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CORRESPONDENCE

Comparative efficacy and safety of mometasone furoate dry powder inhaler and budesonide Turbuhaler®

To the Editor:

BOUSQUET *et al.* [1] recently compared the efficacy and safety of mometasone furoate dry powder inhaler (MF DPI) and budesonide DPI (Turbuhaler®) for the treatment of moderate persistent asthma. They concluded that lower doses of MF DPI appeared to be more effective than a clinically recommended dose of budesonide DPI, while providing a comparable degree of safety.

For several reasons we do not agree with this conclusion. Experiences gained during the last decade have taught us that the greatest amount of care must be taken in the design of studies where the relative efficacy of inhaled steroids are to be investigated. Not least has it repeatedly been seen that the dose-response curves for these drugs on most antiasthma variables are very flat, which means that traditional dose-response studies are acceptable for comparisons of relative efficacy only if several doses are selected over a wide dose range [2]. For budesonide, several studies have shown that a four-fold difference in dose may be necessary for ensuring statistically significant dose-differences [3, 4]. In the study by BOUSQUET *et al.* [1] only one dose of budesonide Turbuhaler® (800 $\mu g \cdot day^{-1}$) was compared to three doses of MF DPI (200, 400 and 800 $\mu g \cdot day^{-1}$). The budesonide dose was as high as the highest dose of MF, so no information of what a lower dose of budesonide could have achieved in this patient population could be obtained. The lack of multiple doses of budesonide also turned out to be less ideal as the 800 μg dose of MF did not show any improvement over the 400 μg dose. Thus, for MF DPI also, a dose-response curve could not be constructed. Overall, the design chosen cannot prove any relative efficacy ratio between the two drugs.

It is also noticeable that one-third of the patients were already treated with similar doses of budesonide (mean doses 663 μg) when entering the study and for these patients a further improvement on 800 μg could hardly be expected. Patient expectations regarding treatment benefit would thus be nonexistent in this group as compared to other patients given the new inhaler. Also, one would have anticipated a more thorough compliance check, given the delicacy in comparing a new but similar inhaled steroid DPI treatment with an established one.

The most serious flaw is of course that the study was not blinded to the patients and that no double dummy technique was used. This might be difficult to obtain in dose-response studies, but alternative designs are available; in a double-blind study in asthmatic children utilizing dose-reduction of budesonide Turbuhaler® and fluticasone Diskhaler® every 5 weeks, minimal effective doses of the two preparations could be calculated [5]. The study showed that there was no significant difference in clinical efficacy between the two preparations at similar doses. This result should be kept in mind as there have been claims that mometasone DPI and fluticasone Diskhaler® are comparable in efficacy [6].

The MF DPI seems to have been developed with Turbuhaler® as a close prototype. It differs, however, in some crucial dose-activating characteristics, *e.g.* the turning of the cap activates the dose-metering unit. More importantly, the MF DPI is labelled in delivered doses, whereas budesonide Turbuhaler® is labelled in metered doses. Thus, the 800 μg mometasone DPI dose that was used in the study by BOUSQUET *et al.* [1] was not compared with an identical dose of budesonide, but rather 560 μg, these are the doses that are delivered from the respective inhalers. This difference between the two preparations was not stated in the article, but may contribute to any claim regarding higher potency for the MF DPI *versus* other inhaled formulations.

Regarding the safety characteristics of mometasone furoate dry powder inhaler, the authors claim that both drugs provide a comparable degree of safety based on the lack of effect on the hypothalamic-pituitary-adrenal axis. However, these results are what would be expected given the low sensitivity of morning cortisol assessment to detect differences between treatment regimens [2]. In the present study, this is evidenced by the same cortisol suppression following treatment with the lowest mometasone furoate dry powder inhaler dose (200 $\mu g \cdot day^{-1}$) as at baseline, where patients were given 400 – 800 $\mu g \cdot day^{-1}$ of other inhaled steroids. It still remains to be proven if the low systemic availability, claimed after inhalation of mometasone furoate [7], can be translated into low systemic effects, or if any pharmacologically active metabolite might explain the hypothalamic-pituitary-adrenal effects seen after inhaled doses of mometasone furoate [8, 9].

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Lung cancer in young females

To the Editor:

We read with interest the article by LIENERT *et al.* [1]. Based on data of the clinical cancer registry at the Lungenklinik Heckeshorn, Berlin, 1986–1995, the authors examined whether young female lung cancer patients (≤45 yrs of age, n=96) differ from all other lung cancer patients (n=4,843) with respect to risk factors, histology and clinical features. They found a higher proportion of adenocarcinomas (38%) and carcinoids in young females. Other main characteristics of young females were a high proportion of ever-smokers (88%) and a large number of patients who reported a first degree relative with lung cancer (13%). We would like to add our recent findings of a large-scaled, case-control study of lung cancer conducted in Germany from 1990–1996 [2, 3], which aimed to investigate risk factors for lung cancer in young adults. This study included 251 young patients and 280 population controls (≤45 yrs of age), as well as 2,009 older cases and 2,039 older controls (55–69 yrs of age). Adenocarcinomas were more frequent in young males (41%) and young and older females (44% and 47%, respectively) than in older males (28%). Differences in histology between age groups could be explained, in part, by differences in smoking patterns. However, there are still unknown factors that appear to favour the development of adenocarcinoma in the young [3]. A history of lung cancer in first degree relatives was associated with a 2.6-fold (95% confidence interval (CI) 1.1–6.0) increased risk in the young, while no elevated risk was observed in the older group (odds ratio=1.2 95% CI 0.9–1.6). Additional evidence for an age-specific genetic predisposition in lung cancer was recently provided by GAUDERMAN and MORRISON [4]. About 80% of our young female cases were current smokers, demonstrating a 30-fold increased lung cancer risk compared to never-smoking young females [2]. As stated by LIENERT *et al.* [1], smoking is the main risk factor for lung cancer in young females. This was recently supported in a pooled analysis of European case-control studies of lung cancer in young females [5], where 84% of female patients aged 40–45 yrs could be attributed to active smoking.

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From the authors:

The valuable data of our colleagues M. Kreuzer and H.E. Wichmann support the main results from our own series. Yet it is remarkable that in their patients, adenocarcinoma in older females (55–69 yrs of age)