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Combination therapy with maintenance budesonide and formoterol in COPD

To the Editors:

CALVERLEY *et al.* [1] provide further evidence for combination therapy with inhaled corticosteroids and long-acting β-agonists in severe chronic obstructive pulmonary disease (COPD) as maintenance therapy. In addition, a previous study, also confirming such benefit, showed an advantage for monotherapy with fluticasone in reducing exacerbations [2]. The study by CALVERLEY *et al.* [1] did not show a benefit for budesonide monotherapy in exacerbation reductions. Does monotherapy with inhaled steroids reduce exacerbations in severe COPD?

The conclusion that "additional clinical benefit when combined in a single inhaler" would surely be further strengthened by assessing the effectiveness of the fixed-dose single inhaler combination against the same drugs in separate inhalers? As there are sound cellular reasons for combining these two classes of drug [3], would there not be a potential advantage in the use of these two drugs as separate inhalers to allow greater dose flexibility, although this is of greater relevance in asthma? Or, if fixed-dose combinations are superior to separate inhalers taken together, then would this also be an important finding to favour the former?

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From the author:

We are grateful for A.R.L. Medford's interest in our study [1]. The patients in our trial had relatively severe chronic obstructive pulmonary disease (COPD; mean forced expiratory volume in one second (FEV1) 36% predicted), as did those in a companion study of the same treatment that used a different trial design [2]. In both trials, budesonide *via* a dry powder reservoir delivery system was less effective in preventing exacerbations than fluticisone delivered in a slightly higher dose in the TRial of Inhaled STeroids ANd long-acting β-agonists (TRISTAN) of patients with a mean FEV1 44% pred [3]. These disparities may reflect differences in the dose given, the delivery system or the effectiveness of inhaled corticosteroids in more severe disease, and our data cannot resolve this point. However, a more recent analysis of the TRISTAN data set, which is currently being prepared for publication, suggests that the effect of the inhaled corticosteroid on exacerbation numbers was less marked in those patients with more severe disease, and this would be in keeping with the findings of our study. We were reassured to see that, in both trials, the budesonide-formoterol combination reduced exacerbation numbers significantly, despite the relatively limited impact of the inhaled corticosteroid given alone. The current guidance on the use of inhaled corticosteroids in COPD recommends that they should be added into maintenance bronchodilator therapy, which should ideally be provided by a long-acting inhaled bronchodilator [4], and the use of inhaled corticosteroid as monotherapy to prevent exacerbations is not recommended.

Our statement about the benefits of combining treatment in a single inhaler was strictly factual, as we were not in a position to conduct the proposed comparison of fixed doses *versus* the same drug given in separate inhalers. Clearly, this is of practical relevance, but, unfortunately, calculating the statistical power of a study that could conclusively establish a difference between such treatment interventions suggests that it would have to be a substantially larger study than any that have been reported so far. We agree that there are good reasons for combining long-acting β-agonists and an inhaled corticosteroid, but the data about dose flexibility in chronic obstructive pulmonary disease has not been explored. There may be some utility in delivering the drugs together in a fixed dose combination at the site of action, rather than potentially allowing for different patterns of airway deposition on individual inhaler actuations. Such concerns remain of theoretical interest, but are hard to test with our existing techniques and in representative populations of chronic obstructive pulmonary disease patients. There are certainly advantages of convenience and, potentially, of treatment adherence by giving both drugs together, but this will need to be established in future studies.

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Progressive damage on high-resolution computed tomography

To the Editors:

We were interested to read the article by DE JONG *et al*. [1]. We are writing to you following enquiries by a number of clinical colleagues who have expressed concerns regarding the regular use of a high-dose technique (*i.e.* high-resolution computed tomography) with groups of young patients and the implications for the substantial radiation doses that may result.

The clinical potential of the procedure has, we are sure, been clearly shown. However, given the very high radiation doses involved and the young age of these patients, there is concern that relatively little information had been given to allow adequate justification of this procedure, in accordance with the relevant European directive [2], which concerns the health protection of individuals against the dangers of ionising radiation in relation to medical exposures.

We would be interested to hear the authors′ views, and, in particular, whether they are able to provide any information to allow a formal risk–benefit analysis to be carried out.

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From the authors:

We thank D. Rawlings and colleagues for their highly relevant question. Our study [1] was performed to compare high-resolution computed tomography (HRCT) with lung function in the assessment of disease progression in cystic fibrosis (CF). It was beyond the scope of this paper to evaluate the complex question of radiation risk *versus* clinical benefit of HRCT in these patients. Determining the risk–benefit profile of HRCT in CF patients is currently a research topic of high priority in our group. At this time, we believe that the use of HRCT in CF patients is consistent with the 1997 European directive [2]. In 1996, we reviewed the literature and performed a systematic review of our chest radiograph results; we concluded that routine chest radiographs were insensitive, and, due to variable techniques, we were unable to provide valid objective data on disease progression. As such, yearly bilateral chest radiographs were exposing patients to unnecessary radiation exposure. In addition, we and others concluded that lung function testing underestimated the severity and progression of lung disease in many CF patients. The question at that time was whether we should stop doing routine chest radiographs or introduce an examination that was undeniably more sensitive, but which provided greater radiation exposure, *i.e.* HRCT. Simply eliminating chest imaging would have left us unable to assess disease progression, which we believed was clinically unacceptable. CF-related lung disease results in a substantial reduction in life expectancy, substantial morbidity and requires the use of aggressive, potentially toxic and expensive therapies. For this reason, enhanced monitoring of disease progression was considered essential. In close collaboration with our radiology department, we designed the monitoring protocol that we have reported [1].

We have found that HRCT findings have allowed us to accurately estimate disease severity and tailor treatment. This conclusion has been confirmed by the retrospective analysis described in our publication [1]. We are currently extending this study with longer-term evaluation of our patients. In addition, we have compared our results to those in a cohort from a Swedish CF centre (Queen Silvia Children′s Hospital, Gothenburg, Sweden) that has used a similar HRCT routine since 1997. Preliminary results from this centre are in agreement with the results we have published in the *European Respiratory Journal* [1].

We agree with D. Rawlings and colleagues that we should aim for the minimal possible radiation exposure that provides acceptable diagnostic information. Recent improvements in scanner technology have allowed us to reduce the radiation dose to one-tenth of our initial protocol with no substantial decrease in image quality. We believe it is likely that further scanner technical advances will allow further reduction in computed tomography radiation dose.

This response is not meant to suggest that we negate the potential risk of regular high-resolution computed tomography in cystic fibrosis children. The risk–benefit ratio for early and regular high-resolution computed tomography