

# 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<sup>1,2</sup> as well as the subsequent period of increased reactivity to allergen,<sup>2</sup> histamine,<sup>3</sup> and methacholine<sup>4</sup> 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.

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

## 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

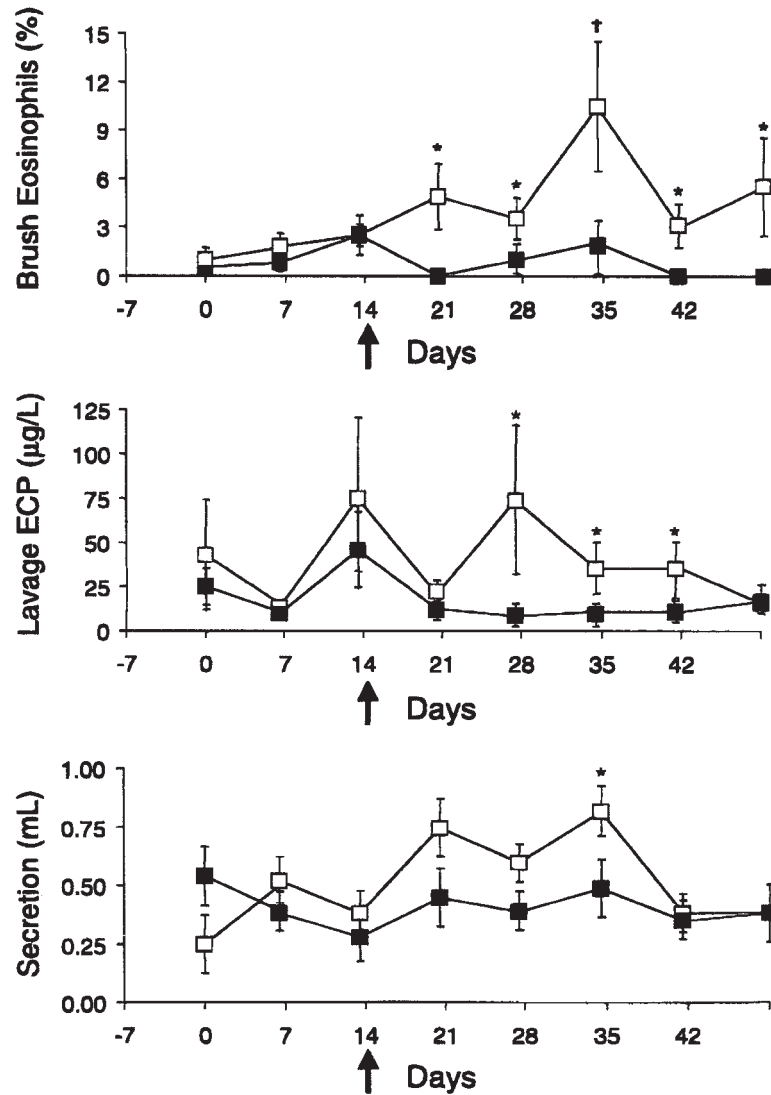
The most prominent effector cell in allergic rhinitis and in the late-phase reaction of the nose to allergen challenge is the eosinophil.<sup>5</sup> The number of eosinophils, particularly activated eosinophils (EG2<sup>+</sup>), increases substantially in the epithelium and lamina propria during the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

Clinical studies have confirmed the ability of intranasal steroids to reduce total<sup>1</sup> and activated<sup>9</sup> eosinophil numbers and eosinophil cationic protein (ECP)<sup>1</sup> in nasal lavage fluid in the late phase of the reaction to allergen challenge and in both seasonal<sup>10</sup> and perennial<sup>7</sup> rhinitis. A study by Klementsson et al<sup>10</sup> 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<sup>7,9</sup> and increased apoptosis, reflecting a direct effect on the eosinophil itself.<sup>8</sup>

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- $\alpha$ , which induce intercellular adhesion

S138



**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 $\alpha$ , 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,<sup>1</sup> 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 Up-regulates ICAM-1	Epithelial cells <sup>13</sup> Macrophages	16	16
IL-4	Up-regulates VCAM-1 IgE isotype switch in B cells Activates T <sub>H</sub> 2 lymphocytes Up-regulates IgE receptors	CD4 <sup>+</sup> T lymphocyte <sup>26</sup> > Mast cells <sup>5,18</sup>	5, 23 17-19	17-19
IL-5	Eosinophil activation and survival	T lymphocytes <sup>26</sup> Mast cells <sup>5,20</sup> Eosinophils <sup>5</sup>	5, 23 17, 18	18 (No 9) 20 (No 9)
IL-6	Promotes IgE synthesis Converts B cells to plasma cells Enhances T-cell activation	Mast cells <sup>20</sup>	20	20 (No 9)
IL-13	Promotes VCAM-1 IgE isotype switch	T lymphocytes > Mast cells <sup>17</sup>	17, 23	17
IL-16	Chemoattractant for CD4 <sup>+</sup> T lymphocytes	Epithelial cells <sup>23</sup> Subepithelial cells <sup>23</sup>	23	23
TNF- $\alpha$	Up-regulates ICAM-1 and VCAM-1	Mast cells <sup>5</sup> T lymphocytes Epithelial cells <sup>13</sup>	5	
GM-CSF	Eosinophil attraction, activation, and survival	Mast cells T lymphocytes <sup>5</sup> Epithelial cells <sup>16</sup>	5, 18 16	16, 25
SCF	Mast cell growth and survival	Epithelial cells <sup>24</sup>	24	24
<b>Chemokine</b>				
RANTES	Eosinophil chemotaxis Histamine-releasing factor		16	16
IL-8	Chemotaxis for mast cells	Epithelial cells <sup>5</sup>	16	16
MP-1a	Chemotaxis Histamine-releasing factor		16	16

AR, Allergic rhinitis; CS, corticosteroid; MIP- $\alpha$ , macrophage inflammatory protein 1a.

mucosal (tryptase only) mast cells<sup>5</sup> and perhaps basophils<sup>1</sup> 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 challenge<sup>1</sup> and prevent the increase in mucosal mast cells with chronic allergic stimulation, both seasonal<sup>7</sup> and perennial.<sup>7,11</sup> Topical corticosteroids do not reduce baseline numbers of mucosal mast cells but do decrease levels of histamine in the mucosa.<sup>12</sup>

### Plasma exudation

Entry of plasma into the nasal lumen has been demonstrated after histamine and allergen challenge and in seasonal allergic rhinitis.<sup>13</sup> 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.<sup>14</sup> This could result from a direct effect on the vascular endothelial cells, be the result of decreased release of permeability factors, or both.<sup>14</sup>

### Adhesion molecule expression

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

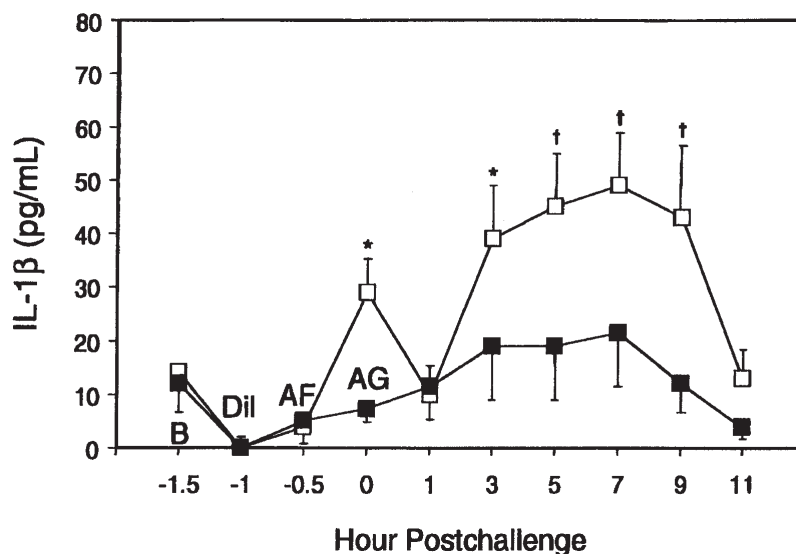
(induced by IL-4 and IL-13) has been reported to be increased in patients with both seasonal and perennial allergic rhinitis.<sup>15</sup> Reduction in the expression of these adhesion molecules by corticosteroids would be anticipated because levels of the inducing cytokines are reduced.<sup>16-20</sup>

### Nasal hyperresponsiveness to allergen, histamine, and methacholine

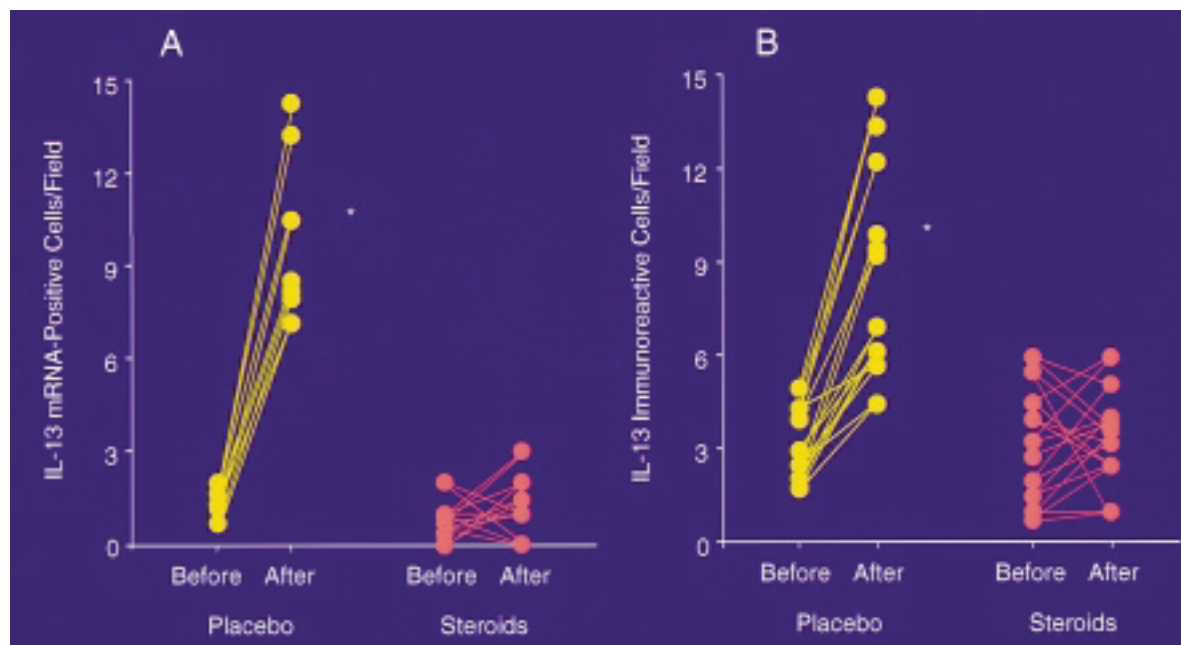
Nonspecific reactivity of the nose to histamine<sup>3</sup> and methacholine<sup>4</sup> is typically increased in perennial allergic rhinitis. Intranasal steroids reduce this hyperresponsiveness and also block the increase in sensitivity to allergen that follows allergen challenge, the so-called priming effect.<sup>2</sup>

### 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 birch<sup>21</sup> and ragweed<sup>22</sup> 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-1 $\beta$  during early and late phases of allergic response compared with placebo. Figure shows hourly levels of IL-1 $\beta$  detected by ELISA in nasal secretions of allergic subjects after antigen challenge. *Open boxes*, Mean values  $\pm$  SEM for the placebo group; *solid boxes*, values obtained for beclomethasone dipropionate treatment group. *B*, Baseline; *Dil*, diluent (saline solution); *AF*, Afrin<sup>7</sup> 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- $\alpha$ ,<sup>13</sup> IL-16,<sup>23</sup> and stem cell factor (SCF).<sup>24</sup> There is substantial evidence that intranasal steroids inhibit the expression or release of many of these cytokines (Table I).<sup>5,13,16,17-20,23-26</sup> 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.<sup>25</sup>

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.<sup>24</sup> 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.<sup>13</sup> Treatment with topical steroids markedly reduces the number of detectable Langerhans' cells.<sup>27</sup> 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.<sup>5</sup> The number of lymphocytes bearing the CD4<sup>+</sup> and CD25<sup>+</sup> (IL-2R) surface antigens has been found to be increased after nasal allergen challenge<sup>28</sup> and in patients with seasonal and perennial allergic rhinitis.<sup>29</sup>

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<sup>+</sup>) in patients with perennial allergic rhinitis.<sup>27</sup> However, 6

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

After nasal allergen challenge, an increase was found in the number of activated T cells (CD25<sup>+</sup>) and CD4<sup>+</sup> T cells expressing mRNA for IL-4 and IL-5.<sup>28</sup> 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<sub>H</sub>2-type T lymphocytes. Topical corticosteroids have been shown to attenuate IL-4<sup>17,18,20</sup> but not IL-5<sup>17,20</sup> or IL-6<sup>20</sup> mRNA expression. With seasonal exposure, there was an increase in the B lymphocytes targeted for isotype switching to IgE production.<sup>19</sup> 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<sub>H</sub>2 CD4<sup>+</sup> 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.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.