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CORRESPONDENCE

Distribution of therapeutic response in asthma control

To the Editor:

The paper by BAUMGARTNER *et al.* [1] raises very important questions pertaining to the interpretation and usefulness of randomised clinical trials, the use of surrogates of little relevance to the patient and the comparison of results using group average values. However, these problems are not adequately addressed.

Whilst reference is given to the Global Initiative for Asthma guidelines to define asthma control, the focus of the study is on percentage of asthma control days defined on a subset of asthma control measures only. This definition carries two weaknesses. First, it ignores important parameters that define asthma control. Lung function, including level of bronchial obstruction and its variability, is an important parameter to account for, so that days with marked obstruction are not misclassified. Secondly, and more importantly, the use of percentage of days ignores the fact that only sustained daily control defines overall control. In this study, $\leqslant$30% of patients had control for $\geqslant$90% of days. In our definition of asthma control we used much more stringent criteria that incorporated all parameters and integrated these over 3 months to provide an overall assessment [2]. We showed that one of the main reasons for not achieving control was bronchial obstruction and that this approach was meaningful to patients, as good control correlates with an improved or even normalised quality of life [3].

The use of distribution analysis to compare therapies is an interesting approach as it allows an assessment of treatment efficacy on a patient basis. It is important to question why the mean percentage of asthma control days showed a clear and significant difference between active treatments but the distribution analysis did not. Examination of the distribution data suggests a simple shift to the right with beclomethasone compared with montelukast treatment. About 5–10% of the patients are shifted from one column to the next, therefore ending with little or no difference for most columns and a clear difference at the extremes. As expected, this difference looks similar to the mean treatment difference. Therefore, one can speculate that most patients improve more with beclomethasone than they would with montelukast treatment. The only design that allows the within-patient difference to be addressed is the crossover design, and its sophisticated version, N of 1 [4]. The use of crossover studies in asthma is a challenge, but we should also recognise that the approach proposed by BAUMGARTNER *et al.* [1] is not suitable for parallel group designs.

It is not surprising that an equivalence testing using an 80% overlap failed to show a true difference. Assay sensitivity is an important issue in equivalence trials [5]. Equivalence boundaries have not been unequivocally established. Experience from development of alternative propellant programmes, general publications [6] and regulatory recommendations [7] suggest a zone of equivalence of $\pm$0.5 or a third of the difference between active and placebo treatment. This placebo-controlled study provides an opportunity to ascertain assay sensitivity as well as validate the boundaries chosen, but these critical results are not presented.

Using traditional measures of asthma, the study by BAUMGARTNER *et al.* [1] showed significant differences in favour of beclomethasone in several variables and a trend in all others, suggesting a true finding. The proposed new analysis method suggests the two treatments are equivalent. It is an illustration that the use of inappropriate methodologies can lead to misleading conclusions.

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From the authors:

We are in agreement with G.L. Braunstein′s comment that it is important to discuss end-points that are of clinical relevance to patients and to describe not just average values but results accounting for the entire population. His letter also provides us with an opportunity to rechallenge some of the commonly held assumptions about the clinical interpretation of asthma data and re-emphasise the clinical advantages of our approach to describing the response of patients to asthma therapy. We particularly wish to focus on the methodological issues that he has raised.

The best definition available of asthma control is from the consensus guidelines; unfortunately, this description is neither population-based nor validated. Difficulties have been encountered in efforts to identify and accurately validate the important clinical measures of asthma control, and it remains