

## PERSPECTIVE

# Comparative studies of inhaled corticosteroids in asthma

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With inhaled corticosteroids being the mainstay of anti-inflammatory treatment in asthma, it is necessary to determine the comparative efficacy and safety of different corticosteroids delivered through different inhaler devices. Over recent years this has assumed considerable importance, with the phasing out of metered dose inhalers using chlorofluorocarbon (CFC) propellants, and with the availability of an increasing number of different dry powder devices or aerosol metered dose inhalers in which alternative hydrofluoroalkane (HFA) propellants have been used. This has led to numerous studies in which the efficacy of inhaled corticosteroid preparations, either dry powder or HFA-containing aerosol metered dose inhalers, have been compared with the same or different inhaled corticosteroids *via* standard CFC-containing preparations in current use.

Although numerous study designs are available for such comparisons, that most commonly employed has been single high dose comparisons, with the lack of statistical significant differences between the two preparations being proposed to indicate equivalent efficacy.

Recently, the Editorial Board of the *European Respiratory Journal* (ERJ) has decided on a policy to give low priority to manuscripts of comparative studies based on such designs and inferences. The major reasons for this are that: 1) inhaled corticosteroids administered in doses 400–800 µg per day of beclomethasone dipropionate (BDP) [1–3] or budesonide [4–6] and 200–500 µg per day of fluticasone [7–9] are near the top of their dose-response curves for clinical efficacy; and 2) in double-blind dose-response studies there have seldom been statistically significant differences between different doses of inhaled corticosteroids (within the above dose range) for clinical outcomes including lung function, beta agonist use, symptoms such as nocturnal waking or major exacerbations [1–10]. Even when four-fold differences in dose have been studied, statistically significant differences may not be observed within dose ranges of 400–1,600 µg per day of BDP or budesonide, or 200–1,000 µg per day of fluticasone [1–10].

As a result, the Editorial Board has developed a policy whereby it will give low priority to the publication of studies utilizing either equal dose or two to one dose

comparisons of different inhaled corticosteroid drugs. As recommended in a recent review [10], the preferred study designs are double-blind placebo-controlled studies which involve: 1) a dose-response comparison in which two drugs are assessed in at least two doses, thus providing a within-trial comparison of dose-response [3]; 2) a dose-response *versus* one dose comparison in which the principal trial drug is given in two or more doses, while the other established corticosteroid is assessed at a single dose level that has previously been shown to be effective [11]; 3) a dose down-titration comparison in which well controlled patients reduce their dose until their asthma becomes uncontrolled, at which stage they are entered into the trial which may involve subsequent dose adjustments to determine the minimum effective dose of each drug [12]; or 4) a single dose or dose-response comparison of the efficacy/safety ratio, utilizing measurement of validated markers of adrenal function in addition to clinical asthma outcomes [13].

While there may be difficulties with interpretation, studies which have employed the above designs are likely to be more informative than those using single dose comparisons.

Finally, while recognizing that comparisons of different inhaled corticosteroids delivered by different inhaler devices are important to determine the relative efficacy and safety of specific inhaled corticosteroid products, it is hoped that ongoing clinical research in this field is not dominated by such studies. In this respect, studies over the last decade which have examined different regimes in which inhaled corticosteroid therapy is prescribed, including early intervention [14, 15], starting "high" *versus* starting "low" dose regimes [16], pulse regimes [17], once daily schedules [18, 19], comparison with other medications [20, 21], combination therapy [22, 23] and their incorporation into an asthma self-management plan system of care [24], have added significantly to the present understanding of the best ways in which this therapy can be used. Other issues which need to be further addressed include the use of different objective markers to measure the clinical efficacy of inhaled corticosteroids [9] or to titrate their dose in long-term management [25], the determination of dose-response curves for both invasive and noninvasive markers of airways inflammation [26], and the mechanisms through which inhaled corticosteroids achieve their anti-inflammatory effects in asthma [27, 28], and consideration of their systemic side effects which enables benefit/risk ratios to be determined [13, 29].

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