Meta-analysis on dose-response relationship of inhaled steroids must be done in homogenous asthma populations

To the Editor:

We would like to draw the readers' attention to the results of the meta-analysis of dose-response of inhaled budesonide in the recent article by MASOLI *et al.* [1], as we think these should be interpreted with great caution.

The dose-response relationship of inhaled steroids in asthma continues to be a topic of discussion, and even after 20 yrs there is no consensus on exactly which dose to use for an individual asthma patient. However, one of the experiences we, and certainly others, have gained is that the dose-response curves differ greatly in different asthma populations and are very much dependent on both the severity of the disease and also on asthma duration. In the latter case, the shorter the duration the lower the dose needed. Although MASOLI *et al.* [1] have excluded studies if they were not placebo-controlled or involved oral steroid-dependent patients, this does not mean that the rest of the asthma population in their meta-analysis is homogenous. Thus the overall approach for the dose-response exercise taken by MASOLI *et al.* [1] needs careful scrutiny, and the dose ranges found may indeed mislead the prescribing physician to use standardised, instead of individualised, doses.

In addition, there are concerns regarding the methodology used for the dose calculations in MASOLI *et al.* [1]. First, the suggested efficacy maximum for budesonide Turbuhaler® or Nebuhaler® was arbitrarily chosen to be 1,600 $\mu g \cdot day^{-1}$ without giving any reason. Secondly, the use of a meta-regression approach to compare the effect of change in dose is less than ideal, as this model implies that a local maximal effect is achieved, which we know is not the case with inhaled steroids because they reach an efficacy plateau. Thirdly, a further weakness in the analysis is the approach of comparing the 400 $\mu g \cdot day^{-1}$ dose with the nearest higher dose. Most of our experience tells us that no difference in clinical efficacy will be detected, for example, when doubling the dose of inhaled steroids.

Regarding the relationship between budesonide and other inhaled steroids, even more caution is required when evaluating clinical findings. It is not possible to compare the results of the meta-analysis performed on fluticasone [2] with the study by MASOLI *et al.* [1], again with the differences in patient populations in mind. In HOLT *et al.* [2] there is also an overall flaw seen by the consistent use of lower doses of fluticasone in the analysed studies. Ideally, the budesonide studies should have included more dose-steps in the range of 100–200 μg, but regrettably such data is not available. However, this reflects the changes in treatment strategies over time and not necessarily any potency differences.

In order to get valid data for the dose-response relationships of inhaled steroids, we believe in performing more studies in defined populations and ideally using several doses of each drug. Also, dose-reduction studies can be used, especially when comparing different steroids or steroid-device combinations. Hopefully most readers are aware that we have used such designs both for the relationship between budesonide Turbuhaler *versus* the pressurised metered dose inhaler [3], as well as for the relationship between budesonide Turbuhaler and fluticasone Diskhaler and Diskus [4, 5], an approach that was very much endorsed in an editorial in the *European Respiratory Journal* 3 yrs ago [6].

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References

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From the authors:

It is helpful to have the opportunity to respond to the letter of J. Ingelf and colleagues to clarify issues relating to the meta-analysis of the dose-response relationship of budesonide in the treatment of adult asthma [1].

The ideal way to explore the relationship between dose and response amongst individuals with different characteristics, such as severity or duration of disease, would be by meta-analysis of individual patient data. Unfortunately, only summary response data were available; a useful extension of our work would have been possible if our attempts to access individual patient data from AstraZeneca had been successful. This point regarding access to individual patient data held by pharmaceutical companies was made in an accompanying editorial with reference to our work on the dose-response relationship of fluticasone [2]. Pending the analysis and publication of these data, we recommend that physicians should prescribe in accordance with the therapeutic dose range, which has been defined in our meta-analysis based on available scientific data.

In response to the methodological issues, the effect obtained with 1,600 $\mu g \cdot day^{-1}$ was considered to be the "maximum effect", as this was the highest dose used in the studies included in the meta-analysis. It will be possible to examine the effects with higher doses if dose-response studies including high doses are undertaken. No attempt was made to determine the dose-response relationship of local side-effects. Indeed, the systemic adverse effects are of considerably greater