An intranasal glucocorticoid inhibits the increase of specific IgE initiated during birch pollen season

Teet Pullerits, MD,[a] Lea Praks, MD, PhD,[b] Margareta Sjöstrand, PhD,[a] Sabina Rak, MD, PhD,[c] Bengt-Eric Skoogh, MD, PhD,[a] and Jan Lötvall, MD, PhD[a]

Gothenburg, Sweden, and Tartu, Estonia

Background: Recent in vitro findings show that glucocorticoids in combination with IL-4 can induce the synthesis of IgE, indicating that glucocorticoids may promote allergy.
Objective: A double-blind, placebo-controlled study was performed to evaluate the effect of an intranasal glucocorticoid on the levels of birch pollen–specific IgE antibodies in serum from patients with allergic rhinitis.
Methods: Eighteen patients with allergic rhinitis received treatment with an intranasal glucocorticoid (beclomethasone dipropionate, 400 μg/day) or placebo for 5 weeks, starting from the beginning of the birch pollen season. Blood samples for anti-birch IgE evaluation were taken before treatment was initiated and at 2 and 5 weeks after the beginning of the study.
Results: The beclomethasone group (n = 9) had significantly lower symptom scores when compared with the placebo group (n = 9) (0.86 ± 0.26 vs 2.79 ± 0.76, p value = 0.01). Both the treatment group and the placebo group showed a trend of an increase in anti-birch IgE levels 2 weeks after the beginning of the treatment (from 33.1 ± 13.1 kU/L to 44.9 ± 20.9 kU/L in the beclomethasone group and from 53.2 ± 18.9 kU/L to 64.1 ± 22.1 kU/L in the placebo group). Treatment with beclomethasone returned anti-birch IgE levels to baseline by the end of the study, whereas in the placebo group the anti-birch IgE levels continued to increase (final values, 33.1 ± 11.9 kU/L vs 72.6 ± 23.2 kU/L, respectively). The change in IgE antibody levels in the placebo group was significantly higher than that in the beclomethasone group. No statistically significant changes in total IgE or soluble CD23 levels were detected.
Conclusion: We conclude that treatment with an intranasal glucocorticoid initiated at the beginning of the pollen season inhibits the induced increase in specific IgE. (J Allergy Clin Immunol 1997;100:601-5.)

Key words: Allergic rhinitis, intranasal glucocorticoids, anti-birch IgE

Abbreviation used
BDP: Beclomethasone dipropionate

The use of intranasal glucocorticoids, which can be administered locally without great risk of systemic adverse effects, has been the most effective pharmacologic approach in the management of allergic rhinitis.[1, 2] Their effect on late inflammatory response, including reduction of the influx of inflammatory cells and mediator release, has been thoroughly studied.[3-6] Also, there is accumulating evidence that repeated administration of topical glucocorticoids has some inhibitory effect on the early allergic response.[7, 8] However, the effect of glucocorticoids on the humoral response to seasonal exposure is less well documented. It is becoming increasingly important to evaluate both total and specific IgE responses after administration of glucocorticoids because several in vitro studies have shown that glucocorticoids enhance IL-4-induced total IgE production,[9-12] and there have been suggestions that this may also be the case in vivo.[13, 14] These findings would therefore imply that glucocorticoids promote allergy, which in theory would mean that the most efficacious treatment is detrimental regarding disease progress. We have designed a study to evaluate the effect of an intranasal glucocorticoid on specific and total IgE production in patients with allergic rhinitis during the pollen season, hypothesizing that despite these in vitro findings, in the clinical situation glucocorticoids reduce allergen-specific IgE antibody production without affecting total IgE levels as previously shown in the rat.[15]

The low-affinity IgE receptor ($Fc_{\epsilon}RII$) of B cells and monocytes appears to mediate a variety of biologic activities including cell adhesion, regulation of B-cell proliferation, and IgE synthesis.[16, 17] IL-4 is known to be the most potent inducer of $Fc_{\epsilon}RII$ (also known as CD23) expression on cells[18] and to play a pivotal role in the subsequent release of CD23 in a soluble form into body fluids.[19] To learn whether administration of topical glucocorticoids can have an effect on this axis, we decided to measure levels of soluble CD23 in sera.

In previously performed studies done on patients with allergic rhinitis sensitive to ragweed, intranasal steroids

From [a]the Lung Pharmacology Group, Department of Clinical Pharmacology and Department of Respiratory Medicine and Allergology, Göteborg University, Gothenburg; [b]Tartu University Lung Hospital, Tartu; and [c]the Department of Respiratory Medicine and Allergology, Göteborg University, Gothenburg.
Supported by the Vårdal Foundation, the Swedish Heart and Lung Foundation, Herman Kreftings Foundation Against Asthma-Allergy, and the Swedish Medical Research Council.
Received for publication Jan. 21, 1997; revised June 17, 1997; accepted for publication June 20, 1997.
Reprint requests: Teet Pullerits, MD, Lung Pharmacology Group, Guldhedsgatan 10A, S-413 46 Gothenburg, Sweden.
Copyright © 1997 by Mosby–Year Book, Inc.
0091-6749/97 $5.00 + 0 **1/1/84500**

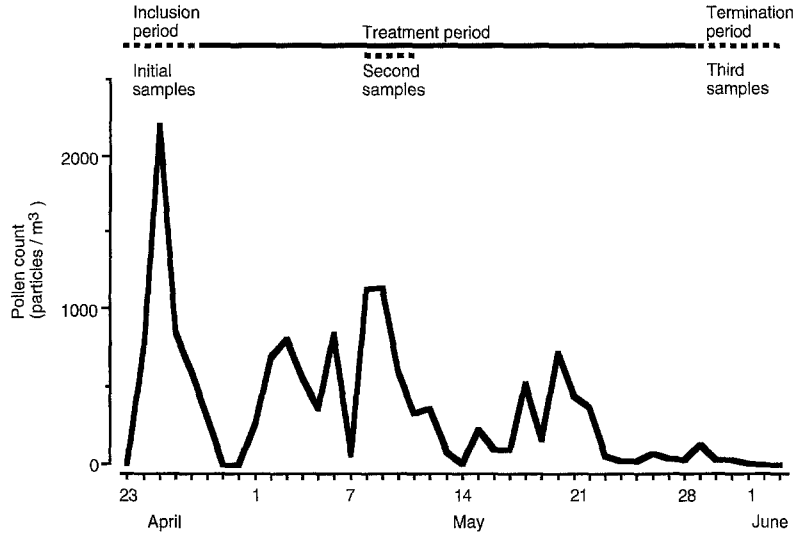

FIG. 1. Study design and birch pollen count in Tartu during the course of the study.

have shown either an inhibiting[20] or no[1] effect on the levels of specific IgE antibodies in serum. However, in these studies the treatment was started 1 week before anticipated ragweed exposure, which may reduce nasal inflammation and alter the amount of allergen penetration already at the beginning of the pollen season, thereby reducing the amount of presented antigen and B-cell switching to IgE production. We wished to start the glucocorticoid treatment concomitantly with the beginning of birch pollen season, which provides an opportunity to study the effect of steroids on already initiated IgE production. Also, in clinical practice patients often start treatment with intranasal steroids only after the symptoms of allergic rhinitis have already occurred.

METHODS

Patients

Twenty patients (7 men and 13 women), 18 to 49 years of age (mean, 31 years), with a history of symptoms of allergic rhinitis during birch pollen season confirmed by a positive response to a skin prick test with aqueous birch pollen extract (ALK, Hørsholm, Denmark) were recruited for the study. Patients were not included in the study if they had a history of marked systemic disease, asthma that required regular treatment, or symptoms of perennial rhinitis. In addition, patients were excluded if they had had acute infections or had used glucocorticoids in any form within 2 weeks before inclusion in the study.

Study design

During an inclusion visit in the first half of April, the health status of each patient was examined, and skin prick tests against birch pollen were performed. Patients were then randomized in a double-blind fashion to receive treatment with either beclomethasone dipropionate (BDP; Becotide Nasal, Glaxo) nasal spray (50 μg) administered twice in each nostril twice a day (400 μg/day) or a matching dose of placebo (produced by Apoteksbolaget, Göteborg, Sweden). The first blood samples were taken concomitantly with the beginning of the birch pollen season, and treatment was initiated after the first blood samples were taken. Two weeks later, during another peak of the birch pollen season, the second blood samples were taken. The final blood samples were taken 5 weeks after the beginning of the study. Patients were instructed to record their daily symptoms for sneezing, rhinorrhea, nasal itch, and blockage by using the following scoring system: 0 = symptom not present; 1 = symptom present, no discomfort; 2 = some discomfort; 3 = marked discomfort, no interference with activities; and 4 = interference with daily activities. Patients were allowed to use antihistamines as rescue medication. The use of antihistamines was recorded as 3 points on the symptom score scale, resulting in a maximum of 19 points per day.

The study was approved by the Ethical Review Committee of Clinical Research Studies of the University of Tartu, and all patients gave their written informed consent.

Assessment of anti-birch and total IgE levels and soluble CD23

Specific anti-birch and total IgE levels in serum were determined by using the CAP fluoroenzyme immunoassay method (Pharmacia & Upjohn, Uppsala, Sweden). Soluble CD23 quantitative determinations were done with a commercial ELISA kit (The Binding Site Ltd., Birmingham, U.K.). Briefly, undiluted serum samples were applied to microwell plates coated with mouse monoclonal antibody recognizing soluble CD23, followed by incubations with sheep anti-soluble CD23 and anti-sheep IgG conjugated on horseradish peroxidase. Bound conjugate was visualized by using 3,3′,5,5′-tetramethylbenzidine, and absorbance was measured at 450 nm.

Data analysis

Data are reported as means ± SEM. The primary variable is the change in birch pollen–specific IgE in serum (levels during and after the season from which baseline levels are subtracted). Secondary end points are total IgE, the serum levels of soluble CD23, and clinical symptoms. Comparisons between groups were performed with the Mann-Whitney U test. A p value less than 0.05 was considered to be significant.

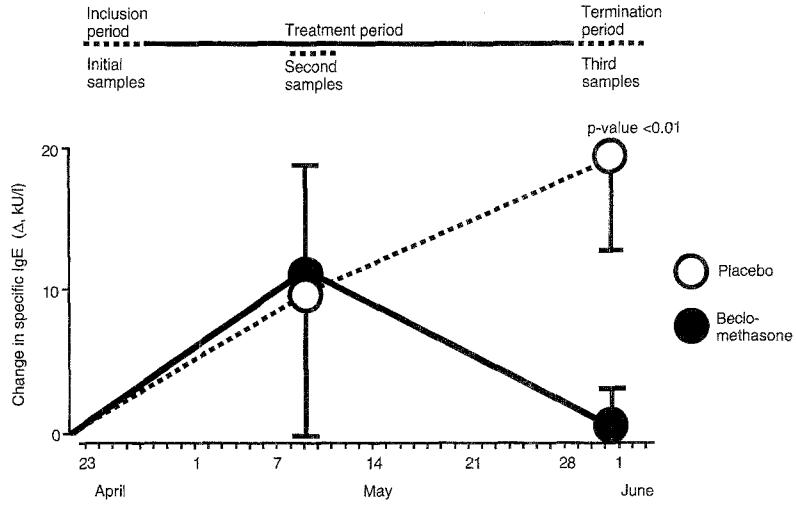

FIG. 2. Change in specific anti-birch IgE antibody levels in patients with allergic rhinitis treated for 5 weeks with intranasal beclomethasone or matching placebo. Data shown are means ± SEM of anti-birch IgE levels during and after the season from which baseline levels are subtracted.

RESULTS

Birch pollen levels in Tartu during the season of 1995 are presented in Fig. 1. The season was of average severity for this region.

All patients completed the study protocol. However, two patients were excluded from further evaluation before we opened the code and did statistical analysis. One patient from the treatment group was excluded because of a severe allergy-like reaction with itchy and watery eye symptoms and headache in relation to painting at the workplace. Another patient was excluded from the placebo group because of a strong suspicion of lack of compliance with treatment and reporting symptoms. Furthermore, when asked, the patient did not understand how to use the nasal spray device properly.

Patients treated with BDP had significantly fewer symptoms when compared with the placebo-treated control group. The average daily symptom score for the whole study period in the group treated with BDP was 0.86 ± 0.26 versus 2.79 ± 0.76 in the control group (p = 0.01). Symptoms in patients treated with BDP were significantly weaker compared with those in the control group during the second, third, and fourth weeks of treatment ($p < 0.01$) but not during the first and last weeks of treatment ($p = 0.12$ and $p = 0.11$, respectively).

The serum levels of birch pollen–specific IgE antibodies (Fig. 2) in the samples taken at the beginning of the study were similar in the two groups (33.1 ± 13.1 kU/L in the BDP treatment group vs 53.2 ± 18.9 kU/L in the placebo group, p = 0.4). In the middle of the birch pollen season, both study groups showed a tendency towards an increase of anti-birch IgE levels (44.9 ± 20.9 kU/L vs 64.1 ± 22.1 kU/L, respectively), and the change in antibody levels between the two groups was not significant (Δ change between groups, p = 0.5). At the end of the birch pollen season, when the third blood samples were taken, six of nine patients in the group treated with BDP and all nine patients in the placebo group showed a rise in specific IgE levels from the beginning of the pollen season. The mean anti-birch IgE level at this time point had returned to baseline in the group treated with BDP (33.1 ± 11.9 kU/L), whereas the levels continued to increase in the placebo group (72.6 ± 23.2 kU/L). The change in anti-birch IgE levels from the initial samples to the final samples was statistically significant between the two groups (p = 0.004).

TABLE I. Total IgE and soluble CD23 levels in patients with allergic rhinitis treated for 5 weeks with intranasal beclomethasone or matching placebo

	Preseason level	Midseason level	Posteason level
Total IgE (kU/L)			
BDP-treated group	249.4 ± 115.5	212.1 ± 95.2	232.1 ± 103.4
Placebo group	465 ± 163.2	372.2 ± 106	399.7 ± 113.6
Soluble CD23 (μg/L)			
BDP-treated group	2.32 ± 0.76	2.65 ± 0.62	2.72 ± 0.52
Placebo group	1.45 ± 0.4	1.62 ± 0.44	2.23 ± 0.61

The total IgE levels were quite stable during the pollen season in both groups (Table I).The p value for the change between groups was 0.51 for 2 weeks and 0.79 for 5 weeks of treatment.

The levels of soluble CD23 did not change significantly over the pollen season and were not significantly affected by beclomethasone (Table I).

DISCUSSION

In this study we have shown that intranasal treatment with the glucocorticoid beclomethasone, started con-

comitantly with the beginning of birch pollen season, inhibits the increase of anti-birch IgE in the serum of patients with allergic rhinitis. The inhibiting effect of beclomethasone became evident after 2 weeks of treatment, whereas up to 2 weeks after the beginning of treatment there were no differences in anti-birch IgE levels between treated and untreated patients. Neither the levels of total IgE nor soluble CD23, a low-affinity receptor for IgE, were affected during treatment.

The increase of specific IgE antibody levels during the pollen season in patients with allergy is well documented.[1, 21-24] In this study the anti-birch IgE levels in untreated patients increased throughout the season and reached the highest values by the end of the study, although the birch pollen levels peaked at the beginning of the study. In the patients treated with BDP, there was a tendency towards an increase in anti-birch IgE levels 2 weeks after initiation of the study, but with treatment the levels returned to baseline values by the end of the trial. These findings are not in agreement with in vitro studies suggesting that glucocorticoids in the presence of IL-4 enhance the generation of IgE.[9-12] However, because glucocorticoids are the most effective treatment for allergic diseases to date, this discrepancy between in vivo and in vitro findings suggests that in vitro experiments do not take into account complex cellular interactions that occur over time and therefore do not always reflect the reality in the body.

The mechanism by which glucocorticoids achieve their attenuating effect on allergen-specific IgE production in vivo needs to be further evaluated but could hardly be explained by a single determinant. One possibility is that glucocorticoids, by reducing local inflammation, also decrease the amount of allergen penetration through the mucosa and the subsequent presentation to T cells. Indeed, in this study the decrease in allergic symptoms preceded the attenuation of IgE synthesis. Furthermore, the number of antigen-presenting Langerhans cells in the nasal mucosa is known to be increased in allergic individuals after exposure to allergen,[25, 26] and this increase is reversed by topical glucocorticoids both in perennial[27] and seasonal allergic rhinitis (Rak, unpublished data, 1996).

It is doubtful whether topically administered glucocorticoids can reduce the amount of circulating IgE antibodies just by decreasing local IgE production in the nose. There have been suggestions that the number of $CD23^+$ B cells in the nasal mucosa of allergic patients decreases during provocation, indicating switch into a memory B-cell phenotype with loss of CD23 expression, which could represent a local source for IgE synthesis.[28] However, recent immunohistochemical studies of nasal biopsy specimens from patients with allergic rhinitis have questioned the presence of IgE-producing B cells in the nasal mucosa, suggesting that IgE may be produced in local lymphoid tissue rather than in the nasal mucosa.[29]

To evaluate the possibility that intranasal glucocorticoids can reduce IgE antibody production systemically, we measured the levels of soluble CD23, a cleavage product of low-affinity receptor for IgE. Upregulation of CD23 expression on the cells and the subsequent release of CD23 in a soluble form from B cells and monocytes have been reported to be induced by IL-4.[17, 18] IL-4, the release of which has been shown to be increased in pollen-sensitized individuals during pollen season,[30] is a key cytokine in IgE class switch.[31-33] Thus measurement of soluble CD23 could serve as an indirect indication that altered IL-4 levels are involved in the mechanism of reduced IgE antibody production. The attenuating effect of glucocorticoids on IL-4 production has been shown in vitro[34, 35] and on IL-4 tissue expression in vivo in patients with allergic rhinitis.[36] Also, glucocorticoids have been reported to inhibit IL-4-induced CD23 expression on B cells and monocytes.[37] However, in our study the levels of soluble CD23 showed only a weak and nonsignificant tendency towards increase over the whole pollen season, and levels were not affected by treatment with glucocorticoids. This implies that systemic IL-4 levels are not altered by topical glucocorticoid treatment or that measurement of soluble CD23 levels may not be sensitive enough to reveal these alterations.

In contrast to Zieg et al.,[14] we could not detect any increase in total IgE levels after treatment with glucocorticoids but rather a tendency towards a decrease in both the treated and the nontreated groups. This finding provides further evidence against concerns about the proallergic effects of glucocorticoids and may imply that total IgE levels are not good tools with which to evaluate changes in allergic status. It may also imply that specific and total IgE are regulated by different mechanisms. Thus we have found in studies with sensitized rats that systemic administration of glucocorticoids, both during and after sensitization, attenuated the development of specific IgE antibodies without affecting total IgE levels.[15] In vitro it has been shown that addition of IL-4 can induce significant induction of total IgE from peripheral blood mononuclear cells from patients allergic to pollen, whereas allergen-specific IgE production was not affected.[38] This finding indicates that the peripheral blood of allergic individuals contains long-lived allergen-specific B cells, which have already switched to IgE production and are no longer sensitive to IL-4 treatment. Thus the possibility that the attenuating effect of BDP on specific IgE production in our study was mediated through decreasing systemic IL-4 levels becomes even more dubious.

Our findings strongly favor the use of intranasal glucocorticoids in the treatment of allergic rhinitis. Although statistically significant improvement in symptom score was achieved only from the second week of treatment, it is well in line with previous findings of a delayed onset of action of intranasal glucocorticoids.[39, 40] The more striking finding, that administration of intranasal glucocorticoids to patients with allergic rhinitis from the beginning of pollen season can inhibit the increase in circulating IgE antibody levels, raises the possibility that topical glucocorticoids are able to alter the natural history of allergic rhinitis.

We thank Glaxo Sweden AB for providing us with beclomethasone dipropionate.

REFERENCES

1. Welsh PW, Stricker WE, Chu CP, Naessens JM, Reese ME, Reed CE, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc 1987;62:125-34.
2. Juniper EF, Kline PA, Hargreave FE, Dolovich J. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989;83:627-33.
3. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. J Allergy Clin Immunol 1988;81:580-9.
4. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge. Effect of systemic steroid pretreatment. Am Rev Respir Dis 1988;138:406-12.
5. Meltzer EO, Orgel HA, Bronsky EA, Furukauer CT, Grossman J, La Force CF, et al. A dose-ranging study of fluticasone propionate aqueous nasal spray for seasonal allergic rhinitis assessed by symptoms, rhinomanometry, and nasal cytology. J Allergy Clin Immunol 1990;86:221-30.
6. Klementsson H, Svensson C, Andersson M, Venge P, Pipkorn U, Persson CG. Eosinophils, secretory responsiveness and glucocorticoid-induced effects on the nasal mucosa during a weak pollen season. Clin Exp Allergy 1991;21:705-10.
7. Pipkorn U. Budesonide and nasal allergen challenge testing in man. Allergy 1982;37:129-34.
8. Bisgaard H, Grønborg H, Mygind N, Dahl R, Lindqvist N, Venge P. Allergen-induced increase of eosinophil cationic protein in nasal lavage fluid: effect of the glucocorticoid budesonide. J Allergy Clin Immunol 1990;85:891-5.
9. Sarfati M, Luo H, Delespesse G. IgE synthesis by chronic lymphocytic leukemia cells. J Exp Med 1989;170:1775-80.
10. Jabara HH, Ahern DJ, Vercelli D, Geha RS. Hydrocortisone and IL-4 induce IgE isotype switching in human B cells. J Immunol 1991;147:1557-60.
11. Wu CY, Sarfati M, Heusser C, Fournier S, Rubio-Trujillo M, Deleman R, et al. Glucocorticoids increase the synthesis of immunoglobulin E by interleukin-4-stimulated human lymphocytes. J Clin Invest 1991;87:870-7.
12. Nüsslein HG, Weber G, Kalden JR. Synthetic glucocorticoids potentiate IgE synthesis. Influence of steroid and nonsteroid hormones on human in vitro IgE secretion. Allergy 1994;49:365-70.
13. Posey WC, Nelson HS, Branch B, Pearlman DS. The effects of acute corticosteroid therapy for asthma on serum immunoglobulin levels. J Allergy Clin Immunol 1978;62:340-8.
14. Zieg G, Lack G, Harbeck RJ, Gelfand EW, Leung DYM. In vivo effects of glucocorticoids on IgE production. J Allergy Clin Immunol 1994;94:222-30.
15. Pullerits T, Dahlgren U, Skoogh BE, Lötvall J. Development of antigen-specific IgE after sensitisation with trimellitic anhydride in rats is attenuated by glucocorticoids and cyclosporin A. Int Arch Allergy Immunol 1997;112:279-86.
16. Bonnefoy JY, Aubry JP, Gauchat JF, Graber P, Life P, Flores-Romo L, et al. Receptors for IgE. Curr Opin Immunol 1993;5:944-9.
17. Aubry JP, Pochon S, Graber P, Jansen KU, Bonnefoy JY. CD21 is a ligand for CD23 and regulates IgE production. Nature 1992;358:505-7.
18. Vercelli D, Jabara HH, Lee BW, Woodland N, Geha RS, Leung DY. Human recombinant interleukin 4 induces $Fc_{\epsilon}R2$/CD23 on normal human monocytes. J Exp Med 1988;167:1406-16.
19. Bonnefoy JY, Defrance T, Peronne C, Menetrier C, Rousset F, Pène J, et al. Human recombinant interleukin 4 induces normal B cells to produce soluble CD23/IgE-binding factor analogous to that spontaneously released by lymphoblastoid B cell lines. Eur J Immunol 1988;18:117-22.
20. Naclerio RM, Adkinson NF Jr, Creticos PS, Baroody FM, Hamilton RG, Norman PS. Intranasal steroids inhibit seasonal increases in ragweed-specific immunoglobulin E antibodies. J Allergy Clin Immunol 1993;92:717-21.
21. Berg T, Johansson SG. In vitro diagnosis of atopic allergy. IV. Seasonal variations of IgE antibodies in children allergic to pollens. Int Arch Allergy Appl Immunol 1971;41:452-62.
22. Deuschl H. Immunoglobulins in nasal secretion with special reference to IgE. II. Seasonal studies of Timothy-specific IgE-antibody in patients with allergic rhinitis. Int Arch Allergy Appl Immunol 1976;52:376-83.
23. Gleich GJ, Jacob GL, Yunginger JW, Henderson LL. Measurement of the absolute levels of IgE antibodies in patients with ragweed hay fever. J Allergy Clin Immunol 1977;60:188-98.
24. Crimi E, Voltolini S, Gianiorio P, Orengo G, Troise C, Brusaco V, et al. Effect of seasonal exposure to pollen on specific bronchial sensitivity in allergic patients. J Allergy Clin Immunol 1990;85:1014-9.
25. Fokkens WJ, Vroom TM, Rijntjes E, Mulder PG. Fluctuation of the number of CD-1(T6)-positive dendritic cells, presumably Langerhans cells, in the nasal mucosa of patients with an isolated grass-pollen allergy before, during, and after the grass-pollen season. J Allergy Clin Immunol 1989;84:39-43.
26. Fokkens WJ, Broekhuis-Fluitsma DM, Rijntjes E, Vroom TM, Hoefsmit EC. Langerhans cells in nasal mucosa of patients with grass pollen allergy. Immunobiology 1991;182:135-42.
27. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. Effect of 3 months' nasal steroid therapy on nasal T cells and Langerhans cells in patients suffering from allergic rhinitis. Allergy 1995;50:204-9.
28. Davidsson A, Karlsson MG, Hellquist HB. Allergen-induced changes of B-cell phenotypes in patients with allergic rhinitis. Rhinology 1994;32:184-90.
29. Igarashi Y, Goldrich MS, Kaliner MA, Irani AM, Schwartz LB, White MV. Quantitation of inflammatory cells in the nasal mucosa of patients with allergic rhinitis and normal subjects. J Allergy Clin Immunol 1995;95:716-25.
30. Lagier B, Pons N, Rivier A, Chanal I, Chanez P, Bousquet J, et al. Seasonal variations of interleukin-4 and interferon-γ release by peripheral blood mononuclear cells from atopic subjects stimulated by polyclonal activators. J Allergy Clin Immunol 1995;96:932-40.
31. Coffman RL, Ohara J, Bond MW, Carty J, Zlotnik A, Paul WE. B cell stimulatory factor-1 enhances the IgE response of lipopolysaccharide-activated. J Immunol 1986;136:4538-41.
32. Del Prete G, Maggi E, Parronchi P, Chrétien I, Tiri A, Macchia D, et al. IL-4 is an essential factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. J Immunol 1988;140:4193-8.
33. Pène J, Rousset F, Brière F, Chrétien I, Bonnefoy JY, Spits H, et al. IgE production by normal human lymphocytes is induced by interleukin 4 and suppressed by interferons-γ and α and prostaglandin E_2. Proc Natl Acad Sci U S A 1988;85:6880-4.
34. Wu CY, Fargeas C, Nakajima T, Delespesse G. Glucocorticoids suppress the production of interleukin 4 by human lymphocytes. Eur J Immunol 1991;21:2645-7.
35. Byron KA, Varigos G, Wootton A. Hydrocortisone inhibition of human interleukin-4. Immunology 1992;77:624-6.
36. Bradding P, Feather IH, Wilson S, Holgate ST, Howarth PH. Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. Am J Respir Crit Care Med 1995;151:1900-6.
37. Delespesse G, Suter U, Mossalayi D, Bettler B, Sarfati M, Hoffstetter H, et al. Expression, structure and function of the CD23 antigen. Adv Immunol 1991;49:149-91.
38. Dolecek C, Steinberger P, Susani M, Kraft D, Valenta R, Boltz-Nitulescu G. Effects of IL-4 and IL-13 on total and allergen specific IgE production by cultured PBMC from allergic patients determined with recombinant pollen allergens. Clin Exp Allergy 1995;25:879-89.
39. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. Br Med J 1973;890:464-6.
40. Small P. Beclomethasone dipropionate nasal aerosol in adult patients with ragweed seasonal rhinitis. Ann Allergy 1982;49:20-2.