

Mechanisms of intranasal steroids in the management of upper respiratory allergic diseases

Harold S. Nelson, MD *Denver, Colo*

Intranasal steroids have proved to be the most effective class of drugs in reducing the symptoms of allergic rhinitis. This clinical response reflects the broad anti-inflammatory activity that has been demonstrated for corticosteroids. Single doses of topical corticosteroids administered before nasal allergen challenge block the late-phase reaction, whereas repeated dosing with intranasal steroids blocks both the early and the late response, as well as the priming phenomenon. Nasal inflammation is accomplished through a number of effector cells and mechanisms, which in turn are produced by director cells through the release of cytokines and chemokines. The anti-inflammatory action of corticosteroids is largely effected through blocking the synthesis and release of these cytokines/chemokines. (*J Allergy Clin Immunol* 1999;104:S138-43)

Key words: *Intranasal steroids, allergic rhinitis, mechanisms of action, cytokines, chemokines*

The clinical features of allergic rhinitis result from a series of inflammatory events that are induced after allergen exposure. Intranasal steroids have proved to be the most effective class of drugs in reducing the symptoms of allergic rhinitis. This clinical response reflects the broad anti-inflammatory activity that has been demonstrated for corticosteroids. Investigations in patients with allergic rhinitis have demonstrated that single doses of topical corticosteroids administered before nasal allergen challenge block the late-phase reaction, whereas repeated dosing with intranasal steroids blocks both the early and the late response^{1,2} as well as the subsequent period of increased reactivity to allergen,² histamine,³ and methacholine⁴ challenge known as priming. These findings suggest that the corticosteroids are interrupting several pathways of the nasal reaction to allergen. Studies of the actions of corticosteroids in patients undergoing nasal allergen challenge or natural allergen exposure confirm the widespread actions of the corticosteroids not only on the effector mechanisms of the allergic response in the nose but also on the cells that are the directors of this response.

Abbreviations used

ECP:	Eosinophil cationic protein
ICAM-1:	Intercellular adhesion molecule-1
mRNA:	Messenger RNA
SCF:	Stem cell factor
VCAM-1:	Vascular cell adhesion molecule-1

EFFECTOR MECHANISMS Eosinophils

The most prominent effector cell in allergic rhinitis and in the late-phase reaction of the nose to allergen challenge is the eosinophil.⁵ The number of eosinophils, particularly activated eosinophils (EG2⁺), increases substantially in the epithelium and lamina propria during the allergic response.⁶ Intranasal steroids reduce eosinophil numbers by inhibiting eosinophil recruitment and migration into the nasal airways and promoting eosinophil apoptosis.^{7,8}

Clinical studies have confirmed the ability of intranasal steroids to reduce total¹ and activated⁹ eosinophil numbers and eosinophil cationic protein (ECP)¹ in nasal lavage fluid in the late phase of the reaction to allergen challenge and in both seasonal¹⁰ and perennial⁷ rhinitis. A study by Klementsson et al¹⁰ compared placebo and budesonide (200 mg given once daily) in 22 patients with allergic rhinitis caused by natural birch pollen exposure. During the birch pollen season patients in the placebo group had increases in the proportion of total and activated eosinophils, increased levels of ECP in nasal lavage fluid, and increased nasal responsiveness to methacholine (Fig 1). Intranasal budesonide significantly reduced the proportion of total and activated eosinophils and blocked the increased nasal responsiveness.

Corticosteroids have no direct effect on eosinophil chemotaxis or degranulation. Therefore reduction in eosinophil numbers probably represents a combination of an inhibition of eosinophil influx as a result of corticosteroid-induced inhibition of cytokine and chemokine production^{7,9} and increased apoptosis, reflecting a direct effect on the eosinophil itself.⁸

The cytokines and chemokines involved in migration and activation of eosinophils include (1) IL-4 and IL-13, which up-regulate vascular cell adhesion molecule-1 (VCAM-1) on the vascular endothelium (VCAM-1 interacts with the adhesion molecule very-late antigen-4 on the surface of the eosinophil promoting margination), (2) IL-1 and TNF- α , which induce intercellular adhesion

From the Department of Medicine, National Jewish Medical and Research Center, and the University of Colorado Health Sciences Center, Denver, Colo.

Supported by an unrestricted educational grant from Schering/Key Pharmaceuticals, Schering Corporation.

Reprint requests: Harold S. Nelson, MD, National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206.

Copyright © 1999 by Mosby, Inc.

0091-6749/99 \$8.00 + 0 1/0/101679

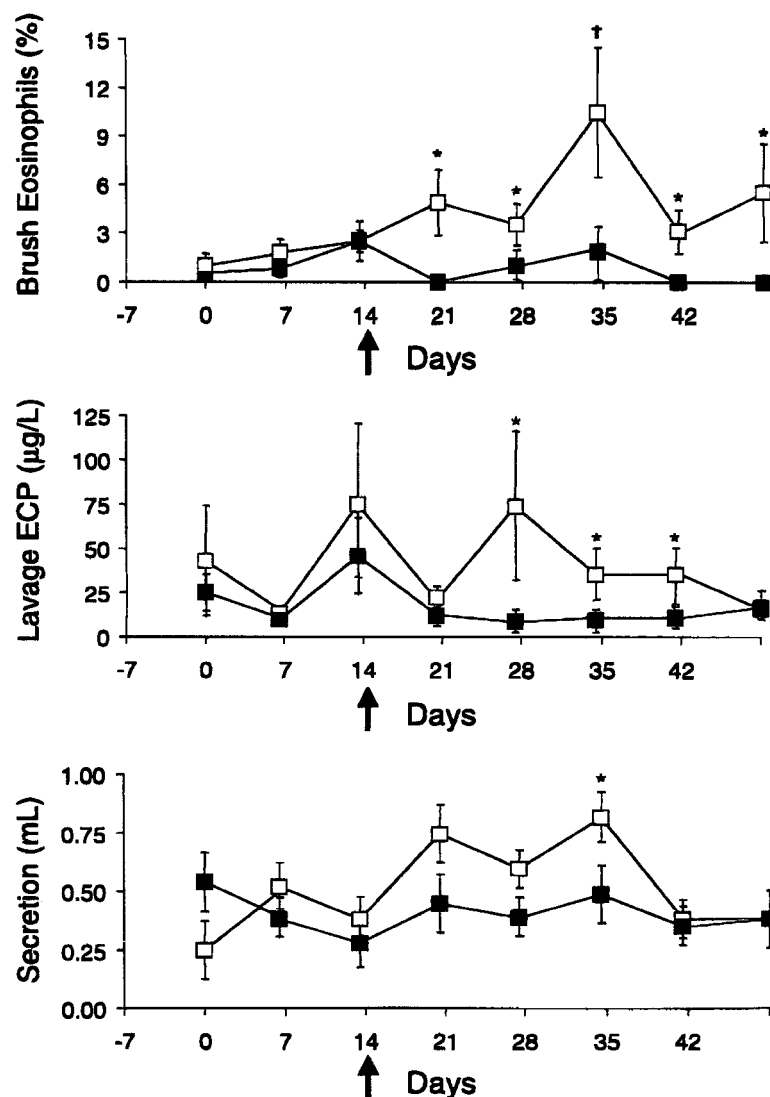


FIG 1. Intranasal steroid treatment during birch pollen season significantly reduced eosinophil influx (**A**) and activation (**B**) and reduced nasal hyperresponsiveness (**C**) compared with placebo. **A**, Proportion of eosinophils harvested from nasal mucosa before and during pollen season. Open boxes, Mean values $\pm$ SEM for placebo group; solid boxes, values obtained during glucocorticoid treatment. Asterisk, $P < .005$; dagger, $P < .001$ for comparisons of active treatment versus placebo. **B**, Levels of ECP in nasal lavage fluid before and during pollen season. Open boxes, Mean values $\pm$ SEM for placebo group; solid boxes, values obtained during glucocorticoid treatment. Arrow, Start of treatment. Asterisk, $P < .05$ for comparisons of active treatment versus placebo. **C**, Methacholine-induced secretion before and during pollen season. Open boxes, Mean values $\pm$ SEM for placebo group; solid boxes, values obtained during glucocorticoid treatment. Asterisk, $P < .05$ for comparisons of active treatment versus placebo. (Adapted with permission from Klementsson H, Svensson C, Anderson M, Venge P, Pipkorn U, Persson CGA. Eosinophils, secretory responsiveness and glucocorticoid-induced effects on the nasal mucosa during a weak pollen season. *Clin Exp Allergy* 1991;21:705-10.)

molecule-1 (ICAM-1) on the vascular endothelium (a contributor to eosinophil migration), (3) the chemokines RANTES and macrophage inflammatory protein-1 α , which are chemotactic for eosinophils, and (4) IL-3, IL-5, and GM-CSF, which promote eosinophil activation and survival.

Basophils and mast cells

An influx of basophils characterizes the late-phase reaction to nasal allergen challenge,¹ whereas the less intense and more prolonged allergen exposure with seasonal and perennial rhinitis results in an increase in

TABLE I. Cytokine/chemokine expression in nasal inflammation and effect of intranasal corticosteroids

Cytokine	Action	Respiratory cell source	References	
			↑ in AR	↓ by CS
IL-1b	Activates B and T lymphocytes	Epithelial cells ¹³	16	16
IL-4	Up-regulates ICAM-1	Macrophages		
	Up-regulates VCAM-1	CD4 ⁺ T lymphocyte ²⁶	5, 23	17-19
	IgE isotype switch in B cells	> Mast cells ^{5,18}	17-19	
	Activates T _H 2 lymphocytes			
IL-5	Up-regulates IgE receptors			
	Eosinophil activation and survival	T lymphocytes ²⁶	5, 23	18 (No 9)
		Mast cells ^{5,20}	17, 18	20 (No 9)
IL-6	Promotes IgE synthesis	Eosinophils ⁵		
	Converts B cells to plasma cells	Mast cells ²⁰	20	20 (No 9)
	Enhances T-cell activation			
IL-13	Promotes VCAM-1	T lymphocytes	17, 23	17
IL-16	IgE isotype switch	> Mast cells ¹⁷		
	Chemoattractant for CD4 ⁺ T lymphocytes	Epithelial cells ²³	23	23
TNF-α	Up-regulates ICAM-1 and VCAM-1	Subepithelial cells ²³		
		Mast cells ⁵	5	
		T lymphocytes		
GM-CSF	Eosinophil attraction, activation, and survival	Epithelial cells ¹³		
		Mast cells	5, 18	16, 25
		T lymphocytes ⁵	16	
		Epithelial cells ¹⁶		
SCF	Mast cell growth and survival	Epithelial cells ²⁴	24	24
Chemokine				
RANTES	Eosinophil chemotaxis		16	16
	Histamine-releasing factor			
IL-8	Chemotaxis for mast cells	Epithelial cells ⁵	16	16
MP-1a	Chemotaxis		16	16
	Histamine-releasing factor			

AR, Allergic rhinitis; CS, corticosteroid; MIP-α, macrophage inflammatory protein 1α.

mucosal (tryptase only) mast cells⁵ and perhaps basophils¹ in the nasal mucosa. Corticosteroids have no effect on mast cell mediator release, but they do inhibit mediator release from basophils. Topical corticosteroids markedly reduce the influx of basophils during the late-phase response to nasal allergen challenge¹ and prevent the increase in mucosal mast cells with chronic allergic stimulation, both seasonal⁷ and perennial.^{7,11} Topical corticosteroids do not reduce baseline numbers of mucosal mast cells but do decrease levels of histamine in the mucosa.¹²

Plasma exudation

Entry of plasma into the nasal lumen has been demonstrated after histamine and allergen challenge and in seasonal allergic rhinitis.¹³ In patients with seasonal allergic rhinitis intranasal steroids have been shown to reduce exudation as measured by nasal lavage fluid levels of bradykinin and fibrinogen.¹⁴ This could result from a direct effect on the vascular endothelial cells, be the result of decreased release of permeability factors, or both.¹⁴

Adhesion molecule expression

Expression of the endothelial adhesion molecules ICAM-1 (induced by IL-1 and TNF-α) and VCAM-1

(induced by IL-4 and IL-13) has been reported to be increased in patients with both seasonal and perennial allergic rhinitis.¹⁵ Reduction in the expression of these adhesion molecules by corticosteroids would be anticipated because levels of the inducing cytokines are reduced.¹⁶⁻²⁰

Nasal hyperresponsiveness to allergen, histamine, and methacholine

Nonspecific reactivity of the nose to histamine³ and methacholine⁴ is typically increased in perennial allergic rhinitis. Intranasal steroids reduce this hyperresponsiveness and also block the increase in sensitivity to allergen that follows allergen challenge, the so-called priming effect.²

Specific IgE response

Circulating levels of allergen-specific IgE increase during seasonal pollen exposure. This increase has been shown to be blocked by treatment with intranasal steroids in seasonal allergic rhinitis caused by birch²¹ and ragweed²² pollen. The mechanism for this reduction in specific IgE antibody could be decreased allergen penetration to T cells, reduction in antigen-presenting Langerhans' cells, or a decrease in the release of IL-4, although the last mechanism is less likely because IL-4 has no effect on committed B cells.

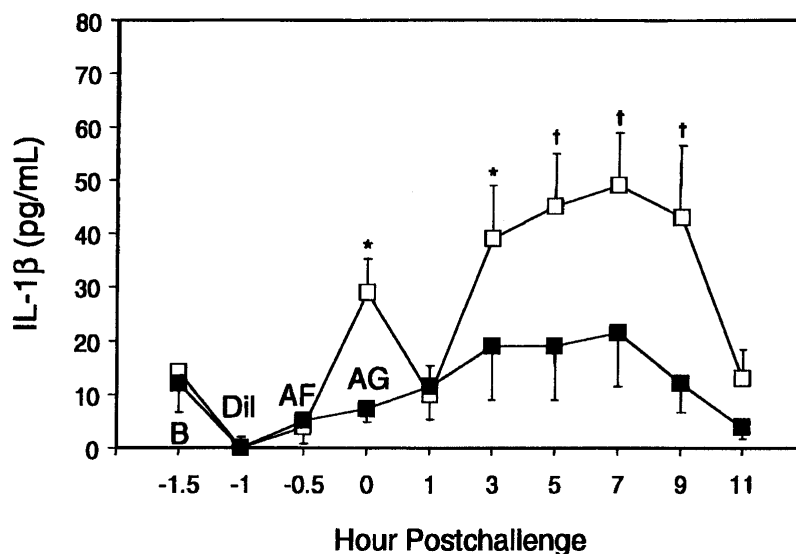


FIG 2. Intranasal steroid treatment during allergen challenge significantly reduced levels of IL-1β during early and late phases of allergic response compared with placebo. Figure shows hourly levels of IL-1β detected by ELISA in nasal secretions of allergic subjects after antigen challenge. Open boxes, Mean values ± SEM for the placebo group; solid boxes, values obtained for beclomethasone dipropionate treatment group. B, Baseline; Dil, diluent (saline solution); AF, Afrin⁷ nasal spray solution; AG, antigen. Asterisk, $P < 0.05$; dagger, $P < .01$. (Adapted with permission from Sim TC, Reece LM, Hilsmeier KA, Grant A, Alam R. Secretion of chemokines and other cytokines in allergen-induced nasal responses: inhibition by topical steroid treatment. *Am J Respir Crit Care Med* 1995;152:927-33. Official journal of the American Thoracic Society. © 1995 American Lung Association.)

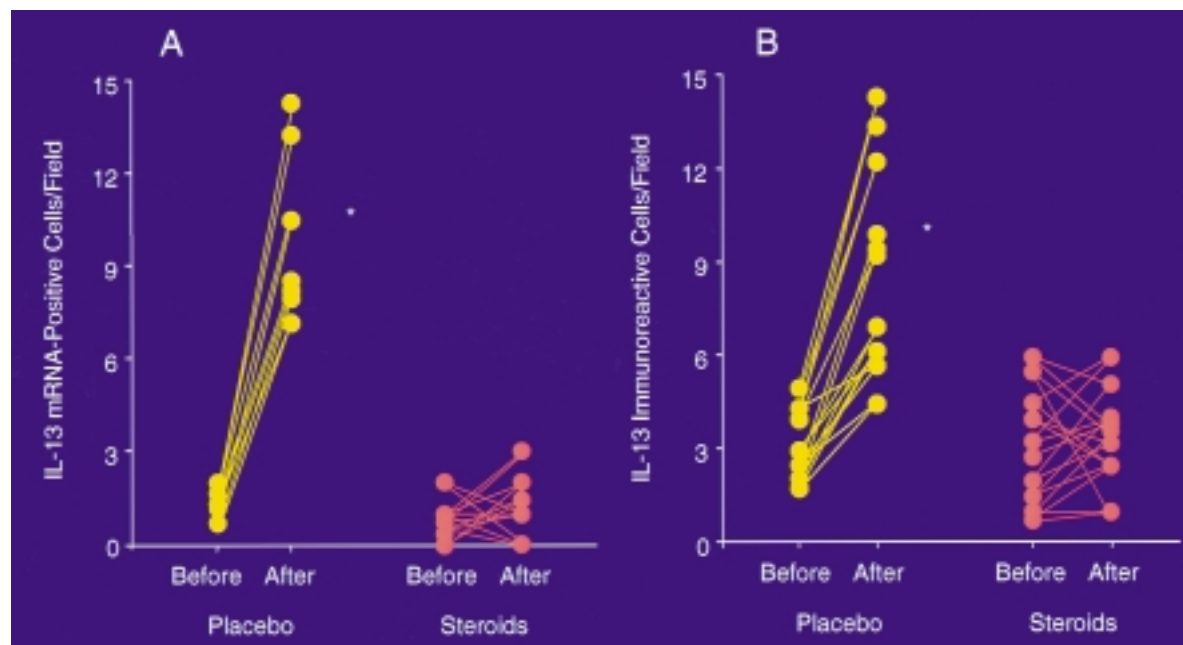


FIG 3. Intranasal steroid treatment significantly inhibited increases in IL-13 mRNA-positive cells (A) and IL-13 immunoreactive cells (B) in patients with allergic rhinitis challenged with allergen. Nasal biopsy specimens were taken at baseline (before) and 24 hours after allergen challenge (after). Results are expressed as number of positive cells per field. Statistical analyses were done with paired t test. $P < .001$. (Adapted with permission from Ghaffar O, Laberge S, Jacobson MR, et al. mRNA and immunoreactivity in allergen-induced rhinitis: comparison with IL-4 expression and modulation by topical glucocorticoid therapy. *Am J Respir Cell Mol Biol* 1997;17:17-24. Official journal of The American Thoracic Society. © 1997 American Lung Association.)

DIRECTOR MECHANISMS

The director mechanisms are the forces behind the effector mechanisms. Important components of the director mechanisms include epithelial cells, antigen-presenting cells, and T lymphocytes. In addition, 2 major effector cells, eosinophils and mast cells, contribute as director cells as well through their release of cytokines (Table I).

Epithelial cells

Epithelial cells are active participants in the inflammatory response. These cells release a variety of chemotactic and proinflammatory cytokines, including IL-1, IL-8, GM-CSF, TNF- α ,¹³ IL-16,²³ and stem cell factor (SCF).²⁴ There is substantial evidence that intranasal steroids inhibit the expression or release of many of these cytokines (Table I).^{5,13,16,17-20,23-26} Corticosteroids may decrease eosinophil survival by abrogating the promoting effect on eosinophil survival by epithelial cells, in part by corticosteroid modulation of GM-CSF release.²⁵

SCF, a major chemoattractant and growth and differentiation factor for mast cells, is produced by epithelial cells, endothelial cells, and fibroblasts. Significantly increased messenger RNA (mRNA) for SCF was found in epithelial cells from patients with allergic rhinitis compared with normal controls.²⁴ Corticosteroid treatment reduced the number of cells producing SCF *in vivo* and *in vitro*. Mast cells are found to be increased in the nasal epithelium of patients with allergic rhinitis. Increased epithelial cell SCF production may be responsible for this increase. Some of the effect of glucocorticosteroids in allergic rhinitis may be through inhibition of growth, differentiation, or chemotaxis of mast cells.

Antigen-presenting cells

Antigen-presenting Langerhans' cells, characterized by the surface antigens CD1a and HLA-DR, ingest allergens in the nasal mucosa and then migrate to the regional lymph nodes, where they stimulate T lymphocytes. The number of Langerhans' cells in the nasal mucosa and lamina propria increases after repeated allergen challenges and during the pollen season.¹³ Treatment with topical steroids markedly reduces the number of detectable Langerhans' cells.²⁷ Whether the number of cells or only their surface markers (CD1a) are reduced is uncertain.

Lymphocytes

T lymphocytes are thought to be the principal cells that orchestrate the immune inflammatory response in the nose.⁵ The number of lymphocytes bearing the CD4⁺ and CD25⁺ (IL-2R) surface antigens has been found to be increased after nasal allergen challenge²⁸ and in patients with seasonal and perennial allergic rhinitis.²⁹

Study results are conflicting regarding the effect of intranasal steroids on the number of T lymphocytes. Intranasal steroids were found not to significantly reduce the number of T cells or their activation (IL-2R⁺) in patients with perennial allergic rhinitis.²⁷ However, 6

weeks of treatment with topical corticosteroids, when followed by nasal allergen challenge, was reported to reduce numbers of T lymphocytes, both CD4⁺ and CD8⁺, to a greater extent in the surface epithelium than in the lamina propria,²³ and corticosteroid treatment was reported to decrease both CD4⁺ and CD8⁺ T lymphocytes in nasal polyps.³⁰ The effect of intranasal steroids on lymphocytes may depend on the intensity of the allergen stimulus and the dose and duration of the therapy.⁶

After nasal allergen challenge, an increase was found in the number of activated T cells (CD25⁺) and CD4⁺ T cells expressing mRNA for IL-4 and IL-5.²⁸ IL-4 is thought to be important in recruiting eosinophils through up-regulation of VCAM-1, in IgE synthesis through inducing isotype switching in B cells, in up-regulating high- and low-affinity IgE receptors, and in activating T_H2-type T lymphocytes. Topical corticosteroids have been shown to attenuate IL-4^{17,18,20} but not IL-5^{17,20} or IL-6²⁰ mRNA expression. With seasonal exposure, there was an increase in the B lymphocytes targeted for isotype switching to IgE production.¹⁹ This was blocked by topical corticosteroids.

The data suggest that an important role of corticosteroids is to block the production and secretion of cytokines by T_H2 CD4⁺ T lymphocytes, which control recruitment and activation of eosinophils, mast cells, and basophils and IgE production.

Cytokines

Studies after nasal allergen challenge or natural exposure have shown increased release of or expression of mRNA for many cytokines and chemokines, which may have relevance in the allergic inflammatory response in the nose (Table I). In most of these studies blocking expression of these cytokines and chemokines by preadministration of intranasal steroids has been demonstrated (Fig 3).

CONCLUSION

Intranasal steroids reduce the influx of inflammatory cells into the nasal mucosa in response to allergic stimuli. This reduces the release of inflammatory mediators and the development of nasal hyperresponsiveness. The inhibition of allergic inflammation results from the action of corticosteroids in blocking the synthesis and release of cytokines and chemokines from T lymphocytes, epithelial cells, eosinophils, and mast cells. Although attenuation of the allergic inflammatory reaction can be demonstrated after single doses of topical corticosteroids, their full benefit is achieved only after regular use over days or weeks.

REFERENCES

1. 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.
2. Andersson M, Andersson P, Pipkorn U. Topical glucocorticosteroids and allergen-induced increase in nasal reactivity: relationship between treatment time and inhibitory effect. *J Allergy Clin Immunol* 1988;82:1019-26.

3. Small P, Black M, Frenkiel S. Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. *J Allergy Clin Immunol* 1982;70:178-82.
4. Malm L, Wihl JA, Lamm CJ, Lindqvist N. Reduction of methacholine-induced nasal secretion by treatment with a new topical steroid in perennial non-allergic rhinitis. *Allergy* 1981;36:209-14.
5. Howarth PH. The cellular basis for allergic rhinitis. *Allergy* 1995;50(23 Suppl):6-10.
6. Fokkens WJ, Godthelp T, Holm AF, Blom H, Klein-Jan A, et al. Allergic rhinitis and inflammation: the effect of nasal corticosteroid therapy. *Allergy* 1997;52:29-32.
7. Meltzer EO. Nasal cytological changes following pharmacological intervention. *Allergy* 1995;50(23 Suppl):15-20.
8. Her E, Frazer J, Austen KF, Owen WF. Eosinophil hematopoietins antagonize the programmed cell death of eosinophils: cytokine and glucocorticoid effects on eosinophils maintained by endothelial cell conditioning medium. *J Clin Invest* 1992;88:1982-7.
9. Lozewicz S, Wang J, Duddle J, Thomas K, Chalstrey S, Reilly G, et al. Topical glucocorticoids inhibit activation by allergen in the upper respiratory tract. *J Allergy Clin Immunol* 1992;89:951-7.
10. Klementsson H, Svensson C, Andersson M, Venge P, Pipkorn U, Persson CGA. Eosinophils, secretory responsiveness and glucocorticoid-induced effects on the nasal mucosa during a weak pollen season. *Clin Exp Allergy* 1991;21:705-10.
11. Okuda M, Sakaguchi K, Ohtsuka H. Intranasal beclomethasone: mode of action in nasal allergy. *Ann Allergy* 1983;50:116-20.
12. Pipkorn U. Effect of topical glucocorticoid treatment on nasal mucosal mast cells in allergic rhinitis. *Allergy* 1983;38:125-9.
13. Mygind N, Dahl R. The rationale for use of topical corticosteroids in allergic rhinitis. *Clin Exp Allergy* 1996;26(3 Suppl):2-10.
14. Svensson C, Klementsson H, Andersson M, Pipkorn U, Alkner U, Persson CGA. Glucocorticoid-induced attenuation of mucosal exudation of fibrinogen and bradykinins in seasonal allergic rhinitis. *Allergy* 1994;49:177-83.
15. Baroody FM, Rouadi P, Driscoll PV, Bochner BS, Naclerio RM. Intranasal beclomethasone reduces allergen-induced symptoms and superficial mucosal eosinophilia without affecting submucosal inflammation. *Am J Respir Crit Care Med* 1998;157:899-906.
16. Sim TC, Reece LM, Hilsmeier KA, Grant A, Alam R. Secretion of chemokines and other cytokines in allergen-induced nasal responses: inhibition by topical steroid treatment. *Am J Respir Crit Care Med* 1995;152:927-33.
17. Ghaffar O, Laberge S, Jacobson MR, Lowhagen O, Rak S, Durham SR, et al. IL-13 mRNA and immunoreactivity in allergen-induced rhinitis: comparison with IL-4 expression and modulation by topical glucocorticoid therapy. *Am J Respir Cell Mol Biol* 1997;17:17-24.
18. Masuyama K, Jacobson MR, Rak S, Meng Q, Sudderick RM, Kay AB, et al. Topical glucocorticosteroid (fluticasone propionate) inhibits cells expressing cytokine mRNA for interleukin-4 in the nasal mucosa in allergen-induced rhinitis. *Immunology* 1994;82:192-9.
19. Cameron LA, Durham SR, Jacobson MR, Masuyama K, Juliusson S, Gould HJ, et al. Expression of IL-4, C_ε RNA and I_ε RNA in the nasal mucosa of patients with seasonal rhinitis: effect of topical corticosteroids. *J Allergy Clin Immunol* 1998;101:330-6.
20. 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.
21. Pullerits T, Praks L, Sjostrand M, Jarak S, Skoogh BE, Lotvall J. An intranasal glucocorticoid inhibits the increase of specific IgE initiated during birch pollen season. *J Allergy Clin Immunol* 1997;100:601-5.
22. 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.
23. Laberge JS, Durham SR, Ghaffar O, Rak S, Center DM, Jacobson M, et al. Expression of IL-16 in allergen-induced late-phase nasal responses and relation to topical glucocorticosteroid treatment. *J Allergy Clin Immunol* 1997;100:569-74.
24. Kim YK, Nakagawa N, Nakano K, Sulakvelidze I, Dolovich J, Denburg J. Stem cell factor in nasal polyposis and allergic rhinitis: increased expression by structural cells is suppressed by in vivo topical corticosteroids. *J Allergy Clin Immunol* 1997;100:389-99.
25. Roca-Ferrer J, Mullol J, Loez E, Xaubet A, Pujols L, Fernandez JC, et al. Effect of topical anti-inflammatory drugs on epithelial cell-induced eosinophil survival and GM-CSF secretion. *Eur Respir J* 1997;10:1489-95.
26. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al. Cytokine messenger RNA expression for IL-3, IL-4, IL-5, and granulocyte/macrophage-colony stimulating factor in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol* 1992;148:2390-4.
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. Varney A, Jacobson MR, Sudderick RM, Robinson DS, Irani AMA, Schwartz B, et al. Immunohistology of the nasal mucosa following allergen-induced rhinitis. *Am Rev Respir Dis* 1992;146:170-6.
29. Calderón MA, Lozewicz S, Prior A, Jordan S, Trigg CJ, Davies RJ. Lymphocyte infiltration and thickness of the nasal mucous membrane in perennial and seasonal allergic rhinitis. *J Allergy Clin Immunol* 1994;93:635-43.
30. Kanai N, Denburg J, Jordana M, Dolovich J. Nasal polyp inflammation: effect of topical nasal steroids. *Am J Respir Crit Care Med* 1994;150:1094-1100.