Equally, it would be interesting to explore whether roflumilast responders show PDE4 polymorphisms.

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REFERENCES

- 1 Bateman ED, Rabe KF, Calverley PM, *et al.* Roflumilast with long-acting β_2 -agonists for COPD: influence of exacerbation history. *Eur Respir J* 2011; 38: 553–560.
- 2 Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur Respir J* 2009; 33: 1165–1185.
- 3 Homma S, Sakamoto T, Hegab AE, *et al.* Association of phosphodiesterase 4D gene polymorphisms with chronic obstructive pulmonary disease: relationship to interleukin 13 gene polymorphism. *Int J Mol Med* 2006; 18: 933–939.
- 4 Mills EJ, Druyts E, Gheiment I, *et al.* Pharmacotherapies for chronic obstructive pulmonary disease: a multiple treatment comparison meta-analysis. *Clin Epidemiol* 2011; 3: 107–129.
- 5 Hansen G, Jin S, Umetsu DT, *et al.* Absence of muscarinic cholinergic airway responses in mice deficient in the cyclic nucleotide phosphodiesterase PDE4D. *Proc Natl Acad Sci USA* 2000; 97: 6751–6756.

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From the authors:

We thank L.M. Blasco for his comments on our article, and for drawing attention to the potential broader effects of phosphodiesterase (PDE) inhibitors in chronic obstructive pulmonary disease (COPD) and its comorbidities [1]. The end-points in our report were limited to those necessary for obtaining registration of roflumilast for use in COPD. However, we agree that it would be unfortunate if future studies focused only on the airways, as this class of drug has potential for addressing several other mechanisms and comorbidities in COPD.

L.M. Blasco challenges the notion that the effects of roflumilast in COPD are the result of an anti-inflammatory effect of the drug. He suggests that these might result from bronchodilation and systemic PDE4 inhibition. We disagree with this explanation for several reasons. First, although he is correct that increased levels of cyclic adenosine monophosphate have smooth muscle relaxant effects, both clinical and *in vitro* studies of the role of selective PDE4 inhibitors, such as roflumilast, have failed to confirm an acute bronchodilator effect [2–4]. These studies include the use of cilomilast in COPD [2] and roflumilast in asthma [3]. Secondly, as L.M. Blasco acknowledges, several pre-clinical studies have shown that roflumilast targets inflammatory processes in COPD, with beneficial effects on tobacco-induced lung inflammation and emphysema, bleomycin-induced lung fibrosis, and mucociliary malfunction and oxidative stress [5], effects that are likely to be highly relevant in COPD. In a 4-week,

placebo-controlled crossover study in patients with COPD, roflumilast treatment resulted in reductions in the absolute number of neutrophils, lymphocytes, macrophages and eosinophils, soluble interleukin-8, neutrophil elastase, eosinophilic cationic protein, and α_2 -macroglobulin in sputum [6]. While we agree that this observation requires confirmation in a prospective lung biopsy study of COPD patients treated with roflumilast, a previously reported study performed with cilomilast administered for 12 weeks confirmed a reduction in inflammatory cell numbers in bronchial biopsy specimens [7]. Therefore, our current hypothesis is that the improvements in lung function and exacerbation reductions seen with roflumilast are most likely the result of anti-inflammatory activity.

Finally, L.M. Blasco refers to the work of HOMMA *et al.* [8] in Japanese patients, which explores the association between PDE4 polymorphisms and the development of COPD. He speculates that these patients might benefit more from PDE4 inhibition. However, it must be noted that a functional consequence of these polymorphisms on PDE4 activity has not yet been demonstrated. To date, upregulation of PDE4 activity has been reported only in alveolar macrophages of smokers with moderate COPD [9] and is attributed to chronic inflammation and the oxidative stress found in COPD. We agree that more research is required to understand the relationship between levels of PDE4 activity in COPD and sustained PDE4 inhibition.

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REFERENCES

- 1 Bateman ED, Rabe KF, Calverley PMA, *et al.* Roflumilast with long-acting β_2 -agonists for COPD: influence of exacerbation history. *Eur Respir J* 2011; 38: 553–560.
- 2 Grootendorst DC, Gauw SA, Baan R, *et al.* Does a single dose of the phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? *Pulm Pharmacol Ther* 2003; 16: 115–120.
- 3 Engelstatter R, Wingertzahn M, Schmid-Wirlitsch C, *et al.* Roflumilast, an oral once-daily phosphodiesterase 4 (PDE4) inhibitor does not exhibit bronchodilator activity. *Ann Allergy Asthma Immunol* 2005; 94: 169.

- 4 Grootendorst DC, Gauw SA, Benschop N, *et al.* Efficacy of the novel phosphodiesterase-4 inhibitor BAY 19-8004 on lung function and airway inflammation in asthma and chronic obstructive pulmonary disease (COPD). *Pulm Pharmacol Ther* 2003; 16: 341–347.
- 5 Hatzelmann A, Morcillo EJ, Lungarella G, *et al.* The preclinical pharmacology of roflumilast – a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2010; 23: 235–256.
- 6 Grootendorst DC, Gauw SA, Verhoosel RM, *et al.* Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* 2007; 62: 1081–1087.
- 7 Gamble E, Grootendorst DC, Brightling CE, *et al.* Antiinflammatory effects of the phosphodiesterase-4 inhibitor cilomilast (Ariflo) in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 976–982.
- 8 Homma S, Sakamoto T, Hegab AE, *et al.* Association of phosphodiesterase 4D gene polymorphisms with chronic obstructive pulmonary disease: relationship to interleukin 13 gene polymorphism. *Int J Mol Med* 2006; 18: 933–939.
- 9 Barber R, Baillie GS, Bergmann R, *et al.* Differential expression of PDE4 cAMP phosphodiesterase isoforms in inflammatory cells of smokers with COPD, smokers without COPD, and nonsmokers. *Am J Physiol Lung Cell Mol Physiol* 2004; 287: L332–L343.

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Why excessive sleepiness may persist in OSA patients receiving adequate CPAP treatment

To the Editors:

We read with interest the paper by VERNET *et al.* [1], which describes the characteristics of residual excessive sleepiness (RES) in obstructive sleep apnoea (OSA) patients treated with continuous positive airway pressure (CPAP). The authors studied two groups of OSA patients, with and without RES. The apnoea/hypopnoea index dramatically decreased in both groups, testifying that CPAP was applied properly. Patients underwent cognitive, psychological, biological and clinical tests, and 24-h sleep analyses. Surprisingly, very few differences were found between patients with and without RES, despite the large disparity in the Epworth Sleepiness Score. In his editorial comment, RODENSTEIN [2] notes that after such a “breath-taking effort... very little comes out” about what may cause RES. In this scenario, even decidedly unorthodox hypotheses may appear as possible mechanisms for explaining RES, worthy of future investigations. For instance, RODENSTEIN [2] suggested considering the effects of “catastrophising” in perceiving and reporting subjective sleepiness, or the hypothesis that diabetes plays a protective role in RES [2].

We would like to suggest, however, two more orthodox explanations for RES in OSA patients properly treated by CPAP. The first explanation regards the presence of the obesity hypoventilation syndrome (OHS), or of a comorbidity with chronic obstructive pulmonary disease, the so-called overlap syndrome (OS), in the OSA group with RES. In fact, both OHS and OS contribute to daytime sleepiness [3, 4] through hypercapnia. Proper CPAP treatment in OSA patients with OHS may make the sleep architecture, the arousal index and the apnoea/hypopnoea index similar to those of CPAP-treated OSA patients without OHS, but nevertheless, hypercapnia may remain significant [5]. Moreover, CPAP treatment does not reduce the high Epworth Sleepiness Score of OS patients [4]. Since arterial carbon dioxide tension was not measured, OHS or OS cannot be excluded in the obese OSA patients with RES studied by VERNET *et al.* [1]. Therefore, RES could be in part explained by the ineffectiveness of CPAP to reduce hypercapnia in OHS or OS patients.

Another explanation for RES could be linked to the possible presence of cardiovascular autonomic dysregulations induced by autonomic or “subcortical” arousals. Autonomic arousals involve brainstem neurons controlling both sleep/vigilance and cardiovascular regulation. They are not necessarily associated with detectable electroencephalographic changes, but are responsible for changes in cardiac autonomic regulation. We have found an association between excessive sleepiness during the day and impaired autonomic cardiac modulation at night when comparing two groups of sleep-disordered breathing patients, with and without excessive daytime sleepiness [6]. Both groups had a wide spectrum of disease severity, from simple snoring to OSA, had similar sleep architecture, and similar apnoea/hypopnoea index and arousal index; but patients with excessive daytime somnolence showed lower baroreflex sensitivity and a greater ratio of low- to high-frequency heart rate powers at night, both indexes of increased sympathetic/vagal balance [7]. The results were confirmed after having removed obese patients to exclude OHS [8]. Thus, cardiovascular autonomic alterations during sleep may be associated with excessive daytime sleepiness, probably because of brainstem dysfunctions involving both alertness and cardiovascular control. Standard polysomnographic studies (like those conducted by VERNET *et al.* [1]) cannot detect these alterations. If such alterations were found, they would support the speculation of VERNET *et al.* [1] that intermittent hypoxia causes a post-hypoxic injury determining “central hypersomnia”. In fact, this is what can be expected if the injury affects specific neuronal groups in the brainstem.

In conclusion, we think that testing for the presence of hypercapnia or of autonomic alterations during sleep could importantly improve understanding of the mechanisms responsible for RES in CPAP-treated OSA patients.

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