

Is conjunctival allergen challenge a model of seasonal rhinoconjunctivitis?

To the Editor,

We read with interest the article by Rosenwasser and colleagues, which presented the results of a conjunctival allergen challenge (CAC) study comparing the efficacy of olopatadine ophthalmic solution (OS) with intranasal fluticasone furoate (FF) in reducing allergic conjunctivitis (AC) symptoms.¹ The results are predictable. A topical antihistamine affects the immediate response to CAC regardless of duration of pretreatment, whereas topical delivery of a corticosteroid to a distant site, not involved with antigen exposure, has no effect. We fear that the casual reader will conclude that olopatadine is superior to fluticasone furoate for the treatment for allergic rhinoconjunctivitis.

The clinical implications of this study relate to the relationship between CAC and clinical disease. There is unequivocal evidence that the placement of antigen in the conjunctiva of a sensitized host will lead to an immediate reaction followed by a late reaction, something not evaluated in this study, is not affected by antihistamines, and may be an important contributor to ocular disease; however more important, is CAC reflective of allergic conjunctivitis? Maybe, if a patient presents with only ocular symptoms. Though we suspect the overwhelming majority of patients with allergic conjunctivitis to inhalants present with rhinoconjunctivitis, and the immediate response to CAC doesn't reflect this clinical disease. We believe that the ocular symptoms of rhinoconjunctivitis result from a combination of direct antigen exposure to the eye, and indirectly from neuronal reflexes originating from allergic nasal inflammation, with the latter being the predominate mechanism.

We suspect for several reasons that the neuronal reflexes originating in the nose are the predominant route for the development of ocular symptoms. First, of the six primary studies designed to test the efficacy of OS, FDA approval for the treatment of ocular itching associated with AC was primarily supported by four CAC studies, because OS use in two natural-exposure studies showed inconsistent efficacy; one showed no efficacy and the other demonstrated relief of itching, but not throughout the day, which suggests that the direct route of ocular antigen exposure is a small component. Second, FF has consistently demonstrated significant relief of both nasal and ocular symptoms as-

sociated with seasonal allergic rhinitis (SAR) under conditions of natural pollen exposure in subjects 12 years and older in five prospectively designed clinical studies.^{2,3,4,5,6} Third, because FF is an intranasal medication with low systemic bioavailability, and, as shown in this study by Rosenwasser, has no direct reduction on ocular symptoms induced by CAC, it would have no effect on ocular symptoms of SAR if direct conjunctival contact with antigen were the predominate mechanism. Fourth, we have shown that nasal antigen challenge produces ocular symptoms by a reflex mechanism that is primed by repetitive antigen exposure as occurs during the season and that is reduced by FF, therefore providing an explanation of how an intranasal steroid can affect ocular symptoms.^{7,8} Fifth, in one of two recent replicated studies of FF and oral fexofenadine, FF was superior for both nasal and ocular symptoms in patients with SAR.^{5,6} Sixth, antigen is actively inhaled into the nose but passively contacts the conjunctiva. For the above reasons, we feel that direct deposition of antigen in the eye is not the predominate cause of ocular symptoms in allergic rhinoconjunctivitis, and thus CAC is not an appropriate model to test the allergic conjunctivitis that occurs with SAR.

The authors note that using a CAC model is appropriate to evaluate the effects of antiallergic ophthalmic medications, and is not typically used for evaluation of intranasal sprays, yet in this study, CAC was used to compare FF with OS. We question the scientific validity of comparing two medications approved for different indications, FF for the symptoms of SAR and topical OS for itching associated with AC, and then inducing only AC symptoms to compare the two products! Not surprisingly, it was concluded that OS, a topical eye drop, was superior to FF, an intranasal steroid, in relieving ocular symptoms of AC. In an absurd analogy, you would not expect an intranasal steroid to affect the immediate response to an allergen skin test.

From a clinical perspective, we would not advocate the use of FF for patients with only ocular itching caused by allergy. We, however, would suggest considering treating patients 12 years and older with SAR first with FF, and adding a topical ocular antihistamine if they have persistent ocular symptoms.

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Robert M. Naclerio, M.D.
Edward E. Philpot M.D.

Response

We thank Dr. Naclerio and Dr. Philpot for their comments, but we clearly have a different view of allergic conjunctivitis and allergic rhinitis. Nowhere in our manuscript was it implied that either olopatadine or fluticasone furoate is a preferential single treatment for allergic rhinoconjunctivitis—that is, providing the most effective relief of both ocular and nasal signs and symptoms associated with seasonal or perennial allergens.

Total ocular symptom scores (TOSS) calculated during trials in seasonal and perennial allergic rhinitis patients is a methodology that obscures true discussion of ocular efficacy. In the studies cited by Dr. Naclerio and Dr. Philpot (Refs. 2–6) in which the individual ocular symptoms were reported (along with the TOSS), they are reported as a mean change in baseline over the entire treatment period, and derived from reflective and instantaneous diary entries. Itching and burning symptoms were grouped together, despite the mechanistic differences between the two symptoms: clinically, itching is indicative of ocular allergy, but burning can be a symptom of a host of conditions, including dry eye. One shouldn't hide the efficacy of an agent in an arbitrary global score where it is impossible to accurately discern effects on the individual signs and symptoms. The reductions seen in ocular signs and

symptoms were likely the result of reduced congestion, thereby facilitating drainage of allergic mediators out of the eye.

The conjunctival allergen challenge (CAC) model of allergic conjunctivitis is well accepted as a correlate of allergic reactions in the clinical state. Much like allergen challenge in the lung and nasal allergen challenge models, they are correlates of asthma and allergic rhinitis, respectively. All the currently available ophthalmic antihistamine/mast cell stabilizers were approved using the CAC model as at least one pivotal trial, because the benefits of the CAC model outweigh the inherent variability of environmental models. Because each sign and symptom is evaluated individually, the CAC model allows for precise and reproducible evaluations of the drug's mechanism of action, the onset and duration of action, and comparisons against positive and negative controls. As described in our manuscript, these rigorous evaluations differ dramatically from the criteria (total ocular or nasal symptom scores) used to evaluate the effects of intranasal sprays on ocular signs and symptoms. It was therefore of interest to investigate whether the ocular effects of an intranasal spray are dramatic enough to warrant an ocular claim or indication similar to that of ophthalmic antihistamine/mast cell stabilizers.

The results presented indicate that an intranasal spray does not have sufficient effects on ocular signs and symptoms to justify an ophthalmic claim using the standard clinical model for establishing efficacy for the treatment of the signs and symptoms associated with allergic conjunctivitis. Intranasal sprays do have significant effects on nasal allergy symptoms, just as ophthalmic antihistamine/mast cell stabilizers have clinically significant effects on ocular allergy signs and symptoms. Both are more effective than oral therapies.^{1–3} Although both ophthalmic antihistamine/mast cell stabilizers and various intranasal sprays have demonstrated some efficacy for the neighboring regions,^{4–8} the greatest benefit is realized when the topical therapies are localized to the affected organ(s),^{3,9} lending credence to treating allergic rhinoconjunctivitis patients with an ophthalmic antihistamine/mast cell stabilizer and an intranasal spray. Surveys do show that ocular symptoms remain one of the most bothersome symptoms despite treatment with intranasal sprays (fourth in the Allergies of America Survey). But as the current study clearly reveals, the effects of an intranasal spray on ocular symptoms in an acute allergic reaction are relatively minor, and an ophthalmic antihistamine/mast cell stabilizer is needed to effectively control ocular symptoms of allergic rhinoconjunctivitis. A 2005 study strongly identified the substantial quality-of-life impact of an ophthalmic antihistamine/mast cell stabilizer on ocular symptoms in patients

already using an intranasal spray or systemic antihistamine.⁹

Clinical experience demonstrates that up to 90% of allergic conjunctivitis patients have allergic rhinitis, and vice-versa.^{10,11} Clearly, the two conditions are linked. In previously published manuscripts, Dr. Naclerio has elegantly proposed a naso-ocular reflex as a potential mechanism for the copresentation of ocular and nasal symptoms. The eyes are open to the environment and are essentially collecting plates for allergens, with only tearing and blinking as defense mechanisms. In contrast, the nose has mucus lining, nasal hair, and a filtration system. Any environmental exposure to allergen that is sufficient to elicit a nasal allergic response is likely to also elicit an allergic response in the eye, which is less protected from allergen infiltration. More arcane explanations for the mechanisms of symptoms in allergic conjunctivitis with or without allergic rhinitis can be made, but the simplest and most direct explanation, namely direct contact of allergen with the conjunctiva, has to be considered in any evaluation of allergic conjunctivitis and rhinitis.

Although the one thing we agree upon is that ocular exposure to allergen occurs, the concept that the ocular allergic response is primarily driven by nasal exposure to allergen is not likely. Drs. Naclerio and Philpot offer the fact that the immediate response of the CAC doesn't reflect the clinical presentation of allergic rhinitis in support of the existence of a naso-ocular reflex. Again, they are overlooking the basic and differential mechanisms of the ocular and nasal allergic responses. When allergen is instilled into the eye, some will drain down the naso-lacrimal duct and, in the majority of atopic individuals, elicit an early-phase allergic response in both the eye and the nose. This study, however, was designed to evaluate ocular, not nasal symptoms, with the purpose of evaluating the distal effects of an intranasal spray in the model that is standardized to evaluate ocular claims. The results suggest that the bioavailability of nasal spray is affected by the amount of congestion. Even with nasal congestion, pollen is still able to enter by way of the eye, and that may well be what perpetuates the nasal reaction.

We recognize the effects of fluticasone and this class of agents, namely intranasal steroids. We also recognize that an ophthalmic antiallergic medication can significantly affect the nose, and an intranasal spray can decrease tearing by means of reduced nasal congestion. Based on the available studies, however, we conclude that there is limited evidence to substantiate the existence of a naso-ocular reflex as a clinical etiology of ocular symptoms. In light of the potential side-effects (albeit rare, glaucoma and posterior subcapsular cataracts) of intranasal therapies in patients with allergic rhinoconjunctivitis, we advocate the use of an oph-

thalmic antihistamine/mast cell stabilizer in conjunction with an intranasal spray. Eventually, if nasal symptoms can be mitigated and sufficiently controlled by the ophthalmic drop, then cessation of the intranasal spray may be indicated.

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Lanny J. Rosenwasser, M.D.
Kansas City, MO

Todd Mahr, M.D.
LaCrosse, WI

Paul J. Gomes, M.S.

Mark B. Abelson, M.D.
Boston, MA

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