2016년 대한천식알레르기학회 추계학술대회

Luncheon Symposium

· **날짜:** 2016년 11월 5일 (토)

· **좌장:** 박춘식(순천향의대 내과)

1. Role of PDE4 inhibitors in airway diseases
정이영(경상의대)

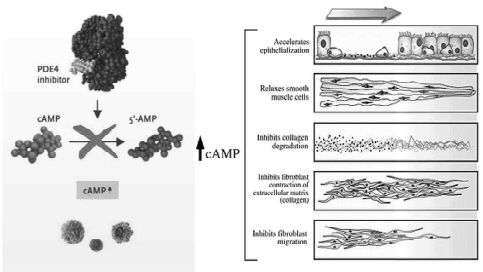
Luncheon Symposium

Role of PDE4 inhibitor in airway disease

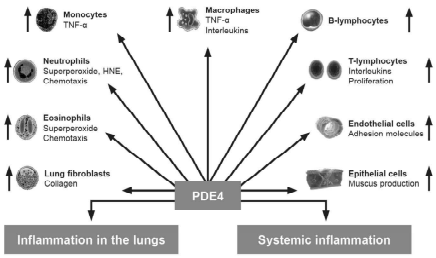
경상대학교병원 호흡기-알레르기내과

정 이 영

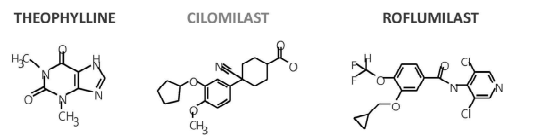
PDE4 is the main selective cAMP-metabolizing enzyme in inflammatory and immune cells



The PDE4 is expressed in all key cells involved in COPD and asthma



Roflumilast is a highly selective PDE4 inhibitor



In the early 1990s,

- The focus for the use of PDE4 inhibitors was on **asthma.**
- However, the **limited and inconsistent efficacy and side effects** of the early compounds made their further development less desirable in asthma, given the widespread use of ICS as a safe and effective alternative.
- Indeed, the **lack of effective antiinflammatory drug treatment for COPD** has shifted the interest in **development toward COPD** in recent years.

CLINICAL USE ;

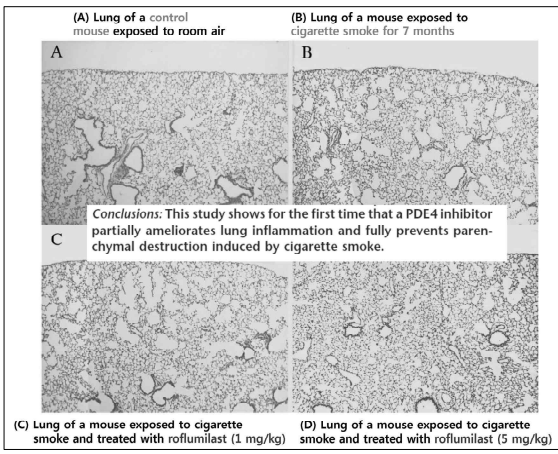
PDE4 Inhibitors in COPD

Roflumilast Fully Prevents Emphysema in Mice Chronically Exposed to Cigarette Smoke

Piero A. Martorana, Rolf Beume, Monica Lucattelli, Lutz Wollin, and Giuseppe Lungarella

Department of Physiopathology and Experimental Medicine, University of Siena, Siena, Italy; and ALTANA Pharma, Konstanz, Germany

Am J Respir Crit Care Med 2005;172:848–853



Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Peter M A Calverley, Klaus F Rabe†, Udo-Michael Goehring, Søren Kristiansen, Leonardo M Fabbri‡, Fernando J Martinez§, for the M2-124 and M2-125 study groups‖*

Summary

Background The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.

Methods In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 μg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV_1) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Findings Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β, agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV_1 increased by 48 mL with roflumilast compared with placebo (p<0·0001). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], p<0·0003). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was −2·17 kg.

Interpretation Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management. This possibility should be explored further in prospective studies.

Lancet 2009;374:685–94

	M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast *vs* placebo
Lung function*			
Change in prebronchodilator FEV_1 (mL)	40 (6); n=1475	−9 (5); n=1511	Difference 48 (35 to 62); p<0·0001
Change in postbronchodilator FEV_1 (mL)	50 (6); n=1453	−4 (6); n=1500	Difference 55 (41 to 69); p<0·0001
Change in prebronchodilator FVC (mL)	64 (10); n=1475	−34 (10); n=1511	Difference 98 (73 to 123); p<0·0001
Change in postbronchodilator FVC (mL)	67 (10); n=1453	−35 (10); n=1500	Difference 101 (77 to 126); p<0·0001
Change in prebronchodilator FEV_1/FVC (%)	0·247 (0·147); n=1475	−0·146 (0·1439); n=1511	Difference 0·393 (0·028 to 0·758); p=0·0350
Change in postbronchodilator FEV_1/FVC (%)	0·517 (0·141); n=1453	0·090 (0·138); n=1500	Difference 0·426 (0·077 to 0·776); p=0·0169

	M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast *vs* placebo
Exacerbations†‡			
Moderate or severe (mean rate, per patient per year [95% CI])	1·14 (1·05–1·24); n=717	1·37 (1·28–1·48); n=821	RR 0·83 (0·75 to 0·92); p=0·0003
Severe (mean rate, per patient per year [95% CI])	0·12 (0·10–0·16); n=157	0·15 (0·12–0·19); n=198	RR 0·82 (0·63 to 1·06); p=0·1334
Moderate (mean rate, per patient per year [95% CI])	0·99 (0·91–1·08); n=624	1·19 (1·10–1·29); n=723	RR 0·83 (0·75 to 0·92); p=0·0007
Treated with systemic corticosteroids, antibiotics, or both (mean rate, per patient per year [95% CI])	1·13 (1·04–1·23); n=700	1·35 (1·26–1·46); n=798	RR 0·84 (0·76 to 0·92); p=0·0003
Median time to first exacerbation (moderate or severe; days [IQR])	80·0 (28·0–190·0)	71·0 (28·0–160·0)	HR 0·89 (0·80 to 0·98); p=0·0185
Median time to second exacerbation (moderate or severe; days [IQR])	177·0 (92·0–767·0)	148·0 (85·0–736·0)	HR 0·79 (0·69 to 0·91); p=0·0014

(Continues on next page)

	M2-124			M2-125*		
	Roflumilast (n=769)†	Placebo (n=755)†	Roflumilast vs placebo (difference, 95% CI)	Roflumilast (n=778)‡	Placebo (n=790)‡	Roflumilast vs placebo (difference, 95% CI)
COPD	70 (9%)	82 (11%)	−1·76% (−4·90 to 1·38)	87 (11%)	122 (15%)	−4·26% (−7·74 to −0·78)
Diarrhoea	63 (8%)	26 (3%)	4·75% (2·28 to 7·21)	67 (9%)	23 (3%)	5·70% (3·28 to 8·12)
Weight loss	92 (12%)	24 (3%)	8·78% (6·04 to 11·52)	65 (8%)	20 (3%)	5·82% (3·46 to 8·18)
Nasopharyngitis	57 (7%)	50 (7%)	0·79% (−1·91 to 3·49)	35 (5%)	47 (6%)	−1·45% (−3·78 to 0·88)
Upper respiratory tract infection	16 (2%)	21 (3%)	−0·70% (−2·48 to 0·98)	33 (4%)	38 (5%)	−0·54% (−2·15 to 1·62)
Headache	26 (3%)	17 (2%)	1·13% (−0·66 to 2·92)	25 (3%)	8 (1%)	2·20% (0·65 to 3·75)
Pneumonia	17 (2%)	15 (2%)	0·77% (−1·35 to 1·79)	15 (2%)	16 (2%)	1·19% (−0·57 to 2·90)
Back pain	27 (4%)	22 (3%)	0·60% (−1·30 to 2·50)	23 (3%)	13 (2%)	1·31% (−0·30 to 2·92)
Acute bronchitis	35 (5%)	40 (5%)	−0·75% (−3·05 to 1·56)	71 (9%)	74 (9%)	−0·34% (−2·17 to 1·44)
Nausea	41 (5%)	15 (2%)	3·34% (1·34 to 5·35)	21 (3%)	15 (2%)	0·80% (−0·81 to 2·41)
Hypertension	20 (3%)	28 (4%)	−1·11% (−2·99 to 0·78)	18 (2%)	20 (3%)	−0·22% (−1·87 to 1·43)
Insomnia	19 (2%)	8 (1%)	1·41% (−0·04 to 2·86)	18 (2%)	12 (2%)	0·79% (−0·69 to 2·28)
Decreased appetite	21 (3%)	2 (<1%)	2·47% (1·13 to 3·81)	15 (2%)	5 (<1%)	1·30% (0·05 to 2·54)
Influenza	27 (4%)	18 (2%)	1·13% (−0·70 to 2·95)	12 (2%)	20 (3%)	−0·99% (−2·51 to 0·53)

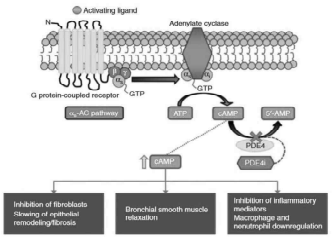
Data are number (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. COPD=chronic obstructive pulmonary disease. *Incidence of adverse events in roflumilast-treated patients in study M2-125 is in descending order. †One patient was randomised twice, and included twice in the safety analysis but only once in the efficacy analysis; four patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for the safety analysis; 765 patients in the roflumilast group and 758 in the placebo group were included in the efficacy analysis. ‡Six patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for safety analysis; 777 patients in the roflumilast group and 796 in the placebo group were included in the efficacy analysis.

Table 3: Adverse events occurring in at least 2·5% of patients in one of the treatment groups

Conclusion

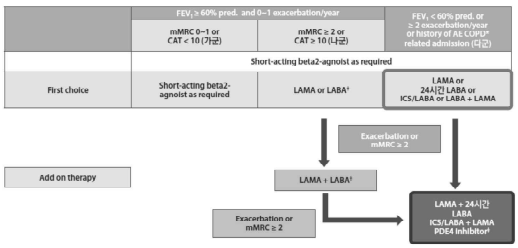
- Roflumilast, a PDE4 inhibitor, improves lung function and reduces the frequency of exacerbations in patients with bronchitic symptoms and severe airflow limitation.
- This treatment is not suitable for all patients because of the presence of class related adverse effects that usually arise soon after initiation of treatment.
- Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management.
- This possibility should be explored further in prospective studies.

Roflumilast: what is it and how does it treat COPD?

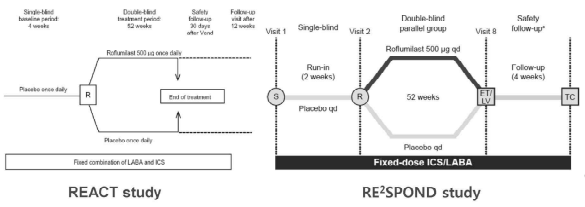


1. Hatzelmann A, et al. Pulm Pharmacol Ther 2010;23:235-56.
2. Grootendorst DC, et al. Thorax 2007;62;1081-7.
3. Martinez FJ, et al. Lancet 2015;385:857-66.

Roflimilast current treatment recommendations in Severe COPD patients



Comparison of the REACT and RE²SPOND trials : study design



REACT study RE²SPOND study

Martinez FJ et al. Lancet 2015; 385: 857–66
Rennard SI et al. Int J of COPD 2016:11 1921–1928
Martinez, et al Am J Respir Crit Care Med 2016;194(5) 559–567

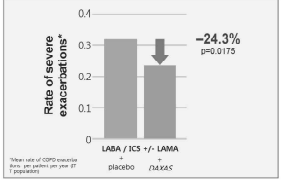
Comparison of the REACT and RE²SPOND trials

	REACT	RE²SPOND
Study design	Double-blind, placebo-controlled, parallel group, multicenter, Phase IV	Double-blind, placebo-controlled, parallel group, multicenter, Phase IV
Trial length	4-week single-blind run-in +52-week DB treatment	2-week single-blind run-in +52-week DB treatment
Number of participants	1,945	2,300 (expected)
Trial sites	203 sites across 21 countries	380 sites across 17 countries
Eligible participants	Diagnosis of severe to very severe COPD with chronic bronchitis and a history of COPD exacerbations	Diagnosis of severe to very severe COPD with chronic bronchitis and a history of COPD exacerbations
Randomization	1:1	1:1, stratified by LAMA use
Treatment	500 µg roflumilast or placebo + FDC ICS/LABA* (>70% of participants were on LAMA* treatment)	500 µg roflumilast or placebo + FDC ICS/LABA* (+ up to 60% of participants allowed LAMA treatment)
Roflumilast formulation	Film-coated tablets (information on file)	Uncoated tablets
Allowed concomitant treatments	Salbutamol, corticosteroids, antibiotics‡	Salbutamol/albuterol, corticosteroids, H1-antihistamines, antibiotics,‡ SAMA*
Follow up	4 weeks (safety) and 12 weeks	4 weeks (safety) or up to the scheduled Week 52 visit for early terminated participants
Primary outcome	Rate of moderate or severe COPD exacerbations per participant per year‡	Rate of moderate or severe COPD exacerbations per participant per year‡
Primary outcome analyses	Poisson regression model with overdispersion correction and negative binomial regression model	Negative binomial regression model and sensitivity analysis
Secondary outcomes	Change in postbronchodilator FEV_1, rate of severe COPD exacerbations, rate of moderate to severe or antibiotic-treated COPD exacerbations, spirometry	Change in prebronchodilator FEV_1; rate of severe COPD exacerbations and rate of moderate, severe, o antibiotic-treated exacerbations
Additional/safety outcomes	Electronic rescue medication diary, CAT, major adverse cardiac events, mortality	Spirometry, electronic rescue medication diary, CAT, EXACT-PRO, major adverse cardiac events, C-SSRS
Pharmacokinetics	Sparse sampling (n=986)	Sparse sampling (n=420), serial sampling (n=40)

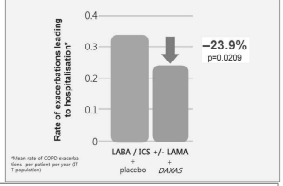
Rennard SI et al. Int J of COPD 2016;11:1921–1928

ROFLUMILAST FURTHER REDUCES EXACERBATIONS WHEN ADDED TO INHALED COMBINATION THERAPY (LABA/ICS) IN PATIENTS STILL SUFFERING FROM FREQUENT EXACERBATIONS: REACT STUDY

Roflumilast significantly reduces the rate of severe exacerbations[1]



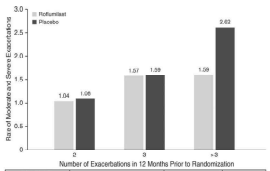
Roflumilast significantly reduces the rate of exacerbations leading to hospitalisation[1]



"the first COPD treatment to decrease the rate of hospitalisation in patients already receiving multiple inhaled treatments."[2]
Professor Klaus F. Rabe[3]

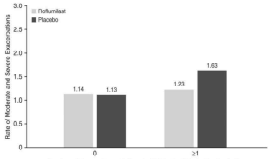
1. Martinez FJ, et al. *Lancet* **2015**;385:857–66.[REACT study]
2. Takeda Pharmaceuticals International GmbH Press release February 13th, 2015
3. Professor of Pulmonary Medicine at the University of Kiel and Director of the Department of Pneumology at Clinic Grosshansdorf

Roflumilast decreased the rate of moderate or severe exacerbations in participants with more than three exacerbations in the prior year and in those with at least one prior severe exacerbation: RE²SPOND study



Number of exacerbations in 12 Months Prior to Randomization	Number of Participants at Risk		Rate Ratio (95% CI)	P Value
	Roflumilast (n=1,179)	Placebo (n=1,174)		
2	874	876	0.96 (0.83, 1.11)	0.586
3	179	180	0.99 (0.77, 1.27)	0.921
>3	112	108	0.61 (0.39, 0.95)	0.030

Rate of moderate or severe exacerbations per patient per year at Week 52 by exacerbation history



Number of Severe Exacerbations in 12 Months Prior to Randomization	Number of Participants at Risk		Rate Ratio (95% CI)	P Value
	Roflumilast (n=1,179)	Placebo (n=1,174)		
0	789	805	1.01 (0.87, 1.18)	0.819
≥1	381	364	0.73 (0.60, 0.90)	0.010

Rate of moderate or severe exacerbations per patient per year by severe exacerbation rate in previous year

Martinez, et al. Am J Respir Crit Care Med 2016;194(5):559–567

Comparison of the REACT and RE²SPOND trials: safety

	Roflumilast group (n=968)	Placebo group (n=967)	Difference between groups (95% CI)
Chronic obstructive pulmonary disease exacerbation	145 (15%)	185 (19%)	4.2% (−5.08 to −3.22)
Diarrhoea	99 (10%)	33 (4%)	6.0% (3.50 to 7.71)
Weight decrease	88 (9%)	27 (3%)	6.3% (4.32 to 7.38)
Nausea	55 (6%)	15 (1%)	4.1% (2.74 to 5.67)
Nasopharyngitis	52 (5%)	52 (5%)	0% (−0.54 to 0.61)
Headache	40 (4%)	21 (2%)	2.0% (1.34 to 2.58)
Pneumonia	39 (4%)	45 (5%)	−0.6% (−0.98 to −0.27)
Decreased appetite	36 (4%)	5 (1%)	3.2% (2.42 to 3.99)
Insomnia	29 (3%)	15 (2%)	1.4% (0.73 to 1.98)
Back pain	27 (3%)	14 (1%)	1.2% (0.82 to 1.85)
Upper abdominal pain	25 (3%)	10 (1%)	1.5% (1.00 to 2.10)
Hypertension	24 (3%)	27 (3%)	−0.3% (−0.56 to −0.06)

Data are n (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. One patient assigned to roflumilast accidentally received placebo for the entire duration of the study and was therefore included in the placebo group for the safety analysis.

Table 2: Adverse events occurring in at least 2·5% of patients in either treatment group

	Roflumilast (n = 1,178)	Placebo (n = 1,174)
Participants with TEAEs, n (%)	804 (68)	768 (65)
TEAE >2.5% of participants (either group), n (%)		
Diarrhea	119 (10)	38 (3)
Weight decreased	91 (8)	28 (2)
Headache	80 (7)	48 (4)
Pneumonia	66 (6)	66 (6)
Upper respiratory tract infection	60 (5)	66 (6)
Nausea	64 (5)	30 (3)
Urinary tract infection	49 (4)	44 (4)
Nasopharyngitis	47 (4)	58 (5)
Insomnia	50 (3)	21 (2)
Influenza	31 (3)	30 (3)
Hypertension	33 (3)	43 (4)
Back pain	33 (3)	27 (2)
Appetite decreased	36 (3)	10 (<1)
Participants with SAFEs, n (%)	180 (15)	167 (14)
Suicidal ideation, n (%)*	99 (8)	90 (8)
Suicidal behavior, n (%)*	29 (3)	20 (2)
Suicidal attempt, n (%)*	13 (1)	12 (1)
Deaths, n (%)†	30 (3)	26 (2)

Definition of abbreviations: SAE = serious adverse event; TEAE=treatment-emergent adverse event
*As assessed by the Columbia-Suicide Severity Rating Scale.
†One completed suicide was associated with roflumilast treatment.

Martinez FJ et al. *Lancet* 2015;385:857–66
Rennard SI et al. Int J of COPD 2016;11:1921–1928
Martinez, et al. Am J Respir Crit Care Med 2016:194(5):559–567

Summary

- While treatment with LABAs and ICS are associated with reductions in exacerbations, patients still suffer from these episodes over time.
- **Roflumilast** has a unique anti-inflammatory MOA
- **Roflumilast** shows the efficacy for improving lung function and decreasing exacerbations in patients with severe to very severe COPD associated with chronic bronchitis.
- **Roflumilast** can be an important and cost-effective in the prevention of exacerbations, particularly for patients with severe to very severe COPD associated with chronic bronchitis and a history of exacerbations.

CLINICAL USE ;

PDE4 Inhibitors in Asthma

Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects

Gail M Gauvreau[1*], Louis-Philippe Boulet[2], Christine Schmid-Wirlitsch[3], Johanne Côté[2], MyLinh Duong[1], Kieran J Killian[1], Joanne Milot[2], Francine Deschesnes[2], Tara Strinich[1], Richard M Watson[1], Dirk Bredenbröker[3] and Paul M O'Byrne[1]

Respiratory Research 2011;12:140

Abstract

Background: Phosphodiesterase 4 (PDE4) inhibitors increase intracellular cyclic adenosine monophosphate (cAMP), leading to regulation of inflammatory cell functions. Roflumilast is a potent and targeted PDE4 inhibitor. The objective of this study was to evaluate the effects of roflumilast on bronchoconstriction, airway hyperresponsiveness (AHR), and airway inflammation in mild asthmatic patients undergoing allergen inhalation challenge.

Methods: 25 subjects with mild allergic asthma were randomized to oral roflumilast 500 mcg or placebo, once daily for 14 days in a double-blind, placebo-controlled, crossover study. Allergen challenge was performed on Day 14, and FEV_1 was measured until 7 h post challenge. Methacholine challenge was performed on Days 1 (pre-dose), 13 (24 h pre-allergen), and 15 (24 h post-allergen), and sputum induction was performed on Days 1, 13, 14 (7 h post-allergen), and 15.

Results: Roflumilast inhibited the allergen-induced late phase response compared to placebo; maximum % fall in FEV_1 ($p = 0.02$) and the area under the curve ($p = 0.01$). Roflumilast had a more impressive effect inhibiting allergen-induced sputum eosinophils, neutrophils, and eosinophil cationic protein (ECP) at 7 h post allergen (all $p = 0.02$), and sputum neutrophils ($p = 0.04$), ECP ($p = 0.02$), neutrophil elastase ($p = 0.0001$) and AHR ($p = 0.004$) at 24 h post-allergen.

Conclusions: This study demonstrates a protective effect of roflumilast on allergen-induced airway inflammation. The observed attenuation of sputum eosinophils and neutrophils demonstrates the anti inflammatory properties of PDE4 inhibition and supports the roles of both cell types in the development of late phase bronchoconstriction and AHR.

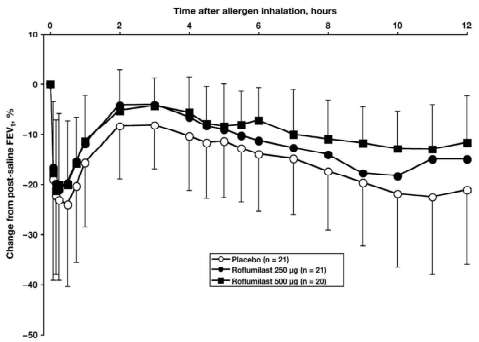
Trial Registration: ClinicalTrials.gov: NCT01365533

Keywords: Allergic asthma, allergen challenge, PDE4 inhibitor, inflammation, sputum, neutrophils, eosinophils

Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, attenuates allergen-induced asthmatic reactions

Emmerentia van Schalkwyk, MBChB,[a] K. Strydom, MBChB,[a] Zelda Williams, RN,[b] Louis Venter, MSc,[c] Stefan Leichtl, PhD,[d] Christine Schmid-Wirlitsch, PhD,[d] Dirk Bredenbröker, MD,[d] and Philip G. Bardin, FRACP, PhD[b] *Cape Town and Rivonia, South Africa, Melbourne, Australia, and Konstanz, Germany*

J Allergy Clin Immunol 2005;116:292-8



Mean percentage decrease of FEV1 from post saline value after allergen challenge.
Roflumilast, 250 and 500 mg, significantly attenuated the EAR (0-2 hours) and LAR (2-12 hours) compared with placebo.

Conclusion

- Once-daily oral roflumilast modestly attenuated early asthmatic reactions and, to a greater extent, LARs to allergen in patients with mild allergic asthma.
- Pronounced suppression of late responses in an allergen challenge model suggests that roflumilast might have anti-inflammatory activity, which could provide clinical efficacy in chronic inflammatory pulmonary diseases, such as asthma.

Roflumilast for asthma: Efficacy findings in placebo-controlled studies

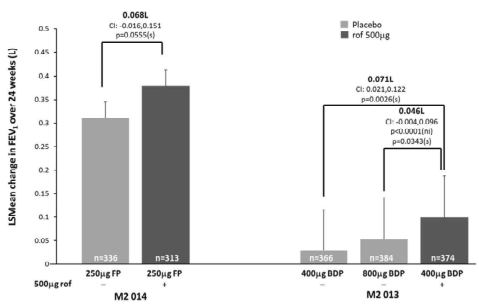
E.O. Meltzer [a,*], P. Chervinsky [b], W. Busse [c], K. Ohta [d], P. Bardin [e], D. Bredenbröker [f], F.D. Bateman [g]

[a] *Department of Pediatrics, Division of Allergy and Immunology, University of California, San Diego, CA, USA*
[b] *Northeast Medical Research Associates, Dartmouth, MA, USA*
[c] *Division of Allergy and Immunology, School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA*
[d] *Department of Respiratory Medicine and Allergology, Tokyo National Hospital, Tokyo, Japan*
[e] *Monash Lung & Sleep, Monash Medical Center and University, Melbourne, Australia*
[f] *Takeda Pharmaceuticals International GmbH, Zurich, Switzerland*
[g] *Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa*

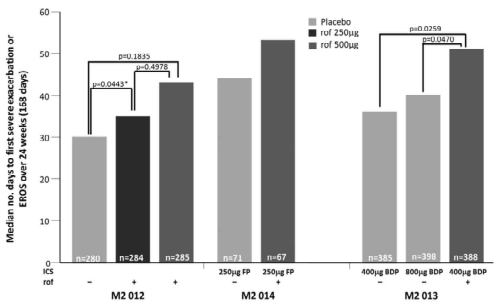
Aim: To evaluate the efficacy of roflumilast in nine randomized proof-of-concept, placebo-controlled monotherapy and combination therapy phase II and III clinical studies performed between 1997 and 2005.
Methods: The studies were conducted at sites in Europe, North and South America, Africa, Australasia and Asia and study length varied from 4 to 24 weeks. Data were analyzed from 4873 patients, 12–70 years of age, of whom 2668 received roflumilast. At randomization patients had a forced expiratory flow (FEV_1) of 45–90%. Roflumilast was investigated at doses of 125, 250 and 500 µg versus placebo. In two studies, 500 µg roflumilast was added on top of standard therapy with inhaled corticosteroids (ICS), 250 µg fluticasone propionate, or 400 µg beclomethasone dipropionate (BDP). Improvement in FEV_1 from baseline was the primary endpoint in seven studies. Key secondary endpoints included asthma symptom scores and time to first severe exacerbation.

Pulmonary Pharmacology & Therapeutics 2015;35:S20-S27

Mean change in FEV1 over 24 weeks in 'add-on' studies M2 013 and M2 014



Median number of days to first severe exacerbation over 24 weeks in studies M2 012, M2 013 and M2 014



Conclusion

- Together these studies show that roflumilast may have potential as an anti-inflammatory therapy for the treatment of asthma.
- When given in addition to ICS (400 mg BDP and 250 mg FP) in two of the larger studies, roflumilast provided additional improvements in lung function.
- Roflumilast may confer added benefits in patients receiving ICS, which are considered to be the mainstay of asthma therapy, and these findings warrant further investigation.

Roflumilast combined with montelukast versus montelukast alone as add-on treatment in patients with moderate-to-severe asthma

Eric D. Bateman, MD,[a] Udo-Michael Goehring, MD,[b] Frank Richard, MD,[c] and Henrik Watz, MD[d] *Cape Town, South Africa, Zurich, Switzerland, and Biberach and Grosshansdorf, Germany*

J Allergy Clin Immunol 2016;138:142-9

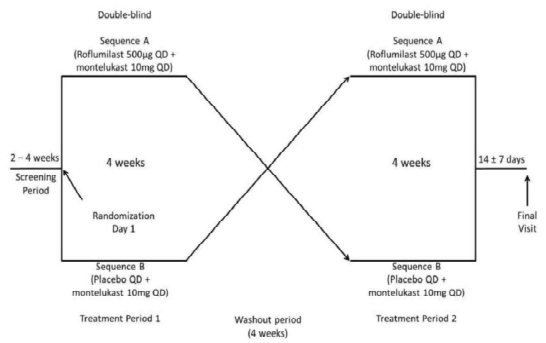
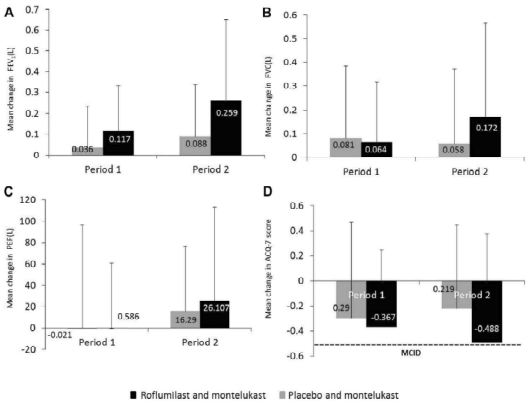


FIG 1. Schematic of the crossover study design: 2- to 4-week screening period, followed by two 4-week double-blind treatment periods separated by a washout period of 4 weeks. A final visit took place 7 to 21 days after the second treatment period. *QD*, Once daily.



Conclusion

- The combination of roflumilast with montelukast compared with montelukast alone improved lung function and asthma control in patients with moderate-to-severe asthma and deserves further study for this indication.
- The PDE-4 inhibitor roflumilast and the leukotriene modifier montelukast provide additive benefit in patients with moderate-to-severe asthma.

J Allergy Clin Immunol 2016;138:142-9

A novel inhaled phosphodiesterase 4 inhibitor (CHF6001) reduces the allergen challenge response in asthmatic patients

D. Singh [a,*], B. Leaker [b], M. Boyce [c], M.A. Nandeuil [d], S. Collarini [e], F. Mariotti [e], D. Santoro [e], P.J. Barnes [f]

[a] University of Manchester, Medicines Evaluation Unit, University Hospital of South Manchester Foundation Trust, Southmoor Road, Manchester, M23 9QZ, United Kingdom
[b] Respiratory Clinical Trials Ltd, 18-22 Queen Anne St, London, W1G 8HU, United Kingdom
[c] Hammersmith Medicines Research, Cumberland Avenue, London, NW10 7EW, United Kingdom
[d] Chiesi S.A., 11 Avenue Dubonnet, 92400, Courbevoie, France
[e] Chiesi Farmaceutici S.p.A., Via Palermo 26/A, 43122, Parma, Italy
[f] National Heart & Lung Institute, Imperial College, London, SW3 6LY, United Kingdom

Pulmonary Pharmacology & Therapeutics 2016;40:1-6

Summary

- Although the potential therapeutic utility of PDE inhibitors has been demonstrated in various animal models of asthma, their clinical efficacy have been restricted by the dose-limiting side effects; no PDE inhibitor has yet been approved for the treatment of patients with asthma.
- Oral roflumilast might be reconsidered for use in patients with moderate-to severe asthma, perhaps as add-on therapy.
- Roflumilast; an interesting possible treatment for severe asthma associated with frequent exacerbations and characterized by neutrophilic inflammation.
- Further data from these new drugs are eagerly anticipated to better understand where these drugs might stand in the future treatment of asthma.