

Intranasal steroids inhibit seasonal increases in ragweed-specific immunoglobulin E antibodies

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We performed two seasonal studies to evaluate the effect of continuous treatment with intranasal steroids, beginning approximately 1 week before the appearance of ragweed pollen, on the level of ragweed-specific IgE antibodies in serum. In both studies the control groups showed the anticipated rise in ragweed-specific IgE antibodies after the ragweed season. In the first study, employing aqueous beclomethasone dipropionate (168 µg twice daily), no rise occurred in serum ragweed IgE after seasonal exposure and the level actually decreased in eight of 12 treated subjects. In the second study, with triamcinolone acetonide (220 µg twice daily), the expected rise in ragweed IgE antibody was also reduced, although less dramatically, probably as a result of the lower potency of the dose delivered. Our studies not only support the benefits of intranasal steroids in the treatment of seasonal allergic rhinitis but also suggest that specific IgE production may be down-regulated by their continuous use, which may alter the subsequent clinical course of the disease. (J ALLERGY CLIN IMMUNOL 1993;92:717-21.)

Key words: Ragweed; intranasal steroids; serum ragweed IgE; beclomethasone; triamcinolone; allergic rhinitis

The development of intranasal steroid preparations has been a major therapeutic advance in the management of allergic rhinitis. Clinical efficacy of nasal steroids has been unequivocally established by placebo-controlled trials,¹ and their clinical potency exceeds that of nasal cromolyn and antihistamines and probably equals that of immunotherapy.²⁻⁶

We and others have attempted to define the mechanism by which intranasal steroids achieve their efficacy. If administered for 1 week before nasal challenge with antigen, they reduce the initial response to antigen and the subsequent inflammatory events.⁷ The latter include the influx

of inflammatory cells, the spontaneous release of mediators, and the recurrence of symptoms during the late phase reactions, and also during the subsequent period of increased reactivity to antigen, histamine, and methacholine.⁸⁻¹⁰ During seasonal exposure intranasal steroids reduce symptoms, the influx of eosinophils and metachromatic cells, and the generation of eosinophil cationic protein.^{11, 12} Many clinical investigators attribute the potency of intranasal steroids to their ability to reduce allergic inflammation.

We designed two clinical trials to evaluate the effect of continuous treatment with intranasal steroids on the specific IgE antibody response that is known to occur after seasonal ragweed exposure. We aimed to expand our knowledge of the effect of intranasal steroids on the humoral response to seasonal exposure, and this has permitted us to postulate about the potential effects of this class of drug on the subsequent clinical course of allergic rhinitis.

METHODS

Subjects

Patients were selected on the basis of a history of allergic symptoms during the ragweed pollen season and a positive intradermal skin test result to aqueous ragweed pollen extract. Subjects were eliminated from

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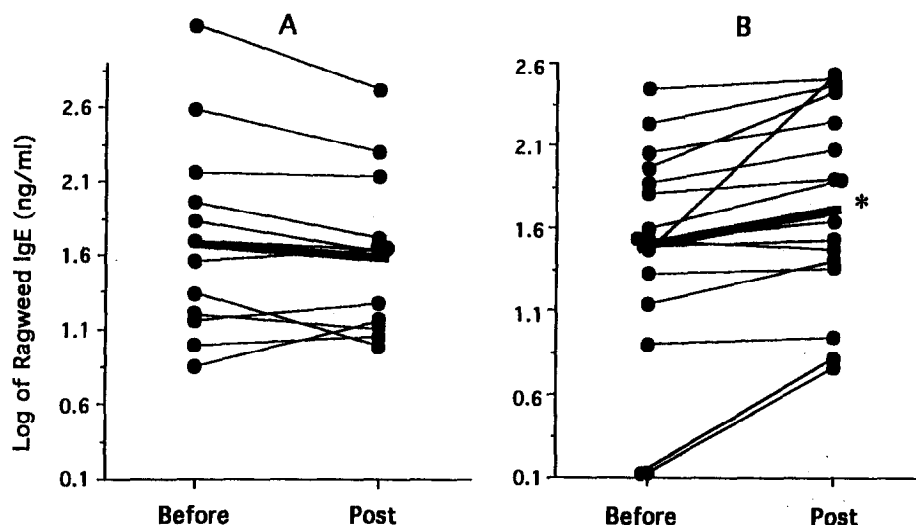


FIG. 1. Level of RW-IgE (nanograms per milliliter) in serum obtained before and after ragweed season. **A**, Effects of continuous intranasal beclomethasone dipropionate treatment; **B**, effect of no treatment. *, $p < 0.05$. Geometric means are shown as bold lines.

the study if they had a history of medical illness other than mild asthma (i.e., they did not require daily medication). In addition, subjects were excluded if they had taken oral steroids or astemizole within the previous month or had received immunotherapy within the 2 prior years. Both studies were approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University, and each subject gave written consent before entry.

Study design

First trial. We selected 12 volunteers with a history of ragweed-induced allergic rhinitis (mean age 37 years, range, 19 to 43 years; three black patients, nine white). The subjects received 42 μ g (one spray) of beclomethasone dipropionate (Beconase AQ) through a metered dose inhaler twice in each nostril twice a day (bid) beginning in the week before anticipated ragweed exposure in Baltimore. The subjects kept symptom diaries during the season, as previously described,¹³ and had blood drawn for the measurement of ragweed-specific IgE antibodies (RW-IgE) before and at the end of the season. Their antibody levels were compared with a group of 19 similar subjects (mean age 35 years, range 25 to 60 years; two black patients, 17 white) participating in the placebo arm of a double-blind protocol to study an orally active antiallergic compound during the same ragweed season.

Second trial. Thirty-seven volunteers participated in a double-blind, placebo-controlled clinical trial with the intranasal steroid triamcinolone acetonide through nasal inhaler. Twenty subjects (mean age 36 years, range 25 to 48 years; three black patients, 14 white) were then randomly assigned to receive intranasal steroid (110 μ g of triamcinolone acetonide (one spray) once in each nostril bid) and 17 (mean age 32 years, range 25 to

48 years; three black patients, 14 white) to placebo treatment beginning before seasonal ragweed exposure. Each patient kept a daily diary of symptoms and medications. The diaries were collected at 2-week intervals. At the same time, a physician examined the nasal mucosa and rated rhinorrhea and mucosal edema on a scale of 0 to 4 (0 = none, 4 = severe). Blood samples were collected before, during, and after the season for the measurement of ragweed-specific antibodies.

Ragweed-specific IgE antibody assay. The RAST employed has been previously described.¹⁴ The assay was standardized in mass/volume units with a human serum calibrated by depletion analysis. The RAST was sensitive to 1 ng/ml.¹⁴ All serum specimens that were obtained from a subject were measured in the same assay, to minimize variability that may result between assays.

Nasal IgE antibody was detected by placing four ragweed-coated disks directly onto the nasal mucosa. After 10 minutes the disks were removed and placed in a RAST buffer overnight. All tubes were washed and then incubated with radioiodinated antihuman IgE overnight. After being washed, the tubes were incubated in a gamma scintillation counter. The results were compared with a standard curve constructed with a human reference serum processed in an identical manner. Results were reported in picograms of IgE bound per disk and considered positive at values greater than 30 pg/disk. Levels up to 28,000 pg/disk did not cause saturation. Placement of the disks did not induce symptoms.

Nonparametric statistics were used for analysis. Friedman analysis of variance was performed when more than two observations were made. Paired data were analyzed by the Wilcoxon matched-pairs signed

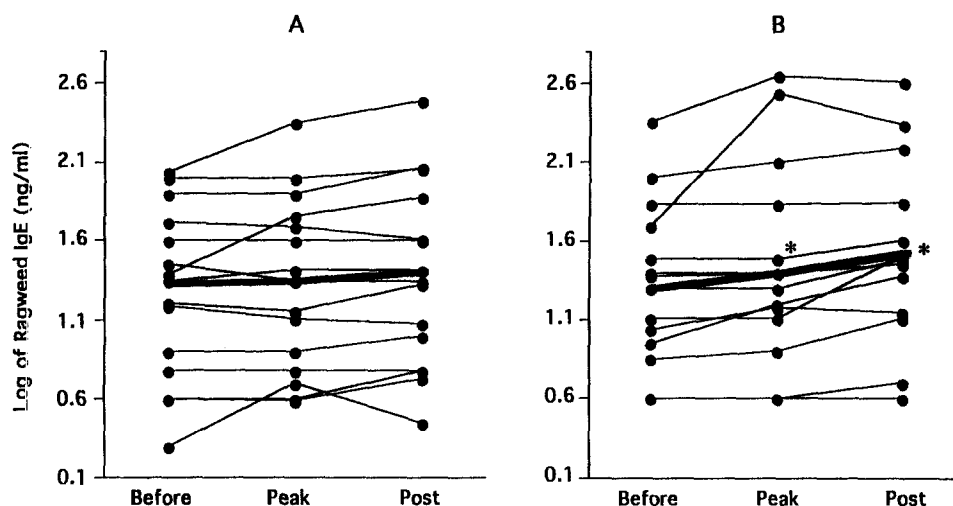


FIG. 2. Level of RW-IgE (nanograms per milliliter) in serum obtained before, during, and after ragweed season. **A**, Effect of continuous intranasal triamcinolone acetonide treatment; **B**, effects of placebo treatment. *, $p < 0.05$. Geometric means are shown as bold lines.

rank test, whereas unpaired data were analyzed by the Mann-Whitney U test. Ragweed values are presented transformed to the log base 10. Two-tailed p values less than 0.05 were considered significant.

RESULTS

In the first trial the levels of RW-IgE were equivalent between the groups before the beginning of the season (Fig. 1). After seasonal exposure the group receiving no steroid treatment showed a significant rise ($p < 0.01$) in their levels of RW-IgE. In contrast, the group receiving intranasal beclomethasone dipropionate showed no significant increase in RW-IgE and in fact eight of 12 subjects had lower levels after the season. The group receiving intranasal steroids reported significantly lower (10.5 ± 1.1 vs. 4.0 ± 1.1) ($p < 0.002$) symptom mediation scores in their diaries.

In the second trial the level of RW-IgE was equal in both groups before the ragweed season (geometric mean 1.33 vs. 1.34 ng/ml). Five subjects in the placebo group and three in the intranasal steroid group had no detectable RW-IgE in their serum before the season, and the level did not change in response to seasonal exposure. These subjects were eliminated from the analysis.

In the placebo group the geometric mean titers of RW-IgE rose from 1.33 ng/ml before the season to 1.45 ng/ml ($p < 0.05$) during the season, and 1.54 ng/ml ($p < 0.001$) after the season (Fig. 2). In contrast, in the group receiving continuous intranasal triamcinolone acetonide the geometric mean levels of RW-IgE were 1.27, 1.33 and 1.37

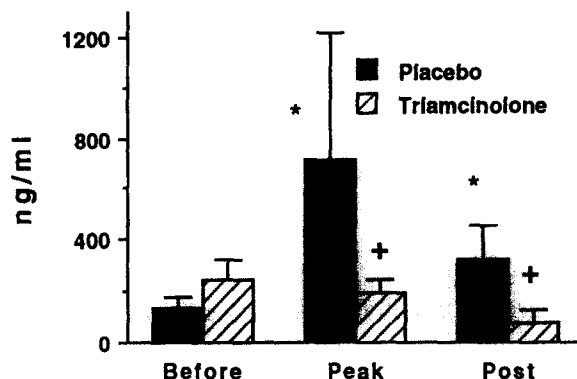


FIG. 3. Level of RW-IgE in nasal secretions obtained before, during, and after ragweed season. Values expressed as mean $\pm$ SEM. *, Significant ($p < 0.05$) increase compared with before; †, significant ($p < 0.05$) decrease compared with preseason values.

ng/ml before, during, and after the season. None of the changes from preseason levels was statistically significant for the steroid-treated group. If the Wilcoxon signed rank test, however, is performed between the preseason and postseason periods, a significant difference is found ($p = 0.05$). Nasal RW-IgE was measured in this study (Fig. 3). The placebo group demonstrated a significant ($p < 0.05$) rise after seasonal exposure, whereas the active group showed a significant decrease ($p < 0.5$). The group receiving intranasal triamcinolone acetonide reported a significantly lower increase in symptoms during the pollen season (3.0 ± 0.6 vs. 5.6 ± 1) ($p < 0.05$).

The physicians observing the subjects at 2-week intervals during the trial observed significantly less rhinorrhea (median [range]: drug, 0 [0 to 3]; vs. placebo, 2 [0 to 4]; $p < 0.008$) and mucosal edema (median [range]: drug, 2 [1 to 3]; vs. placebo, 3 [0 to 4]; $p < 0.03$).

DISCUSSION

Despite the relatively small number of subjects entered into these two trials, we were able to demonstrate the clinical benefits of intranasal steroids on the symptoms of ragweed hay fever. These findings are consistent with previously reported clinical trials.¹ The level of serum-specific ragweed IgE increased after seasonal exposure, which is also consistent with previously reported studies.^{15, 16} The novel finding from our studies was the inhibition of a rise in RW-IgE that we observed in subjects continually treated with intranasal steroids during the season.

The generation of specific IgE antibody is the hallmark of allergic disease. Seasonal exposure to ragweed antigen enhances the humoral response. This may increase the local concentration of IgE, which sensitizes mast cells, basophils, and other cells with IgE receptors.^{17, 18} This process may contribute to the enhanced response to inhaled allergen seen toward the end of the season.¹⁹ Successful immunotherapy suppresses the seasonal rise in RW-IgE, an observation postulated by some as a potential mechanism for its efficacy.¹⁶ The impact of the rise of specific IgE after antigen exposure on the pathogenesis of allergic rhinitis, however, is not fully understood.

The beneficial effect of intranasal steroids has frequently been attributed to antiinflammatory actions on the late events after antigen provocation.⁷ In our previous studies intranasal steroid pretreatment also reduces the immediate response to nasal provocation.⁹ The present studies show that their continuous use may alter another aspect of the disease process, the synthesis of specific IgE antibodies. These studies not only support the continuous prophylactic use of these drugs but may also provide another explanation for their tremendous clinical potential.

Our studies do not provide information regarding a mechanism for the observed action of intranasal steroids. Oral steroids have modest effects on IgG levels, with large doses causing a slight decrease in IgG and IgM and no change or a slight increase in IgE.⁷ Intranasal steroids may have simply reduced nasal inflammation and thereby altered the amount of allergen penetrat-

ing the mucosa, or high mucosal concentrations of steroids could have a direct effect on local IgE synthesis.

The only other study measuring specific IgE antibody before and after seasonal exposure in subjects receiving intranasal steroids was done by Welsh et al.⁴ They used flunisolide nasal solution (0.025%), two sprays in each nostril bid, and beclomethasone nasal solution (0.5%), two sprays in each nostril bid. Blood was drawn before ragweed season and on the final visit after the season. Although the mean levels of RW-IgE were less in the intranasal steroid groups compared with control subjects, they did not achieve statistical significance. The difference between their result and ours may relate to dose, amount of pollen exposure, and/or the timing of the blood sample.

We feel confident in our observations because they occurred in two separate trials performed in two different years. The results of the first trial were more striking, whereas in the second trial the effect was better seen in midseason compared with later in the season. At first glance the latter study may seem to weaken our results, but it actually strengthens our observation by suggesting a dose-response relationship. The dose of beclomethasone dipropionate was approximately five times more potent on a biologic activity basis than the dose of triamcinolone acetonide used.²⁰ Whether the different delivery system also contributed to the outcome could not be determined.

In sum, our studies suggest that continuous use of intranasal steroids alters the humoral response to seasonal ragweed exposure. These results raise the possibility that topical steroids may alter the subsequent clinical course of allergic rhinitis by affecting the generation of specific IgE.

Conventional thinking suggests that only immunotherapy has the potential to alter the natural history of allergic rhinitis, and this remains an important reason for its continued use despite concerns about its safety. Further studies are needed to determine whether continuous nasal steroid use substantially affects the course of allergic rhinitis.

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