Roflumilast: What is the truth in COPD?

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COPD

- A common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases (GOLD)
- Different subsets of patients

- A complex syndrome that involves
  - airway inflammation and airway limitation,
  - oedema
  - mucociliary dysfunction and
  - hypoxic vasoconstriction of pulmonary arterioles
- which reduces perfusion, and consequent airway structural changes, in addition to
- significant systemic effects that lead to comorbid conditions

- Diverse outcomes- sometimes frustrating
- Current drugs- limited improvement
  - Apart from smoking cessation, there are no other treatment that slow down of the lung function decline.

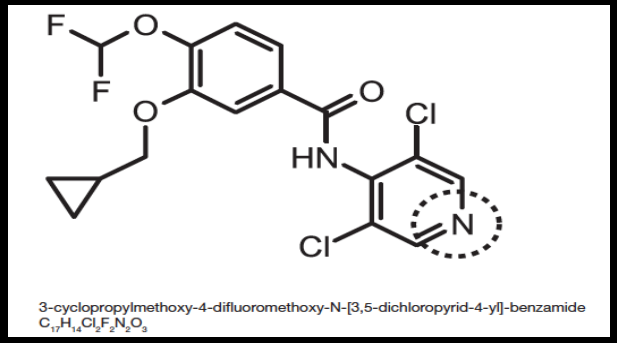
- Functions of inflammatory cells could be inhibited by raising their intracellular levels of 3′′5′′-cyclic adenosine monophosphate (cAMP)
- Wide distribution of phosphodiesterase 4 (PDE4) in inflammatory cells and the lung, prompted the exploration of isoenzyme selective PDE4 inhibitors as a way of reducing inflammation in patients with COPD

Boswell-Smith et al., 2006b; Halpin, 2008

- A novel approach
  - Roflumilast is an oral phosphodiesterase 4 (PDE4) inhibitors proposed to reduce the airway inflammation and bronchoconstriction seen in COPD.
  - Symptom relief and risk reduction of exacerbations, can be targeted more effectively than it is currently possible

Are PDE4 inhibitors the long needed magic pill for COPD patients?

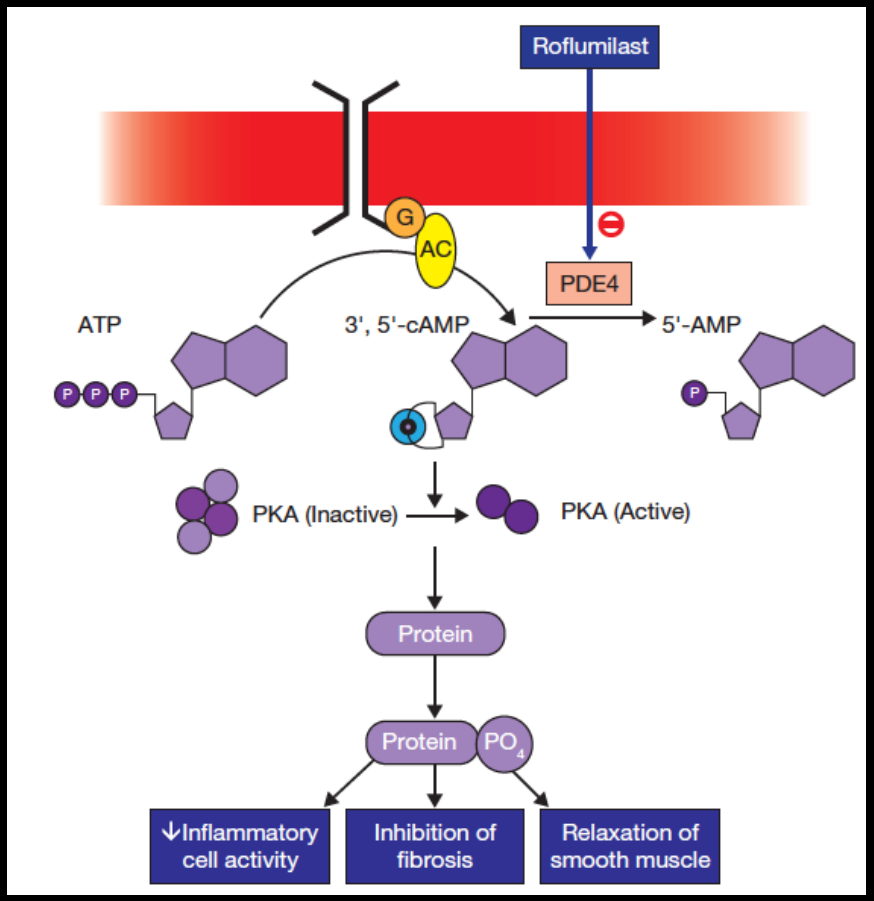
Pharmacology



- Roflumilast (3-cyclopropylmethoxy-4-difluoromethoxy-N-[3,5-dichloropyrid-4-yl]-benzamide)
- An oral PDE4 inhibitor
- High potency and selectivity for competitive inhibition of PDE4, without affecting PDE1, 2, 3 or 5 isoenzymes, within various cells and tissues indicated its potential as a therapeutic agent.

Boswell-Smith et al., 2006
Hatzelmann et al., 2010

Pharmacology



Although increased cAMP levels generally have smooth muscle relaxant effects, roflumilast does not have acute bronchodilator effects

Pharmacokinetics & dynanamics

- Roflumilast is rapidly and almost completely absorbed after oral administration, with maximum plasma concentrations (Cmax) reached within ~1 hr.
- The pharmacokinetic profile of roflumilast is linear and predictable over the dose range of 250–1000 mg (Bethke et al., 2007).
- The therapeutic dose is 500 mg, taken once daily (which can be either in the morning or the evening).

Pharmacokinetics & dynanamics

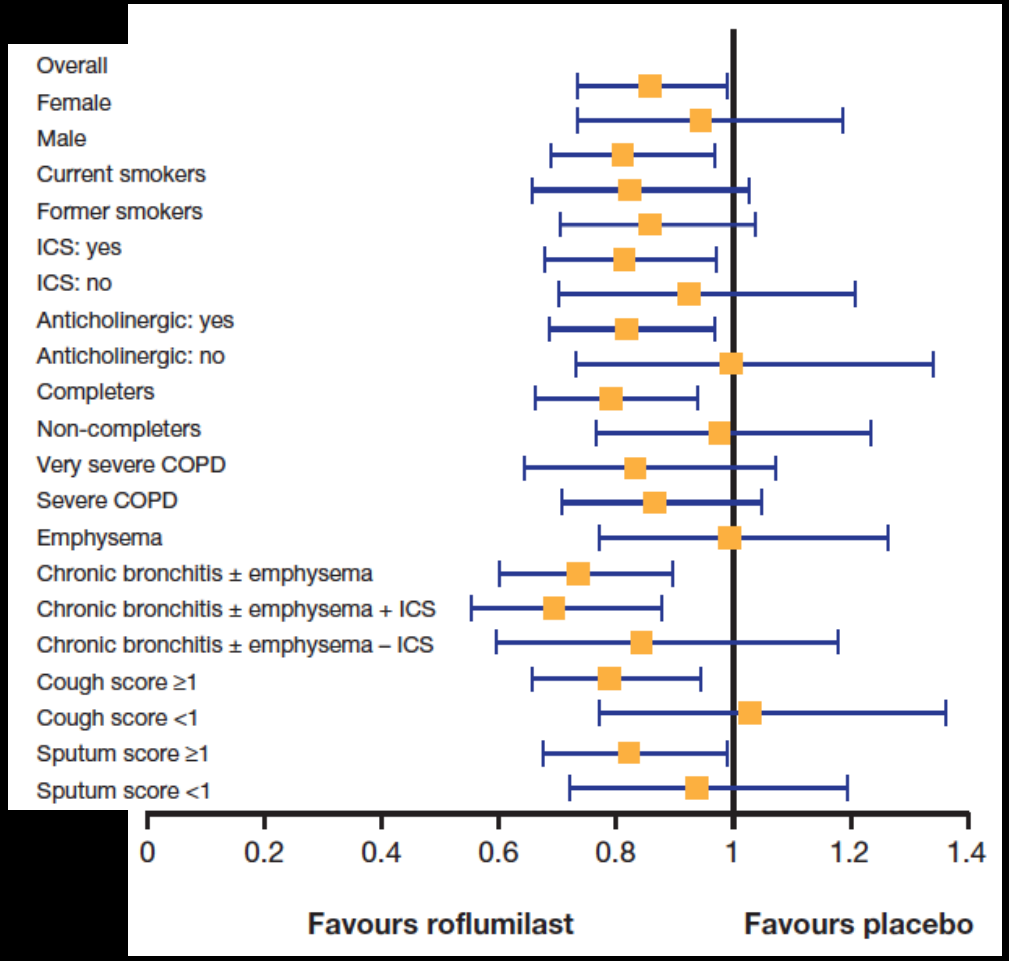
- Co-administration of roflumilast with salbutamol, budesonide or formoterol had no significant effect on the mean tPDE4i activity of roflumilast
- No dose adjustment of roflumilast is required with co-administration of montelukast
- Not indicated with aminophylines

Efficacy: Earlier studies

Study	Patients	Study design	Therapy	Key findings
M2-107 (Rabe *et al.*, 2005)	$N = 1411$ Post-bronchodilator FEV_1 30–80% predicted; post-bronchodilator FEV_1:FVC ratio ≤ 70%	Multicentre, double-blind, parallel-group study	Roflumilast 250 µg ($n = 576$) or 500 µg ($n = 555$) or placebo ($n = 280$) once daily for 24 weeks	Roflumilast 500 µg significantly improved post-bronchodilator FEV_1 compared with placebo (difference 97 mL, $P < 0.0001$) and health-related quality of life
M2-111 (Data on file Nycomed GmbH) (Nycomed GmbH, 2010a)	$N = 1176$ Post-bronchodilator FEV_1:FVC ratio ≤ 70% Post-bronchodilator ≤ 50% predicted	Multicentre, double-blind, parallel-group study	Roflumilast 500 µg ($n = 568$) or placebo ($n = 608$) once daily for 52 weeks	Roflumilast 500 µg significantly improved pre-bronchodilator FEV_1 compared with placebo (difference 36 mL, $P < 0.0001$) Roflumilast 500 µg significantly improved post-bronchodilator FEV_1 compared with placebo (difference 38 mL, $P < 0.0001$)
M2-112 (Calverley *et al.*, 2007)	$N = 1513$ Post-bronchodilator FEV_1 ≤ 50% predicted, post-bronchodilator FEV_1:FVC ratio ≤ 0.70	Multicentre, randomized, placebo-controlled, double-blind, parallel-group trial (identical to study M2-111)	Roflumilast, 500 µg once daily or placebo for 1 year Note: unlike M2-124/125, patients in this study were not required to have symptoms of chronic bronchitis or a history of exacerbations	Post-bronchodilator FEV_1 increased by 39 mL with roflumilast compared with placebo by 52 weeks ($P = 0.001$) The mean exacerbation rate per patient per year was low and comparable (0.86 vs 0.92 for roflumilast and placebo respectively). In a retrospective analysis, the exacerbation rate per patient per year in patients in GOLD stage IV disease was 36% lower in patients treated with roflumilast than in those treated with placebo (1.01 vs. 1.59, respectively; $P = 0.024$)

Post-hoc, pooled analysis of two replicate 12-month studies (M2-111 and M2-112)

14.3% reduction in the rate of moderateto- severe exacerbations with roflumilast vs. placebo (0.52 vs. 0.61 exacerbations per year; P = 0.026).



Rennard et al., 2011

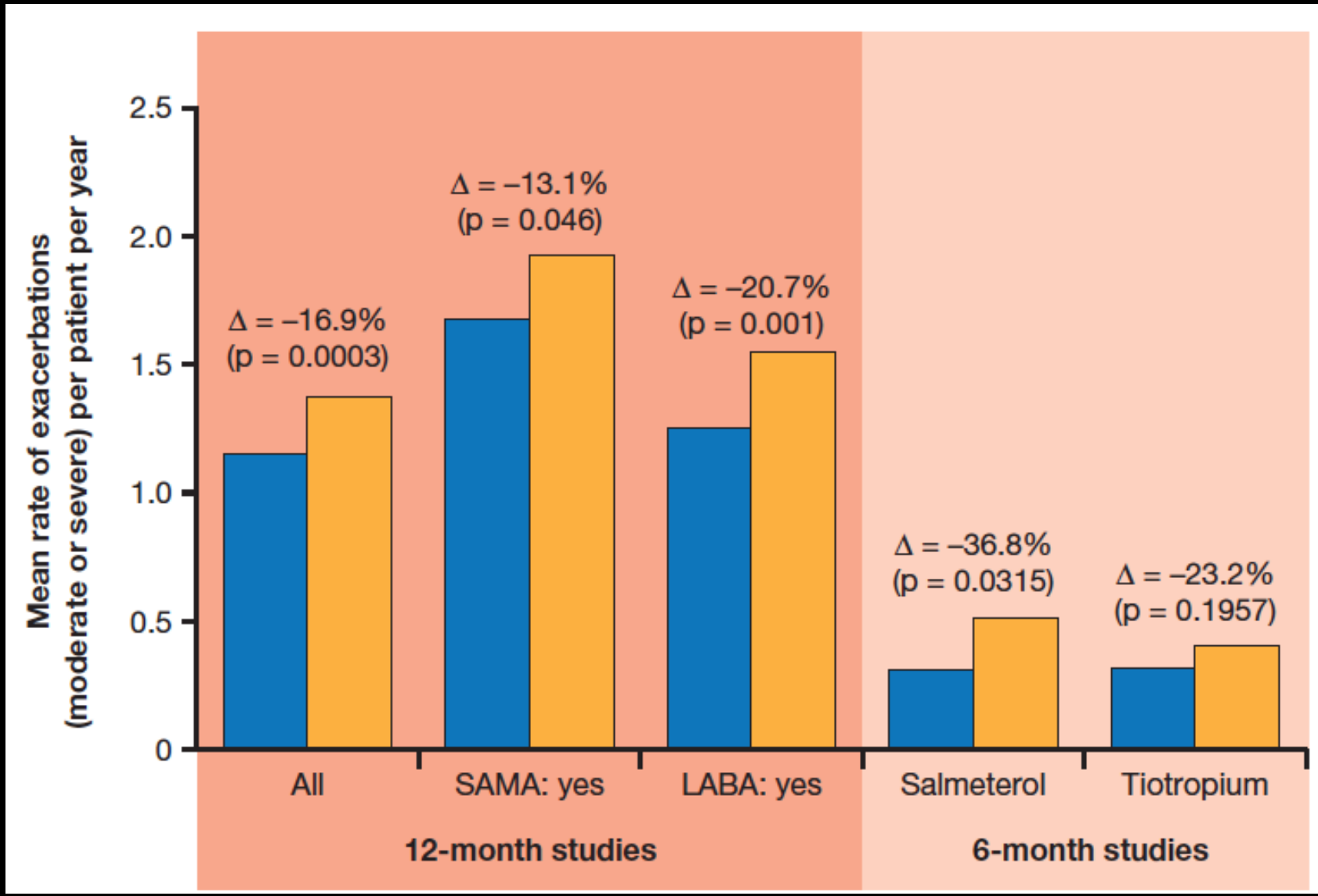
- Identified responsive patient subgroups that show greatest benefit with roflumilast:
  - patients with chronic bronchitis or with high cough or sputum scores, and
  - patients receiving concomitant ICS or SAMAs

- The preferential effect of roflumilast in certain patient subgroups suggested that a tailored approach was required to optimize treatment for COPD.
- This analysis facilitated the design of subsequent clinical trials, which consistently demonstrated the efficacy of roflumilast, focussing on the identified patient groups

Eficacy: Recent studies

Study	Patients	Study design	Therapy	Key findings
M2-124 (Calverley *et al.*, 2009)	$N = 1523$ Post-bronchodilator FEV_1 $\leq$ 50% predicted, bronchitic symptoms, and a history of exacerbations	Multicentre, double-blind, randomized, parallel-group study	Roflumilast 500 µg ($n = 765$) once daily or placebo ($n = 758$) for 1 year	Pre-bronchodilator FEV_1 increased in the roflumilast group by 46 mL, but was almost unchanged (8 mL increase) in the placebo group ($P = 0.0003$) There was also 14.9% reduction in the exacerbation rate in the roflumilast group vs placebo ($P = 0.0278$)
M2-125 (Calverley *et al.*, 2009)	$N = 1568$ Post-bronchodilator FEV_1 $\leq$ 50% predicted, bronchitic symptoms, and a history of exacerbations	Multicentre, double-blind, randomized, parallel-group study	Roflumilast 500 µg once daily ($n = 772$) or placebo ($n = 796$) for 1 year	Roflumilast increased pre-bronchodilator FEV_1 by 33 mL compared with a 25 mL decrease in the placebo group ($P < 0.0001$) Roflumilast also reduced the rate of moderate or severe COPD exacerbations compared with placebo by 18.5%; $P = 0.0035$
M2-127 (Fabbri *et al.*, 2009)	$N = 933$ Post-bronchodilator FEV_1 40–70% predicted	Double-blind, randomized, parallel-group, multicentre study	Roflumilast 500 µg ($n = 466$) or placebo ($n = 467$), once daily for 24 weeks, in addition to salmeterol 50 µg twice daily	Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV_1 by 49 mL ($P < 0.0001$) in patients treated with salmeterol. Similar improvement in post-bronchodilator FEV_1 was noted. Furthermore, roflumilast had beneficial effects on other lung function measurements and on selected patient-reported outcomes
M2-128 (Fabbri *et al.*, 2009)	$N = 743$ Post-bronchodilator FEV_1 40–70% predicted	Double-blind, randomized, parallel-group, multicentre study	Roflumilast 500 µg ($n = 371$) or placebo ($n = 372$) once daily for 24 weeks, in addition to tiotropium 18 µg once daily	Compared with placebo, roflumilast consistently improved mean pre-bronchodilator FEV_1 by 80 mL ($P < 0.0001$) in those treated with tiotropium. Similar improvement in post-bronchodilator FEV_1 was noted. Furthermore, roflumilast had beneficial effects on other lung function measurements and on selected patient-reported outcomes

Pooled analysis of studies M2-124 and M2-125, M2-127 and M2-128



Effects on moderate or severe exacerbations after treatment with roflumilast 500 mg or placebo in patients receiving concomitant short-acting muscarinic antagonists (SAMAs) or long-acting beta2-adrenergic receptor agonists (LABAs)

- Roflumilast can provide additional benefit to patients already receiving long acting bronchodilator therapy.
- Both pre-bronchodilator (improvement of 48 mL) and postbronchodilator FEV1 (improvement of 55 mL) were also significantly improved in patients treated with roflumilast compared with placebo, irrespective of concomitant LABA or SAMA use or previous ICS treatment ($P < 0.0001$).

- The meta-analyses show mixed results for benefit and harm outcomes: roflumilast reduce the risk for exacerbations and led to improvements of lung function of unclear clinical relevance compared to placebo,

but

- left symptoms, health-related quality of life or exercise capacity essentially unaffected.

Safety

- The most common adverse events observed are those that would be expected with PDE4 inhibitors, namely gastrointestinal effects and weight loss.
- Higher rates of diarrhoea, weight decrease, nausea, headache, back pain, insomnia, decreased appetite and dizziness were reported with roflumilast 500 mg than with placebo.

- Side effects were most evident in the first 4–12 weeks of therapy and were mostly mild or moderate in intensity
- Discontinuation due to adverse events were more common with roflumilast (14%) than with placebo (11%) in the 12-month M2-124 and M2-125 studies

Safety: Psychiatric disorders

- In the COPD safety pool, in 6.0% of patients compared with 3.0% of placebo patients.
  - depression (1.21% vs. 0.82%) and
  - suicidal ideation/attempt (0.03% vs. 0.02%)
- The incidence of completed suicide: two in the 500-mg group and one in the 250-mg group vs. none receiving placebo)
  - a subject of significant concern by the US FDA

Risk-Benefit ratio

- Difficult to judge the net benefit of PDE4 inhibitors, and whether the benefits outweigh the harms.

FDA approval

- FDA advisory board voted in April 2010 against roflumilast because of too many adverse effects that would offset the modest benefits.
- European Medicines Agency approved roflumilast in 2010, and FDA recently followed this decision with approval of roflumilast for the indication of reducing the risk for exacerbations (March 2011).

- FDA asked for another trial where “The design of the trial should be appropriate to demonstrate a clinically relevant beneficial effect of roflumilast as an add-on therapy compared to a long acting beta agonist and inhaled corticosteroid fixed-dose combination treatment”, which does, however, not seem to address the safety concerns that exist.

- The recent update of COPD guidelines incorporated roflumilast as one of second-line agents, the place and role of roflumilast in COPD management are still unclear

Conclusion

- COPD is an important cause of morbidity and mortality
- PDE4 Inhibitors provide an novel approach to counteract the inflammation
- Should be selective to subsets
- Adverse effects are a concern and should be followed up

Thank you