require independent, expert review.

Malignancy

Whether roflumilast is associated with malignancy or not is currently a topic of debate [39]. Roflumilast has been found to be carcinogenic in animal (rodent) studies [15]. In the pooled safety analysis by the FDA, tumours were found in 1.5% of the roflumilast-treated subjects and 1.3% of the placebo-treated subjects. There were significant increases in lung, prostate, and colorectal cancers in the roflumilast treated COPD patients compared to placebo [15]. Comparison with age-matched non-COPD cohorts has not been made. The majority of tumours were solid tumours, which are known to develop slowly over several years and the majority, were diagnosed during the first 6 months of treatment, with no difference between placebo- and roflumilast-treated subjects after 6 months of treatment, suggesting against a causal relationship with roflumilast [28].

Contraindications

The current listed contraindications to roflumilast therapy are hypersensitivity to roflumilast or one of the components of Daxas® and moderate to severe liver impairment (Child-Pugh class B or C) [22].

Warnings and precautions

The Swiss product information for Daxas® warns against the use of roflumilast in the treatment of acute bronchospasm, highlights the association with weight loss found in the phase 3 studies M2-124 and M2-125 [38], advises caution when treating patients with a history of psychiatric symptoms and advises against treatment of patients with a past history of suicidal ideation or suicide attempts. Furthermore, roflumilast therapy is not recommended in patients who are immunosuppressed, patients with severe acute infections and patients with malignancy (other than basal cell skin cancer). The US product information does not warn against the use of roflumilast in these latter three groups of patients.

The National Institute for Health and Clinical Excellence (NICE, UK), which assesses newly licensed therapies for their benefit to patients and for cost-effectiveness has recently issued a guidance recommending that roflumilast only be given "in the context of research as part of a clinical trial" (http://guidance.nice.org.uk/TA244).

Current ongoing studies with roflumilast

The "REACT" study ("Roflumilast in Chronic Obstructive Pulmonary Disease (COPD) Patients Treated With Fixed Combinations of Long-acting β2-agonists (LABA) and Inhaled Glucocorticosteroid (ICS)" NCT01329029) is currently recruiting patients primarily in Europe and is projected to finish in January 2014 [19]. This large randomised trial of 1 year duration has the determination of exacerbation rates in patients who fulfil the current licensed indication for roflumilast and are treated with either roflumilast or placebo as its primary end point. A similar study (Roflumilast in Chronic Obstructive Pulmonary Disease (COPD) Patients Treated With Fixed Dose Combinations of Long-acting β2-agonist (LABA) and Inhaled Corticosteroid (ICS) NCT 01443845) is currently underway primarily in the United States with estimated study completion in May 2014 [19]. Of 33 roflumilast trials listed on clinicaltrials.gov, 6 are actively recruiting and two are active but not yet recruiting COPD patients, 1 is recruiting healthy volun-

teers for a cognition study and 1 is active but not yet recruiting for an asthma study [19].

Conclusion

Roflumilast is the first-in-class phosphodiesterase 4 inhibitor licensed for add-on therapy in patients with moderate to severe COPD and frequent exacerbations who are already receiving a long-acting bronchodilator. Roflumilast is designed to target both the systemic and pulmonary inflammation associated with chronic obstructive pulmonary disease. Clinical efficacy in terms of a modest gain in FEV_1% and a reduction in exacerbation rate has been demonstrated in phase 3 clinical trials and roflumilast has been recently incorporated into international COPD treatment guidelines. The effect of roflumilast when given as add-on therapy to patients already taking long-acting bronchodilators and ICS (standard therapy) is currently not known, however data from a large randomised controlled trial addressing this question are expected in 2014. Data from phase 4 post-marketing studies are required to determine both the incidence and severity of adverse events as well as the long-term beneficial effects of roflumilast as a maintenance therapy for COPD in every-day clinical practice.

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Correspondence: *Anne B. Taegtmeyer, MRCP (UK), PhD, Department of Clinical Pharmacology & Toxicology, University Hospital Basel, Hebelstrasse 2, CH-4031 Basel, Switzerland, ataegtmeyer[at]uhbs.ch*

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