The role of nebulised budesonide in the treatment of acute exacerbations of COPD

From the authors:

We have read with interest the letter concerning our manuscript recently published in the *European Respiratory Journal* [1] and appreciate the concerns raised by A. Singh. Underlining chronic obstructive pulmonary disease (COPD) as a systemic disorder has gained wide acceptance among pulmonary physicians. The main evidence supporting this approach is the increased levels of systemic inflammatory markers (tumour necrosis factor-α, C-reactive protein and interleukins) and the presence of cachexia and muscle weakness/wasting [2, 3]. It is not yet known what kind of extrapulmonary problems these increased inflammatory markers indicate or give rise to. They have been shown to be strongly related to the level of inflammation in the lungs, and do not seem to indicate any kind of abnormal systemic process independent of the pathology within the lungs of COPD patients [4]. Cachexia and muscle weakness/wasting mainly occur due to the increased work of breathing, decreased appetite and avoidance of eating behavior due to increased breathlessness in COPD patients.

It is still not clear which potential systemic abnormalities occurring during exacerbations of COPD (ECOPD) may be relieved by systemic corticosteroid administration alone. Therefore, from a practical point of view, we are not yet convinced that there is a significant difference between treating COPD as a systemic or local disease. Secondly, the rationale of high-dose nebulised corticosteroid administration in severe COPD is the same as that for the administration of systemic corticosteroids. No published data currently exist that directly test the efficacy of systemic corticosteroid administration and the severity of COPD exacerbation according to dominant cell type in the lower airways. Nebulised corticosteroid administration has the advantage of enabling the clinician to avoid the systemic side-effects of corticosteroids. Thirdly, it is difficult to discuss the response to high-dose nebulised corticosteroid administration according to the cause of exacerbation and the dominant cell type in any specific cause of exacerbation, due to a lack of any published data. These issues were not addressed in our study. However, it must be remembered that since patients were randomly included in our study, there should be no difference between the groups with respect to the cause of exacerbation and dominant cell type in the lower airways. The important point here is that we did not find any difference between the efficacies of high-dose nebulised budesonide and systemic corticosteroid administration, with a lower side-effect profile in the nebulised corticosteroid arm. We agree with A. Singh that 10% of patients with COPD have some characteristics of asthma, and their response to the high-dose nebulised budesonide may potentially differ from that of other COPD patients. However, these patients were not excluded or were not separately evaluated in our study. We believe that if any COPD patients with asthmatic features were included in our study, they did not have significant impact on the results as they were randomly distributed among the groups.

Although there are a limited number of studies regarding the clinical efficacy of nebulised corticosteroids in exacerbations of bronchial asthma and COPD [5–10]; the majority indicate a positive opinion on their use. However, due to the differences in study design, study population, drug dosages and follow-up periods, these previous studies are almost incomparable. Before drawing any firm conclusions, the results of large multicentre randomised clinical trials should be awaited. The dosages used to test the clinical efficacy of high-dose nebulised corticosteroids in patients with ECOPD and asthma are very low compared with systemic corticosteroid doses (1–8 $mg \cdot day^{-1}$ *versus* 30–60 $mg \cdot day^{-1}$, respectively). Moreover, there is very little systemic absorption of inhaled/nebulised corticosteroids. For these reasons, it seems very difficult to attribute any of the positive or negative systemic effects to the short-term nebulised corticosteroid use.

Finally, a large percentage of chronic obstructive pulmonary disease patients hospitalised with exacerbations of chronic obstructive pulmonary disease have received treatment with high-dose inhaled corticosteroids (1,000–2,000 $\mu g \cdot day^{-1}$) prior to exacerbation and hospitalisation. Administration of a similar dose of nebulised corticosteroid during an exacerbation does not sound reasonable to the current authors. We believe that higher doses of corticosteroids should be tested to determine their efficacy in patients hospitalised with exacerbations of chronic obstructive pulmonary disease.

H. Gunen, S.S. Hacievliyagil, O. Yetkin and G. Gulbas
Dept of Pulmonary Medicine, Turgut Ozal Research Centre, Inonu University, Malatya, Turkey.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Gunen H, Hacievliyagil SS, Yetkin O, Gulbas G, In E. The role of nebulised budesonide in the treatment of exacerbations of COPD. *Eur Respir J* 2007; 29: 660–667.
2 Pinto-Plata VM, Livnat G, Girish M, *et al.* Systemic cytokines, clinical and physiological changes in patients hospitalized for exacerbation of COPD. *Chest* 2007; 131: 37–43.
3 Hansel TT, Barnes PJ. Clinical aspects of COPD. *In*: Hansel TT, Barnes PJ, eds. An Atlas of Chronic Obstructive Pulmonary Disease. New York, The Parthenon Publishing Group, 2004; pp. 69–115.
4 Hacievliyagil SS, Gunen H, Mutlu LC, Karabulut AB, Tenel I. Association between cytokines in induced sputum and severity of chronic obstructive pulmonary disease. *Respir Med* 2006; 100: 846–854.

5 Levy ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. *Thorax* 1996; 51: 1087–1092.
6 Westbroek J, Saarelainen S, Laher M, O'Brien J, Barnacle H, Efthimiou J. Oral steroid sparing effect of two doses of nebulized fluticasone and placebo in patients with severe chronic asthma. *Respir Med* 1999; 93: 689–699.
7 Manjra AI, Price J, Lenney W, Hughes S, Barnacle H. Efficacy of nebulized fluticasone propionate compared with oral prednisolone in children with an acute exacerbation of asthma. *Respir Med* 2000; 94: 1206–1214.
8 Morice AH, Morris D, Lawson-Matthew P. A comparison of nebulized budesonide with oral prednisolone in the treatment of exacerbations of obstructive pulmonary disease. *Clin Pharmacol Ther* 1996; 60: 675–678.
9 Maltais F, Ostinelli J, Bourbeau J, *et al.* Comparison of nebulized budesonide and oral perdnisolone with placebo in the treatment of acute exacerbations of COPD. *Am J Respir Crit Care Med* 2002; 165: 698–703.
10 Mirici A, Meral M, Akgun M. Comparison of efficacy of nebulized budesonide with parenteral corticosteroids in the treatment of acute exacerbations of COPD. *Clin Drug Invest* 2003; 23: 55–62.

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