

EDITORIAL

Glucocorticoids and immunoglobulin E: no new *in vivo* paradigms

In the Editorial of the November 2000 issue of *Clinical and Experimental Allergy*, Salvi, Babu and Holgate discussed the effect of glucocorticoids on immunoglobulin (Ig)E synthesis [1] based on the article published in the same issue of the Journal about the enhancing effect of hydrocortisone on allergen-specific IgE production *in vitro* [2]. Not arguing against the findings presented by Cho et al. in the original paper, we would like to further address one part of the Editorial, namely the discussion about the effect of glucocorticoids on IgE production *in vivo*.

It is the second time *Clinical and Experimental Allergy* dedicates an Editorial to the issue of glucocorticoids and IgE production. The first one appeared in 1994 under the title 'Glucocorticoids and IgE: an *in vitro* paradox' and clearly indicated that while *in vitro* data suggest enhancement of IgE synthesis by glucocorticoids, this is not the case *in vivo* [3]. The present Editorial 'Glucocorticoids enhance IgE synthesis. Are we heading towards new paradigms?', however, unanimously states that glucocorticoids enhance IgE synthesis not only *in vitro*, but also *in vivo* and *ex vivo*. A careful reader will certainly wonder what kind of new evidence has surfaced during the last six years to confirm that speculation. Besides citing two studies from the end of the 1970s [4,5] on the polyclonal rise of circulating IgE after oral prednisolone treatment, the authors of the Editorial also refer to two reports from the middle of the 1990s which were claimed to show an *in vivo* increase of total as well as allergen-specific IgE levels following both long- and short-term glucocorticoid administration [6,7]. However, in the first of these publications in which the use of oral prednisone with the median daily dose of 20 mg and median treatment duration of 2 years was examined, no reporting on changes in IgE levels exists [6]. Instead, the investigators evaluated the effect of long-term oral glucocorticoid therapy on the results of skin prick tests (SPT), being unable to demonstrate any significant alterations in SPT reactivity following the treatment period. The median size of SPT after glucocorticoid therapy was similar to the pretreatment values and although an increase in the number of positive SPTs was observed in almost 50% of these steroid-dependent asthma patients, the new sensitivities were very few.

The second referred study by Zieg et al. reported a polyclonal rise in serum IgE levels following a 7-day course of high-dose prednisone (40 mg daily) in ten patients with asthma [7]. Importantly, this was an uncontrolled study comparing pre- and post-treatment IgE levels on the same subject and thereby does not allow the drawing of firm conclusions. The importance of including a placebo-treated control group can be well demonstrated in a study in which we have recently participated in and published. In that study, birch-allergic rhinitis patients were treated with nasal beclomethasone or placebo over the birch pollen season [8]. If we had only included active treatment as in the study reported by Zieg et al. we would have demonstrated

that nasal beclomethasone reduces the levels of total serum IgE! However, since that reduction was not statistically significantly different from the one observed in the placebo-treated patients we did, of course, not report this observation. On the other hand, compared to placebo-treatment, nasal beclomethasone (400 µg/day) significantly inhibited the birch pollen-induced increase in allergen-specific serum IgE levels in allergic rhinitis patients (Fig. 1). Naclerio and colleagues [9] had previously reported similar findings with triamcinolone, in a study that was performed during the ragweed pollen season. The inhibition of pollen-induced increase in serum IgE occurs irrespective of whether treatment with nasal glucocorticoids is initiated one week prior to [9], or concomitantly with [8], the beginning of the pollen season. Thus, nasal glucocorticoids can inhibit an ongoing allergen-specific IgE production and do not reduce specific serum IgE levels only by altering the amount of allergen penetration and subsequent presentation as a result of preventing nasal inflammation from the beginning of the pollen season.

In support of the view that glucocorticoids attenuate IgE levels *in vivo* by affecting its synthesis and not just via some non-specific anti-inflammatory action, three studies in allergic rhinitis patients have demonstrated a down-regulatory effect of topical glucocorticoids on the expression of RNA for the germ-line promoter site of IgE (I ϵ), the unrearranged IgE heavy chain gene (C ϵ) or on IgE-producing cells [10–12]. This has been demonstrated in nasal mucosal biopsies in placebo-controlled studies both following allergen challenge [10] and during the naturally occurring pollen season [11], and in nasal lavage fluids following allergen challenge [12]. Similarly, topical budesonide treatment reversed the pollen-induced increase in total IgE levels in nasal fluids from children with seasonal allergic rhinitis, although this study did not include a placebo arm [13]. Furthermore, results from an animal study have indicated that glucocorticoid treatment, given either during or following shortly after sensitization, can inhibit development of allergen specific IgE antibodies in previously unsensitized animals without having any increasing effect on total IgE levels [14].

Thus, there is significant evidence to support the view that glucocorticoid treatment does not enhance, but actually reduces, the levels of clinically relevant specific IgE antibodies *in vivo*. This evidence was not present in the Editorial by Salvi et al. Locally administered glucocorticoids have revolutionized the treatment of asthma and allergic rhinitis over the last three decades, and have proven to be the most effective safe treatment options for patients with inflammatory airway disease [15,16]. Although it has been easy to demonstrate the striking effectiveness of local glucocorticoids, physicians around the world have struggled to overcome the patients' fear and prejudice for such treatment. The reader should therefore remember that controlled studies do demonstrate the inhibitory effect of local glucocorticoids on allergen-specific IgE production.

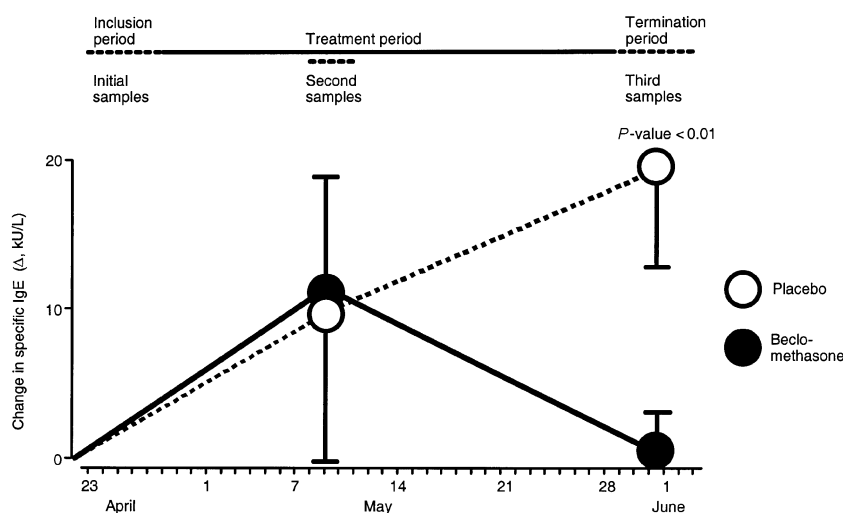


Fig. 1. Change in specific anti-birch IgE antibody levels in patients with allergic rhinitis treated for 5 weeks with intranasal beclomethasone or matching placebo. Data shown are means $\pm$ SEM of anti-birch IgE levels during and after the season from which baseline levels are subtracted. (From [8] with permission).

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