

Intranasal corticosteroids and the eye: from negative ocular effects to clinical efficacy as a class effect

Leonard Bielory, MD

Glucocorticosteroids, in their various formulations, ranging from oral to topical ophthalmic, have been associated with negative “ocular effects” that include infections, increased intraocular pressure leading to a risk for glaucoma, scleral thinning, and cataracts.¹ In addition, there have been concerns about the systemic effects of inhaled and intranasal steroids on growth, bones, and the hypothalamic-pituitary-adrenal axis and about local adverse events. These concerns led to the development of a position statement from a Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology, recommending that intranasal corticosteroids (INSs) should remain prescription-only drugs and not be indicated for over-the-counter use.² A particular concern of many ophthalmologists has been the possible development of increased intraocular pressure during treatment with corticosteroids. In a study³ of patients being treated for glaucoma who were also receiving an INS, the discontinuation of challenge and rechallenge studies with various INS formulations led to a significant reduction in intraocular pressure.

However, increasing recent interest is focusing on whether the INSs, as a class effect, may have beneficial effects on the eye, especially in reducing the symptoms of allergic conjunctivitis frequently found in patients with allergic rhinitis (AR). The eye is especially susceptible to the symptoms of AR—itching (pruritus), tearing (epiphora), and redness (erythema)—because it lacks a mechanical barrier that could prevent the deposition of allergens, such as pollen, on the conjunctival surface.⁴ These ocular symptoms have been described as examples of the type 1 immediate hypersensitivity reaction.⁵

A number of recently published clinical studies apparently support the positive effect of INS agents on ocular allergy

symptoms. One possible reason that the INSs were not regarded as effective for ocular symptoms earlier is that studies published before the late 1990s did not consistently focus on the ocular domain of allergy symptoms. Instead, they included ocular and other nonnasal symptoms (eg, otic and palatal pruritus) into a single component of the total nonnasal symptom score in AR studies. However, studies published during the past 5 years have collected and reported ocular allergy signs and symptoms separately as part of a total ocular symptom score (TOSS).

One of the earliest reports demonstrating the positive effects of INSs as a class on ocular allergy domains is a meta-analysis published almost a decade ago of studies (conducted between 1966 and 1997) that compared oral antihistamines with INSs. The meta-analysis⁶ concluded that the INSs and oral antihistamines had a similar effect on ocular symptoms in AR studies and recommended the use of INSs over oral antihistamines as first-line treatment for AR. These results have been verified in many of the more recent studies^{7–16} with INS agents. Studies with fluticasone propionate,^{7,8} mometasone furoate nasal spray,^{9–11} fluticasone furoate,¹² budesonide,¹³ and, to some degree, triamcinolone acetonide aqueous nasal spray¹⁴ and beclomethasone dipropionate aqueous nasal spray^{15,16} provide further support for the favorable effect of INSs for ocular symptoms.

For example, Bernstein et al⁷ concluded from a 28-day study with fluticasone propionate, oral loratadine, and vehicle placebo that patients treated with fluticasone propionate had statistically significant decreases compared with placebo in TOSS, which was the sum of scores for the symptoms of itching, tearing, and redness. The data also suggested that fluticasone propionate had reduced ocular symptoms more than or comparable to oral loratadine.⁷ Furthermore, an analysis of pooled data from the fluticasone propionate and placebo arms of 7 studies found that, after 7 and 14 days of treatment, patients receiving fluticasone propionate experienced significantly greater reductions in TOSS (sum of itching, tearing, redness, and puffiness symptom scores) than did patients in the placebo group.⁸

The positive effect of mometasone furoate nasal spray on ocular allergy symptoms was seen in an analysis of pooled data from 4 randomized, placebo-controlled, double-blind,

Affiliations: Division of Allergy, Immunology, and Rheumatology, Departments of Medicine, Pediatrics, Ophthalmology and Visual Sciences, UMDNJ–New Jersey Medical School, Newark, New Jersey.

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clinical studies of adults and adolescents (N = 991) with seasonal AR.⁹⁻¹¹ Patients who received mometasone furoate nasal spray had significantly greater reductions in TOSS and in the individual component symptoms of itching, tearing, and redness than those who received placebo during the entire 2-week study. An analysis of a subgroup with moderate-to-severe ocular symptoms showed significantly greater improvement in TOSS and individual ocular symptoms with mometasone furoate nasal spray than with placebo.¹¹

Fluticasone furoate was associated with significant ($P \leq .03$) improvement in TOSS and each of the individual symptoms.¹² Mometasone furoate nasal spray and fluticasone furoate seem to have a relatively early onset of effect, within 24 to 72 hours of initiation, with a statistically significant mean change from baseline during the 15 days of the studies.^{11,12} The pooled analysis of the studies with mometasone furoate nasal spray found that improvements for individual symptoms occurred as early as day 2 of treatment.¹¹

In a study¹³ of budesonide in a pediatric population with perennial AR, eye symptom scores related to allergic conjunctivitis significantly decreased after 1 year of treatment. Older studies with triamcinolone acetonide, budesonide, and beclomethasone dipropionate provide further support of the positive effect of INSs in managing ocular allergy symptoms.⁶ Most of the published triamcinolone acetonide studies with ocular data are comparisons with an antihistamine (loratadine or astemizole). In 3 separate studies, triamcinolone acetonide was significantly more effective than or comparably effective with the antihistamine in reducing ocular symptoms, as was reported in the meta-analysis of Weiner et al⁶ and in other publications.¹⁴

Similar evidence of a positive effect of INSs on ocular allergy symptoms associated with seasonal AR can be found as far back as 1985 with beclomethasone dipropionate,¹⁵ although this early study did not find a significant improvement with the INS compared with an antihistamine. In a more recent study of patients with allergic or nonallergic chronic rhinosinusitis, Giger et al¹⁶ compared once-daily with twice-daily use of beclomethasone dipropionate and found a significant improvement for both groups in ocular tearing, itching, and redness and in blepharodema.

A further indication of the positive effect of INSs on the ocular symptoms of AR was seen in a systematic meta-analysis of clinical studies conducted from 1997 through 2000, which compared the effects of INSs and topical antihistamines. The meta-analysis¹⁷ concluded that there was no significant difference between INSs and topical antihistamines in the control of ocular symptoms.

Several mechanisms of action have been proposed to explain the effect of INSs in reducing ocular symptoms related to AR. These possibilities include the following: (1) improved drainage of the nasolacrimal duct related to the anti-inflammatory action of the INSs reduces exposure of the conjunctiva to allergens, (2) application of the steroid to the eye through either systemic absorption or nasolacrimal reflux, (3) reduced nasal inflammation moderates the allergen-

caused increases in reflex neuronal activity, and (4) the systemic immune effect, as reflected by the decreased immune profile found in the lung when the upper airway is treated, perhaps a further extension of the one airway, one disease concept.^{8,9,18} However, despite apparently substantial evidence of reduction of ocular symptoms with INSs, the mechanism or mechanisms of action have not been conclusively determined.

The increasing evidence about the effect of INSs on ocular allergy symptoms may result in further inquiries into the mechanism of action, greater awareness among treating physicians of the positive effect of INSs for ocular symptoms, and the possible inclusion of INSs in the treatment algorithm of patients with allergic rhinoconjunctivitis. Notably, the recent guidelines from the International Primary Care Respiratory Group¹⁹ indicate the acceptance of INSs in this regard because they note that INSs do have an effect on eye symptoms associated with AR.

There is compelling evidence from various studies that INSs reduce ocular symptoms in adult patients, although an indication for this use has not yet been approved by a regulatory agency. Much less evidence is available regarding the effect of INSs on ocular symptoms in the pediatric population. Therefore, additional well-planned trials in adult and pediatric populations would be helpful. Finally, research toward a firmly established theory of an INS mechanism of action for reduction of ocular symptoms, and studies investigating the likelihood of potentially negative ocular effects, such as increased intraocular pressure, would be most welcome.

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- Requests for reprints should be addressed to:*
Leonard Bielory, MD
Departments of Medicine, Pediatrics, and Ophthalmology
UMDNJ–New Jersey Medical School
90 Bergen St
DOC Ste 4700
Newark, NJ 07103
E-mail: bielory@umdnj.edu
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