

Allergic Conjunctivitis and the Impact of Allergic Rhinitis

Leonard Bielory

© Springer Science+Business Media, LLC 2010

Abstract Although nasal allergy has been prominent in allergy research, ocular allergy is increasingly recognized as a distinct symptom complex that imposes its own disease burden and reduction in patients' quality of life. In the past year, knowledge of the relationships between allergic conjunctivitis and allergic rhinitis has increased. Allergic conjunctivitis is highly prevalent and has a close epidemiologic relationship with allergic rhinitis. Both conditions also exhibit similar pathophysiologic mechanisms. Pathways of communication are thought to increase the likelihood of an inflammatory reaction at both sites following allergen exposure of nasal or ocular tissue. Clinical trials of intranasal therapies have demonstrated efficacy in allergic conjunctivitis and rhinitis. Newer intranasal steroids decrease ocular symptoms, potentially achieving efficacy by suppressing the naso-ocular reflex, downregulation of inflammatory cell expression, or restoration of nasolacrimal duct patency. Proposed pathophysiologic interactions between allergic rhinitis and ocular allergy underscore the need for therapies with efficacy in both symptom sets.

Keywords Ocular allergy · Rhinoconjunctivitis · Antihistamines · Intranasal steroids

Introduction

Allergic rhinitis (AR) affects multiple aspects of patients' well-being, functioning, and productivity. In a recent US survey ($n=7,024$ respondents), individuals who experienced AR symptoms within the preceding 4 weeks reported more negative effects on sleep, cognition, and overall quality of life than nonsufferers. The survey also noted that the mean number of entire school or work days missed was significantly higher among AR sufferers than nonsufferers (0.4 vs 0.2; $P<0.05$) [1].

Ocular allergy, including seasonal conjunctivitis (SAC) or perennial conjunctivitis (PAC), is closely linked to AR, demonstrating similarities in epidemiologic mechanisms and treatment modalities. Seasonal AR (SAR) and SAC are triggered by various outdoor aeroallergens, whereas perennial AR (PAR) and PAC are primarily associated with exposure to household aeroallergens. Ocular allergy and nasal allergy nevertheless are different conditions: not all patients with symptoms at one site experience symptoms at the other. Furthermore, ocular allergy also encompasses severe forms of conjunctivitis, such as vernal keratoconjunctivitis or atopic keratoconjunctivitis, which seem to have distinct pathophysiologic characteristics relative to the more common seasonal or perennial allergies [2].

Ocular symptoms associated with AR, which are considered underdiagnosed and undertreated, are recognized as imposing a substantial burden of disease and medical cost on allergy patients. Studies of SAC sufferers have demonstrated that ocular symptoms, including itching, burning, tearing, and conjunctival swelling and redness, exert negative effects on quality of life. In a United Kingdom study, patients with SAC reported a mean reduction in productive time of 2.3 h/wk during the allergy season [3]. A US study found that 17% of patients with

L. Bielory (✉)
STARx Allergy and Center and Clinical Research Center,
Rutgers University,
400 Mountain Avenue,
Springfield, NJ 07081, USA
e-mail: drlbielory@gmail.com

ocular allergy symptoms could not perform daily tasks when symptoms were present [4], and in Spain, the total annual per patient cost of SAC was estimated to be about 350 Euros [5].

Research devoted specifically to the treatment of ocular allergy is in its infancy, as it has only been ongoing during the past 20 years. This review primarily discusses the advances made during the previous year in our understanding of SAC and PAC (as they comprise most of the research) and examines how these findings illuminate the relationship between ocular and nasal allergic symptoms [6].

Epidemiology

Prevalence and Comorbidity

Recent data confirm the widespread prevalence of AR and ocular allergy and the close epidemiologic relationship between the two conditions. As reflected in changes detected in the National Health and Nutrition Examination Survey (NHANES) and other surveys, the prevalence of AR prevalence seems to be increasing. In 1993, a US survey reported AR in 14% of the population [7], whereas a similar survey conducted in 2004 demonstrated a 30% prevalence of self-reported seasonal and/or perennial nasal symptoms [8]. In the 1994 European Community Respiratory Health Survey study, nasal allergy prevalence among adults ranged in various European countries (United Kingdom, 24–29%; Germany, 13–23%; Italy, 13–17%) [9]. In a recent review of the NHANES III data, 40% of a US population sample reported symptoms consistent with ocular allergy [10]. Overall, the apparent increase may have been a result of differences in methodology or a true rise in prevalence that may be reflective of “climate change.”

Nasal and ocular allergy demonstrate the characteristic Gaussian biological distribution, with more than 80% of allergic patients having AR and AC, about 10% having AR with AC, and another 10% having AC and no AR. This has been demonstrated in various clinical studies. For example, in one European study, 509 allergy patients reported rhinoconjunctivitis (85.3%), conjunctivitis without rhinitis (8%), or rhinitis without conjunctivitis (6.7%) [11]. A recent French survey revealed that 31% of interviewees ($n=10,038$) had AR, 52% of whom reported ocular symptoms [12]. Among patients presenting for allergology services in Spain, 55% were diagnosed with AR, 65% of whom were also diagnosed with AC and 37% with asthma [13]. A review of US NHANES data indicated that 29.7% of respondents reported nasal and ocular allergy symptoms, 16.5% reported nasal symptoms alone, and 6.4% reported ocular symptoms alone [14]. In another study of 61 adults

referred to treatment for SAC or PAC, 55 (90%) exhibited positive nasal provocation tests ($n=103$); 82% of these responses were associated with ocular symptoms [15•].

Pediatric Epidemiology

Extensive allergic epidemiologic data exist for the pediatric population. The International Study of Asthma and Allergies in Childhood (1993–1997) examined global patterns of allergic rhinoconjunctivitis (ARC). Five to 10 years later (1998–2003), in the third phase of the study, a slight overall increase in prevalence was noted, particularly among 13- to 14-year-olds, with wide regional differences and no consistent, discernable trend. Overall, rhinoconjunctivitis symptom prevalence was 14.6% among 13- to 14-year-olds (range, 1–45.1%). Severe symptoms were most common in Latin America (1.1%) and Africa (2.1%) but relatively rare in Western Europe (0.4%). Rhinoconjunctivitis symptoms were present in 8.5% of 6- to 7-year-olds, also with wide geographic variations [16, 17].

Except for more affluent, urbanized areas (eg, Japan, Hong Kong, Singapore), Asia exhibited a lower prevalence of allergic diseases compared with other parts of the world, although increases were observed in nearly all countries in the region [18] and seemed to correlate with the increase in industrialization. Using data from 1992 and 2002 among students 6–12 years old, Nishima and colleagues [19] found increases in AR (from 16 to 20.5%; $P<0.001$), in AC (from 6.8 to 9.8%; $P<0.001$), and in cedar pollinosis (from 3.7 to 5.8%; $P<0.001$). Kusunoki and colleagues [20] compared survey data from 1996 and 2006 in children 7–15 years old that indicated increases in AR (from 20.3 to 27.4%; $P<0.0001$) and AC (from 13.3 to 25.2%; $P<0.0001$).

The association of rhinoconjunctivitis and asthma seems to have remained unchanged in the developing countries. In the analysis of International Study of Asthma and Allergies in Childhood data from Brazil, 81% of adolescents with symptoms of rhinoconjunctivitis had persistent probable asthma, and 32% of patients with asthma had rhinoconjunctivitis. Rhinoconjunctivitis alone was present in 10% of the sample, probable asthma alone in 11%, and both conditions together in 5% [21].

Risk Factors

Epidemiologic evidence exists for several putative allergy risk factors, including genetics, allergen exposure, small household size, urban residence, and air pollution (indoor or outdoor) [22]. An area of current controversy is the so-called hygiene hypothesis, in which early exposure to infectious or commensal, nonpathogenic microorganisms may promote immune system maturation and protect the development of an allergic diathesis, whereas a lack of

exposure in early life may disrupt normal development of T-regulatory cell activity and increase the risk of allergic disease [22, 23]. Similarly, antibiotic use in infancy leading to a decrease in microbiota was thought to potentially increase the subsequent risk of allergies. However, in a 5-year longitudinal study of 198 children, 54% of whom received at least one course of antibiotics in the first year of life, no increase was seen in atopy, including in ARC, asthma, or eczema [24].

Running counter to the hygiene hypothesis are the possible effects of parasitic worm infestation, which may increase or decrease the response to aeroallergens by redirecting the T-helper type 2 and IgE response toward or away from allergens. This effect would depend on variables such as parasite species, the timing or intensity of infection, and individual host genetics [25, 26]. A study of Cuban children found that the likelihood of having ARC was increased in those with a history of infection with *Enterobius vermicularis* (OR, 1.34; $P=0.048$) or hookworm (OR, 2.81; $P=0.017$), whereas a positive culture for *Ascaris lumbricoides* was negatively correlated with the presence of atopic dermatitis (OR, 0.23; $P=0.011$) [27]. Another interesting finding demonstrated that treatment for allergic rhinoconjunctivitis with a helminth (*Trichuris suis*) induced a clinical and immunologic response as evidence of the infection but did not demonstrate any therapeutic effect on AR [28].

Pathophysiology of Rhinoconjunctivitis

Inflammatory Response in the Nasal Mucosa and Conjunctiva

The allergic inflammatory response unfolds in a similar manner in both the nasal mucosa and conjunctiva. Histamine is the primary mediator of the early phase of the allergic response and is characterized by ocular symptoms such as itching, swelling, redness, and lacrimation, and by nasal symptoms such as itching, sneezing, and rhinorrhea. The late-phase responses of the eye and nose are similar: late-phase ocular symptoms include itching, redness, lacrimation, and foreign body sensation, whereas late-phase nasal symptoms include congestion, rhinorrhea, and sneezing [22, 29–33].

Nasal allergen challenge produces an immediate early-phase response and may produce late-phase symptoms at 3–11 h [34]. Early-phase ocular symptoms commence rapidly after challenge and peak at 15–20 min [35]. Late-phase ocular symptoms may appear 4–24 h after initial exposure [33].

Although the allergic mechanism is similar in nasal and ocular tissues, pathophysiologic mechanisms do not seem identical (Table 1). The inflammatory response is milder in

AC than in AR, as demonstrated by the relative lack of eosinophil infiltration in the conjunctival epithelium following allergen exposure [36]. This may be attributable to allergen dose, as the dose of allergen on the conjunctiva due to impaction is about 100- to 1,000-fold less than the allergen deposition in the nose due to the vortex of inhaled air past the nasal mucosa [2, 37].

Interaction of Nasal and Ocular Allergic Responses

AR and AC are also linked by other features. Primary allergen challenge to the nasal mucosa or conjunctiva has been observed to elicit secondary symptoms at the other site. The epidemiologic associations of nasal and ocular symptoms associated with AR are supported by putative pathways of communication between nasal and ocular tissues. Drainage of allergen into the nasolacrimal duct, blockage of the nasolacrimal duct, the presence of a naso-ocular reflex, and an association of local inflammation with systemic immune effects are presently the most convincing explanations.

Allergen Drainage

Drainage of allergens and inflammatory mediators present in the conjunctiva from the eye downward to the nose via the nasolacrimal duct seems to provide a route for ocular allergen exposure to affect the nasal mucosa. On the other hand, although it has been reported, upward migration from the nose to the eye (ie, nasolacrimal reflux) is unlikely [38, 39].

Blockage of the Nasolacrimal Duct

Increase in ocular tear-fluid retention of allergens and inflammatory mediators may result in obstruction of the nasolacrimal duct and would be expected from a mechanical perspective to increase the symptom of tearing in ocular allergy. Treatment of nasal allergies with oral or intranasal medication relieved tearing in 20 patients with unilateral epiphora in one study [40]. In another study, restoration of duct patency and improvement in ocular allergy symptoms were observed following intranasal corticosteroid (INS) therapy [41]. However, in a study in which the Jones test was administered to assess nasolacrimal duct patency following a nasal allergen challenge, nasolacrimal drainage was maintained despite the presence of nasal symptoms [38].

Naso-Ocular Reflex

Clinical studies have yielded evidence that nasal allergen challenge stimulates ocular itching and tearing via a

Table 1 Similarities and differences in the pathophysiology of nasal and ocular allergy**Similarities in the inflammatory response of the nasal mucosa and conjunctiva**

- Histamine-mediated early inflammatory response
- Inflammatory cell recruitment in late-phase response

Differences in the inflammatory response of the nasal mucosa and conjunctiva

- Greater allergen exposure of the nasal mucosa due to nasal vortex of air versus impaction of air on the conjunctival surface
- Lack of eosinophil infiltration to the conjunctiva in the late-phase response

Interaction of nasal and ocular allergic responses

- Allergen drainage via nasolacrimal duct
- Inflammation-induced blockage of the nasolacrimal duct
- Naso-ocular reflex
- Systemic inflammatory response

centrally mediated naso-ocular reflex [11, 42, 43]. It is believed that histamine released in the nasal mucosa stimulates afferent nerves, leading to a parasympathetic response in the conjunctiva bilaterally and in the contralateral nares (the nasonasal reflex) [37, 44, 45]. In a study supporting this model, patients with ocular symptoms induced by isolated nasal challenge did not demonstrate increased levels of histamine in ocular secretions. Furthermore, administration of a topical antihistamine at the challenge site blocked the itching and tearing response seen in the placebo-treated patients [37].

Systemic Inflammatory Response

Animal and human data indicate that local nasal allergen exposure is associated with upregulation of the systemic inflammatory response. A murine model of AR demonstrated increased levels of immature and mature eosinophils in bone marrow and peripheral blood, possibly induced via the cytokines interleukin-5 and eotaxin [46]. Nasal allergen challenge in humans was associated with circulating basophil activation [47]. A cell-trafficking model has been proposed in which progenitors of mast cells and other inflammatory cells migrate into the target tissues, where they differentiate into mature inflammatory cells [48]. By increasing the number of circulating progenitor cells, AR may facilitate more rapid and intense infiltration of inflammatory cells into the conjunctiva after direct conjunctival allergen provocation [49].

Ocular Allergy Treatment: Review of Recent Clinical Trials

A range of therapies is available for treatment of ocular allergy symptoms (Table 2). Efficacy in ocular symptoms would be expected from topical ocular therapies, and the systemic absorption of oral therapies exposes ocular

tissues to ingested drugs. The efficacy of intranasal therapies, particularly corticosteroids, in treating ocular allergy symptoms holds more interest for the question of how AR and ocular allergy are related. The following section reviews clinical trial findings on ocular outcomes from the past year obtained with antiallergy therapies. A subsequent section discusses the implications of the available clinical data for our understanding of the relationship between nasal and ocular allergy.

Intranasal Corticosteroids

Studies of INS therapy conducted in 2009 demonstrated efficacy in alleviating ocular symptoms, supporting earlier findings on the utility of this drug class as an ocular allergy therapy, including comparative research that indicates that INS provide equal or greater relief of ocular allergy symptoms as compared with intranasal [50] or oral antihistamines [40, 51–53]. Data published in the past year are reviewed below.

A double-blind, noninferiority study ($n=130$) was conducted to compare intranasal olopatadine, 0.6% (2 sprays/nostril twice daily), and intranasal fluticasone propionate, 50 μ g (2 sprays/nostril daily), in SAR during 2 weeks of treatment in a real world setting. The primary efficacy end point—reflective total nasal symptom score averaged over the study period—did not significantly differ between treatments. Average 2-week percent changes from baseline were similar between intranasal olopatadine and intranasal fluticasone propionate for all nasal and ocular symptoms. Changes in morning instantaneous predose ocular symptom scores, a common parameter for evaluating 24-h efficacy, were not reported. Consistent with the known rapid onset of antihistamine action, a faster initial reduction in all nasal and ocular symptoms was observed with olopatadine [54].

Recently, a 16-day, 544-patient study comparing intranasal olopatadine, 0.6%, with intranasal azelastine, 0.1%, found statistically comparable reductions in reflective total

Table 2 Treatment of naso-ocular symptoms: summary of overall therapeutic impact of classes of agents and several specific agents

Agent	Strength of evidence		Publication type	Nasal outcomes		Ocular outcomes
	Nasal	Ocular				
Immunotherapy	Ia	Ia	Metaanalysis	Significant improvement vs placebo in nasal symptoms in 8 studies [97]		Significant improvement vs placebo in ocular symptoms in 3 studies [97]
Intranasal treatments						
Intranasal antihistamines plus mast cell stabilizer						
Olopatadine	Ib	Ib	RCTs	$P=0.6771$ (noninferior) vs fluticasone propionate in rTNSS [54] $P=0.003$ vs placebo and noninferior vs azelastine in rTNSS [55] $P<0.05$ vs placebo in TNSS [98] $P\leq 0.004$ vs placebo for olopatadine, 0.6% and 0.4%, in rTNSS [75] $P<0.001$ vs placebo in rTNSS [99]	$P=0.8402$ propionate (noninferior) vs fluticasone in rTOSS [54] Ocular outcomes not reported [55] Ocular outcomes not reported [98] $P\leq 0.05$ vs placebo for olopatadine, 0.6%, in symptoms of itchy eyes and watery eyes $P=NS$ vs placebo for olopatadine, 0.4%, in symptoms of itchy eyes and watery eyes [75] $P\leq 0.009$ vs placebo in symptoms of itchy eyes and watery eyes [99]	
Azelastine	Ib	Ib	Metaanalysis RCTs	Azelastine was efficacious in the treatment of allergic rhinitis in clinical studies. No specific nasal or ocular symptoms were evaluated in the global analysis of efficacy [100]. Significant improvement vs placebo in rhinorrhea ($P=0.03$), but not in congestion, sneezing, or nasal pruritus [101] No significant differences between azelastine and oral cetirizine in any nasal symptoms (rhinorrhea, stuffiness, pruritus, sneezing) [102] Significant ($P\leq 0.05$) improvement with 2 sprays/nostril twice daily (1.04 mg/d) vs placebo in nasal itch. No significant improvements with 2 sprays twice daily in sneeze, stuffiness, runny nose, number of nose blows, or postnasal drip No significant improvement with 2 sprays/nostril daily (0.52 mg/d) vs placebo in nasal itch, sneeze, stuffiness, runny nose, number of nose blows, or postnasal drip [103] Significant ($P\leq 0.05$) improvement with 2 sprays/nostril twice daily (1.1 mg/d) vs placebo in sneeze, stuffy nose, runny nose, and itchy nose No significant improvement with 2 sprays/nostril daily (0.55 mg/d) vs placebo in sneeze, stuffy nose, runny nose, or itchy nose [104]	No significant improvement vs placebo in ocular pruritus [101] No significant differences between azelastine and oral cetirizine in any ocular symptoms (lacrimation, redness, irritation, swelling) [102] Significant ($P\leq 0.05$) improvement with 2 sprays/nostril twice daily (1.04 mg/d) vs placebo in watery eyes and itchy eyes/ears/throat/palate No significant improvement with 2 sprays/nostril daily (0.52 mg/d) vs placebo in watery eyes or itchy eyes/ears/throat/palate [103] Significant ($P\leq 0.05$) improvement with 2 sprays/nostril twice daily (1.1 mg/d) vs placebo in watery eyes and itchy eyes/ears/throat/palate No significant improvement with 2 sprays/nostril daily (0.55 mg/d) vs placebo in watery eyes or itchy eyes/ears/throat/palate [104]	
Intranasal mast cell stabilizers			Review RCT	Cromolyn is efficacious in the treatment of nasal allergy symptoms [105]. Effective vs placebo in sneezing ($P=0.01$) and congestion ($P=0.03$) [107]	A single study indicated that cromolyn is efficacious in the treatment of ocular symptoms [105, 106]. No ocular outcomes reported [107]	

Table 2 (continued)

Agent	Strength of evidence		Publication type	Nasal outcomes		Ocular outcomes
	Nasal	Ocular				
Intranasal corticosteroids	Ia	Ia	Metaanalyses	INS significantly superior to topical antihistamines in nasal symptoms [50]	INS equivalent to topical antihistamines in nasal symptoms [50]	
	NA	Ib	Pooled analysis	INS significantly superior to oral antihistamines in reducing nasal blockage, nasal discharge, sneezing, nasal itch, postnasal drip, and total nasal symptoms [51]	INS equivalent to oral antihistamines in reducing ocular symptoms [51]	
				Effects on nasal symptoms not analyzed [80]		
	Ib	Ib	RCTs	$P<0.001$ vs placebo and $P<0.001$ vs fexofenadine in nighttime rTNSS in 2 studies [60•]	$P<0.001$ vs placebo in TOSS [80]	
				$P<0.001$ vs placebo and $P=0.106$ vs fexofenadine in nighttime rTOSS in study 1 $P=0.034$ vs placebo and $P=0.002$ vs fexofenadine in nighttime rTOSS in study 2 [60•] $P=0.001$ vs placebo in rTOSS [108] $P\leq 0.013$ vs placebo in rTOSS [109] $P=0.004$ vs placebo in rTOSS [110] $P<0.00001$ vs placebo in TNSS [111]		
Mometasone furoate	Ia	Ib	Pooled analysis	$P<0.001$ vs placebo in rTNSS [108]	$P=0.001$ vs placebo in TOSS [81]	
			Pooled analyses	$P<0.001$ vs placebo in rTNSS [109]	$P<0.05$ vs placebo in TOSS [112]	
			Post hoc analysis	$P<0.001$ vs placebo in rTNSS [110]	$P=0.02$ vs placebo in TOSS [61•]	
			RCTs	$P<0.00001$ vs placebo in TNSS [111]	$P<0.05$ vs placebo in total eye symptoms [82]	
Triamcinolone	Ia	III		Effects on nasal symptoms not analyzed [81] Effects on nasal symptoms not analyzed [112] $P<0.001$ vs placebo in TNSS [61•] $P<0.05$ vs placebo in nasal stuffiness, nasal discharge, sneezing, and nasal itching [82] Equally efficacious as intranasal beclomethasone in reducing nasal stuffiness, nasal discharge, and nasal itching. Significantly ($P\leq 0.05$) less effective than beclomethasone in reducing sneezing [113] Equivalent to fluticasone propionate in improving TNSS [114] Equivalent to fluticasone propionate in improving TNSS [115] $P=0.001$ vs oral loratadine in TNSS [116]	Equally efficacious as intranasal beclomethasone in reducing total eye symptoms [113] Equivalent to fluticasone propionate in improving ocular itching/tearing/redness [114] Equivalent to fluticasone propionate in improving RQLQ eye symptoms [115] Comparable efficacy to oral loratadine in reducing ocular symptoms [116] Ocular outcomes not reported [117] Ocular outcomes not reported [118] Ocular outcomes not reported [119] $P<0.05$ in RQLQ non-nose/eye symptoms [120] No significant improvement vs placebo in RQLQ eye symptoms [120]	
Ciclesonide	Ib	NA	RCTs	$P\leq 0.01$ vs placebo in rTNSS [117] $P<0.001$ vs placebo in rTNSS [118] $P\leq 0.04$ vs placebo in rTNSS [119] $P<0.001$ vs placebo in rTNSS [120] $P<0.001$ vs placebo in rTNSS [121]	Ocular outcomes not reported [117] Ocular outcomes not reported [118] Ocular outcomes not reported [119] $P<0.05$ in RQLQ non-nose/eye symptoms [120] No significant improvement vs placebo in RQLQ eye symptoms [120]	

Oral medications

Antihistamines (eg, desloratadine, bilastine, fexofenadine, levocetirizine)	Ib	Ib	Literature review	Clinical trial data indicated the efficacy of oral antihistamines in the treatment of nasal allergy symptoms [122].	Clinical trial data indicated the efficacy of oral antihistamines in the treatment of ocular allergy symptoms [122].
			RCTs	$P < 0.05$ for desloratadine vs placebo in total nasal symptoms [123]	$P \leq 0.04$ for desloratadine vs placebo in total non-nasal symptoms [123]
				Effects on nasal symptoms not analyzed [124]	$P < 0.05$ for desloratadine vs placebo in ocular itching, ciliary redness, episcleral redness, chemosis, lid swelling, and tearing [124]
				Bilastine improved NSS significantly vs placebo and similarly to desloratadine [62].	Bilastine improved NNSS significantly vs placebo and similarly to desloratadine [62].
				Bilastine improved NSS significantly vs placebo and similarly to cetirizine [63].	Bilastine improved NNSS significantly vs placebo and similarly to cetirizine [63].
				$P \leq 0.05$ for fexofenadine vs placebo in a composite score of nasal and non-nasal symptoms [125]	$P \leq 0.05$ for fexofenadine vs placebo in a composite score of nasal and non-nasal symptoms [125]
				$P < 0.002$ for levocetirizine vs placebo in sneezing, rhinorrhea, and itchy nose [126]	$P < 0.002$ for levocetirizine vs placebo in itchy eyes [126]

Each agent that has reported during the past 3 years is listed and scored. If no studies in the past 3 years were found, further background searches were performed to provide a comparative score. The scoring system is based on clinical evidence as used in the Joint Task Force Practice Parameters [127, 128].

INS intranasal corticosteroids; *NNSS* non-nasal symptom score; *NS* not significant; *NSS* nasal symptom score; *RCT* randomized controlled trial; *RQLQ* Rhinoconjunctivitis Quality of Life Questionnaire; *rTOSS* reflective total nasal symptom score; *rTOSS* reflective total ocular symptom score; *TNNS* total non-nasal symptom score; *TNSS* total nasal symptom score; *TOSS* total ocular symptom score

nasal symptom score with each agent as compared with placebo [55]. It remains to be seen whether the mild somnolence reported with the use of high-dose intranasal azelastine [56] will emerge with greater clinical experience in using other new-generation intranasal antihistamines. A new sucralose-containing formulation of azelastine demonstrated improvement in nasal allergy symptoms comparable to that of the original azelastine formulation in a naturalistic 14-day study. Effects on ocular symptoms were not reported, however [57•].

Another study with the primary objective of determining onset of action used the ocular challenge method to compare a topical ocular antihistamine/mast cell stabilizer (olopatadine) and the INS fluticasone furoate in patients with ARC within the short time frame of 20 min, although INS onset of action ranges from 12 h to several days [58]. As would be expected from the route of administration, olopatadine-treated patients experienced significantly greater relief of ocular symptoms than fluticasone furoate-treated patients following challenge. Changes in nasal symptoms were not reported [59].

Two similarly designed, randomized, double-blind studies (study 1, $n=936$; study 2, $n=680$) compared intranasal fluticasone furoate (110 µg), oral fexofenadine (180 mg), and placebo once daily in the treatment of nocturnal SAR symptoms in real world conditions. Ocular symptoms were assessed as secondary outcomes. In study 1, fluticasone-treated patients experienced significantly greater mean improvement from baseline in nighttime reflective total ocular symptom scores (TOSS) and predose instantaneous TOSS compared with placebo-treated patients. In study 2, fluticasone furoate-treated patients experienced significantly greater mean improvement in nighttime reflective TOSS and predose instantaneous TOSS compared with those treated with fexofenadine or placebo [60•].

Mometasone furoate, 200 µg once daily, was compared with placebo in a post hoc analysis of data from adolescent SAR patients ($n=168$; ages, 12–17 years) enrolled in a randomized, double-blind, 15-day, real world study. As minimum ocular severity score was not an entry criterion, some study participants had essentially no ocular symptoms (ie, a TOSS score close to 0) prior to treatment. Thus, to study ocular effects, a subgroup analysis was performed for patients who had mild to severe ocular symptoms at baseline (ie, a TOSS score ≥ 4 ; $n=109$). In this group, TOSS score improved significantly more with mometasone (−29.4%) compared with placebo (−16%; $P=0.02$) [61•].

Antihistamines: Bilastine and Bepotastine

Recent clinical data suggest an ocular and nasal allergy efficacy profile for bilastine, a new oral antihistamine, similar to that of established oral antihistamines, including

desloratadine [62] and cetirizine [63]. In addition, another oral antihistamine agent, bepotastine, was shown to be effective and well-tolerated in patients with Japanese cedar allergen-induced symptoms in an exposure chamber and was recently approved in the United States in an ophthalmic formulation with a very similar profile to those of olopatadine and epinastine [64, 65].

Understanding the Ocular Effects of Intranasal Treatments in Allergic Conjunctivitis

Proposed Mechanisms of Action

Data from the past year confirm that INS improve ocular allergy symptoms, raising the question of how treatment administered at one site can affect allergic symptoms at another. Corticosteroids are known to decrease allergic inflammation via multiple pathways, including reduction in levels of proinflammatory mediators (eg, leukotrienes, prostaglandins), inhibition of cytokine release, and suppression of the number and migration of inflammatory cells [66]. The present question is why INS therapy exerts benefits away from the area of local application, thus improving ocular symptoms.

Reflux of intranasally administered steroids through the nasolacrimal duct is a possible explanation, although no evidence for such an effect exists [29, 38]. However, the reduction in inflammation and restoration of duct patency by INS could improve ocular symptoms.

Systemic absorption of INS seems an unlikely explanation for effects on the eye. Newer INS have a very low systemic absorption; the absolute bioavailability of mometasone furoate is 0.46%; of fluticasone propionate, 0.42% [67]; and of fluticasone furoate, 0.5% [68]. Adverse ocular effects seen with the use of oral corticosteroids, such as cataract formation and elevated intraocular pressure [67], are, accordingly, not increased in patients who use intranasal fluticasone propionate, mometasone furoate, or fluticasone furoate [69–74]. The lack of such ocular adverse effects also weighs against the idea that INS can pass upward to the eye via the nasolacrimal duct.

Systemic exposure has been suggested as an explanation for the effects of intranasal antihistamines on ocular allergy symptoms [75]. This is a more plausible mechanism for intranasal antihistamines than for INS, as intranasal antihistamines are associated with greater systemic bioavailability (levocabastine, 60–80%; azelastine, 40%) than the newer INS [76]. There seems to be little published research on potential mechanisms of action of intranasal antihistamines in ocular allergy.

Suppression of inflammatory mediators linked to the naso-ocular reflex may provide a mechanism for the ocular

efficacy of antiallergy medications administered intranasally. As discussed previously, bilateral ocular tearing and itching were induced by unilateral nasal allergen challenge. Pretreatment with intranasal azelastine at the challenge site blocked the occurrence of these symptoms, suggesting a central role for histamine in the naso-ocular reflex [37, 44]. Recent data suggest that INS also improve ocular symptoms, at least in part by inhibiting the naso-ocular reflex. These agents have been shown to inhibit allergen-induced release of histamine in the nasal mucosa [77]. In a recent study, nasal and ocular symptoms were provoked with a unilateral nasal antigen challenge following pretreatment with intranasal fluticasone furoate. Compared with placebo, fluticasone furoate significantly reduced ocular symptoms (itching and tearing), nasal symptoms, and nasal eosinophil recruitment [45].

INS may also reduce systemic upregulation of inflammatory cells after nasal challenge. By decreasing the available pool of inflammatory cells, INS may impede recruitment of inflammatory cells to the site of local inflammation. In fact, INS have been shown to improve the clinical control of asthma in patients with comorbid asthma and AR [78]. These benefits have been attributed to local inhibition of hemopoietic cytokines, which promote differentiation and upregulation of eosinophils, basophils, and mast cell progenitors [48]. Administration of the oral antihistamine desloratadine to patients with comorbid asthma and SAR reduced the eosinophilia typically seen after nasal allergen provocation [79]. It would be interesting to determine whether local administration of intranasal antihistamines would exert a similar systemic effect on the inflammatory cells as that seen with INS.

Is Efficacy in Ocular Symptoms a Class Effect of INS?

The proposed inflammation-mediated mechanisms of INS efficacy would imply that efficacy in ocular symptoms is shared by all agents in this class, a conclusion supported by extensive clinical study data [80–85]. In a recent systematic review, the authors suggested that differences between individual steroids may be discernable [86], although the detection of true differences would require head-to-head comparative studies.

Rigorously designed ocular allergy trials and direct (head-to-head) comparisons are required to study the impact of different INS in ocular allergy. Ocular allergy symptoms only recently have received substantial attention in clinical trials, and ocular outcome measures are in need of greater refinement. Symptom scoring methods in previous studies have differed substantially, clearly blunting their potential effect, as in some trials, ocular symptoms were bundled in the “non-nasal” symptom score. Entry criteria with regard to ocular symptoms, if used at all, have been divergent in trials of AR patients, and ocular outcomes

have sometimes been analyzed post hoc. Greater agreement on the assessment of ocular allergy symptoms, as well as prospective analyses of ocular outcomes will increase our understanding of the treatment of this condition [87].

Seasonal Versus Perennial Allergy

A recent study of fluticasone furoate nasal spray in adult and adolescent PAR patients indicated significant improvement over placebo in daily reflective and morning predose instantaneous scores for eye itching/burning and eye tearing/watering ($P<0.03$ for each score). Fluticasone furoate was associated with significant improvement compared with placebo in daily reflective eye redness score ($P=0.01$), but not in morning predose instantaneous eye redness score ($P=0.076$) [88].

A meta-analysis of placebo-controlled studies assessed the efficacy of mometasone furoate, 200 µg once daily, in treating ocular symptoms associated with SAR or PAR. Significant improvement over placebo occurred with all ocular symptoms associated with SAR (reductions vs placebo: itching, -0.08 ; redness, -0.09 ; tearing, -0.11 ; $P<0.00001$ for all comparisons). Mometasone furoate was also associated with significant improvement over placebo in all ocular symptoms associated with PAR, although the magnitude of improvement was smaller than in patients with SAR (reductions vs placebo: itching, -0.02 ; $P\leq 0.02$; redness, -0.02 ; $P\leq 0.02$; tearing, -0.04 ; $P\leq 0.00001$) [89]. In other studies of patients with perennial allergy symptoms, fluticasone furoate and mometasone furoate were associated with improvements in nasal, but not ocular, symptoms [90, 91].

One potential explanation for this discrepancy is that the anti-inflammatory effects of therapy may be that ocular symptoms seem to be less intense in PAR than SAR due to the high-intensity exposure to seasonal allergens and the severe SAR symptoms they elicit more than the consistent, low-level allergen exposure and less severe symptoms characteristic of PAR. Also, results from studies of PAR are more difficult to replicate than those of SAR given the greater variation in exposure to perennial compared with seasonal allergens [88].

Do Ophthalmic Allergy Therapies Decrease Nasal Symptoms?

Daily instillation of ophthalmic olopatadine was associated with a reduction in some nasal symptoms in two randomized studies. Patients with a history of AC or rhinoconjunctivitis received olopatadine, 0.2% solution, or placebo for 12 weeks (fall study) or 10 weeks (spring study). In the fall study, patients who received olopatadine reported significantly decreased frequency and severity of sneezing, frequency and severity of itchy nose, and severity of runny nose but no significant decreases in frequency of runny nose, frequency

and severity of stuffy nose, or frequency and severity of postnasal drip. In the spring study, the frequencies of sneezing and runny nose were significantly reduced in olopatadine-treated patients, whereas the frequencies of itchy nose, stuffy nose, and postnasal drip were not [92]. These results are consistent with a profile of antihistamines showing greatest efficacy against early-phase, histamine-mediated symptoms (eg, itching, rhinorrhea) and lesser efficacy in treating late-phase symptoms (eg, congestion).

The ophthalmic antihistamine/mast cell stabilizer ketotifen was evaluated in a randomized, double-blind study against oral desloratadine and a ketotifen–desloratadine combination. Total nasal symptom scores were similar with topical ocular ketotifen monotherapy and oral desloratadine monotherapy following allergen challenge. Allergen challenge was applied to the conjunctiva only; thus, nasal symptoms were secondary to ocular allergen exposure [39]. In a randomized, placebo-controlled study of the efficacy of azelastine eyedrops in decreasing nasal allergy symptoms, patients were exposed to both nasal and conjunctival allergen challenge under conditions designed to mimic a real world setting (the Vienna Challenge Chamber). Azelastine was found to be effective in alleviating ocular itching and redness, but it had no effect on nasal symptoms [93]. A newly approved ophthalmic agent, Bepreve™ 1.5 has also been reported to improve nasal symptoms scores [94].

A likely mechanism of action for ophthalmic allergy therapies in decreasing nasal allergy symptoms is the passage of ocular secretions into the nose through the nasolacrimal duct. Allergens and inflammatory mediators drain from the eye into the nose, triggering nasal symptoms. Thus, ocular allergy treatment would be expected to inhibit nasal symptoms by decreasing the flow of inflammatory mediators into the nose and by enabling downward passage of the drug itself [92]. This mechanism would also explain the limited efficacy of ocular antihistamines in relieving nasal allergy, as the nasolacrimal duct is not the sole route of allergen introduction into the nose in real world conditions, as shown in the Vienna Challenge Chamber study. Rather, direct exposure of the conjunctiva and nasal mucosa occurs.

Discussion

Recent epidemiologic data indicate that nasal and ocular allergies are widespread and may be increasing in prevalence. The disorders often coexist in the same patient and seem to be associated with other inflammatory conditions, such as asthma.

Currently available effective ocular allergy therapies include oral, intranasal, or topical antihistamines and INS. Recent studies support earlier findings suggesting a class effect of INS in the treatment of ocular allergy, with a level of efficacy more than that of oral or intranasal antihistamines.

Topical ocular antihistamines also improve ocular allergy symptoms, with a rapid onset of action, but they have demonstrated modest results for nasal symptoms, which often coexist with ocular symptoms. Importantly, nasal symptoms are usually considered the most troublesome among patients with both disorders. In the United States, 58.8% of patients held this view, compared with 13.6% who found ocular symptoms to be the most problematic [95]. In Europe, 49.8% of allergy patients designated nasal (vs ocular) symptoms as the most troublesome, whereas 19.7% found the reverse to be true [96]. INS have consistently demonstrated efficacy in nasal symptoms and are the recommended first-line treatment [56]. Intranasal antihistamines also alleviate nasal symptoms and exhibit benefits in ocular allergy. A recent study of intranasal olopatadine suggested comparable ocular and nasal outcomes with the INS fluticasone propionate, although interpretation of these data remains uncertain given the large body of evidence supporting the superior nasal effects of INS.

Conclusions

Intranasal therapies that initially demonstrated efficacy in nasal allergy symptoms also have been shown to alleviate symptoms of ocular allergy. Attempts to explain these benefits have focused on possible mechanisms of action of INS, including restoration of nasolacrimal duct patency, suppression of the naso-ocular reflex, and decreased inflammatory cell recruitment. Additional comparative studies of allergy therapies in the treatment of ocular symptoms will increase our knowledge and understanding of pharmacologic mechanisms of action and therapeutic profiles of individual agents. In current clinical practice, the efficacy of INS in both nasal and ocular allergy enables physicians to address a broad range of symptoms with a single therapy. This is a key consideration, as most patients present with both ocular and nasal complaints.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

- Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 2009;30:244–54.
- Bielory L. Allergic diseases of the eye. *Med Clin North Am* 2006;90:129–48.
- Pitt AD, Smith AF, Lindsell L, et al. Economic and quality-of-life impact of seasonal allergic conjunctivitis in Oxfordshire. *Ophthalmic Epidemiol* 2004;11:17–33.
- Buchholz PM, Wlat J, Lorenz D, et al. Patient impact of allergic conjunctivitis as measured by the Eye Allergy Patient Impact Questionnaire (EAPIQ) [poster B438]. Poster presented at the Association for Research in Vision and Ophthalmology. Fort Lauderdale, FL; May 7, 2003.
- Smith AF, Pitt AD, Rodriguez AE, et al. The economic and quality of life impact of seasonal allergic conjunctivitis in a Spanish setting. *Ophthalmic Epidemiol* 2005;12:233–42.
- Uchio E, Kimura R, Migita H, et al. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. *Graefes Arch Clin Exp Ophthalmol* 2008;246:291–6.
- Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S808–814.
- Nathan RA, Meltzer EO, Derebery J, et al. The prevalence of nasal symptoms attributed to allergies in the United States: findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 2008;29:600–608.
- European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687–95.
- Singh K, Bielory L. Epidemiology of ocular allergy symptoms in United States adults (1988–1994) [abstract 34]. Abstract presented at the American College of Allergy, Asthma & Immunology Annual Meeting. Philadelphia, PA; November 9–15, 2006.
- Wüthrich B, Brignoli R, Canevascini M, Gerber M. Epidemiological survey in hay fever patients: symptom prevalence and severity and influence on patient management. *Schweiz Med Wochenschr* 1998;128:139–43.
- Klossek JM, Annesi-Maesano I, Pribil C, Didier A. INSTANT: national survey of allergic rhinitis in a French adult population based-sample. *Presse Med* 2009;38:1220–29.
- Navarro A, Colás C, Antón E, et al. Rhinoconjunctivitis Committee of the SEAIC: epidemiology of allergic rhinitis in allergy consultations in Spain. *J Investig Allergol Clin Immunol* 2009;19(Suppl 2):7–13.
- Axelrod SH, Singh K, Bielory L. Epidemiology of ocular allergy: an NHANES III data review, 1988–1994 [abstract 484]. *J Allergy Clin Immunol* 2009;123:S127.
- Pelikan Z. Seasonal and perennial allergic conjunctivitis: the possible role of nasal allergy. *Clin Experiment Ophthalmol* 2009;37:448–57. *This was an interesting study reflecting that more than 80% of positive nasal provocation with allergens induced an ocular response, thus supporting the concept of the naso-ocular reflex.*
- Ait-Khaled N, Pearce N, Anderson HR, et al. the ISAAC Phase Three Study Group: global map of the prevalence of symptoms of rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. *Allergy* 2009;64:123–48.
- Björkstén B, Clayton T, Ellwood P, et al. The ISAAC Phase III Study Group: Worldwide time trends for symptoms of rhinitis and conjunctivitis: phase III of the International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 2008;19:110–22.
- Fok AO, Wong GW. What have we learned from ISAAC phase III in the Asia-Pacific rim? *Curr Opin Allergy Clin Immunol* 2009;9:116–22.
- Nishima S, Chisaka H, Fujiwara T, et al. Allergy Prevalence Survey Group; West Japan Pediatric Allergy Association:

- surveys on the prevalence of pediatric bronchial asthma in Japan: a comparison between the 1982, 1992, and 2002 surveys conducted in the same region using the same methodology. *Allergol Intern* 2009;58:37–53.
20. Kusunoki T, Morimoto T, Nishikomori R, et al. Changing prevalence and severity of childhood allergic diseases in Kyoto, Japan, from 1996 to 2006. *Allergol Intern* 2009;58:543–8.
 21. de Brito RC, da Silva GA, Motta ME, Brito MC. The association of rhinoconjunctivitis and asthma symptoms in adolescents. *Rev Port Pneumol* 2009;15:613–28.
 22. Bousquet J, Van Cauwenberge P, Khaltaev N; the Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108(5 Suppl):S147–334.
 23. Björkstén B. The hygiene hypothesis: do we still believe in it? *Nestle Nutr Workshop Ser Pediatr Program* 2009;64:11–18; discussion 18–22, 251–257.
 24. Kusel MM, de Klerk N, Holt PG, Sly PD. Antibiotic use in the first year of life and risk of atopic disease in early childhood. *Clin Exp Allergy* 2008;38:1921–28.
 25. Mainardi T, Bielory L, Bielory B. Conserved domains (CDs) present in parasites and allergens. *Ann Allergy Asthma Immunol* 2009;102(Suppl 1):A59.
 26. Cooper PJ. Interactions between helminth parasites and allergy. *Curr Opin Allergy Clin Immunol* 2009;9:29–37.
 27. Wördemann M, Diaz RJ, Heredia LM, et al. Association of atopy, asthma, allergic rhinoconjunctivitis, atopic dermatitis and intestinal helminth infections in Cuban children. *Trop Med Int Health* 2008;13:180–86.
 28. Bager P, Arnved J, Ronborg S, et al. Trichuris suis ova therapy for allergic rhinitis: a randomized, double-blind, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2009 Oct 2 (Epub ahead of print).
 29. Blaiss M. Evolving paradigm in the management of allergic rhinitis-associated ocular symptoms: role of intranasal corticosteroids. *Curr Med Res Opin* 2008;24:821–36.
 30. Butrus S, Portela R. Ocular allergy: diagnosis and treatment. *Ophthalmol Clin North Am* 2005;18:485–92.
 31. Leonardi A, Motterle L, Bortolotti M. Allergy and the eye. *Clin Exp Immunol* 2008;153(Suppl 1):17–21.
 32. Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. *Allergy* 2000;55(Suppl 64):7–16.
 33. Choi SH, Bielory L. Late-phase reaction in ocular allergy. *Curr Opin Allergy Clin Immunol* 2008;8:438–44.
 34. Naclerio RM, Proud D, Togias AG, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;313:65–70.
 35. Bacon AS, Ahluwalia P, Irani AM, et al. Tear and conjunctival changes during the allergen-induced early- and late-phase responses. *J Allergy Clin Immunol* 2000;106:948–54.
 36. Watelet JB, McGill JI, Church DS, Church MK. Allergic rhinitis and conjunctivitis: update on pathophysiology. In *Allergy Frontiers: Clinical Manifestations*. Edited by Pawankar R, Holgate ST, Rosenwasser LJ. Japan: Springer; 2009:1–23.
 37. • Baroody FM, Shenaq D, DeTineo M, et al. Fluticasone furoate nasal spray reduces the nasal-ocular reflex: a mechanism for the efficacy of topical steroids in controlling allergic eye symptoms. *J Allergy Clin Immunol* 2009;123:1342–48. *In this clinical study, intranasal fluticasone furoate decreased nasal and ocular symptoms following a unilateral nasal allergen challenge. The results suggest that INS therapy may improve ocular allergy symptoms in part via suppression of the naso-ocular reflex.*
 38. Spangler DL, Abelson MB, Ober A, Gotnes PJ. Randomized, double-masked comparison of olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. *Clin Ther* 2003;25:2245–67.
 39. Crampton HJ. Comparison of ketotifen fumarate ophthalmic solution alone, desloratadine alone, and their combination for inhibition of the signs and symptoms of seasonal ARC in the conjunctival allergen challenge model: a double-masked, placebo- and active-controlled trial. *Clin Ther* 2003;25:1975–87.
 40. Sanke RF. Pseudonasolacrimal duct obstruction caused by nasal allergy. *Ophthalmic Surg* 1989;20:63–7.
 41. Bernstein DI, Levy AL, Hampel FC, et al. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2004;34:952–7.
 42. Philip G, Baroody FM, Proud D, et al. The human nasal response to capsaicin. *J Allergy Clin Immunol* 1994;94:1035–45.
 43. Zilstorff-Pedersen K. Quantitative measurements of the nasolacrimal reflex. *Arch Otolaryngol* 1965;81:457–62.
 44. Naclerio RM, Pinto J, deTineo M, Baroody FM. Elucidating the mechanism underlying the ocular symptoms associated with allergic rhinitis. *Allergy Asthma Proc* 2008;29:24–8.
 45. Baroody FM, Foster KA, Markaryan A, et al. Nasal ocular reflexes and eye symptoms in patients with allergic rhinitis. *Ann Allergy Asthma Immunol* 2008;100:194–9.
 46. Li J, Saito H, Crawford L, et al. Haemopoietic mechanisms in murine allergic upper and lower airway inflammation. *Immunology* 2005;114:386–96.
 47. Saini S, Bloom DC, Bieneman A, et al. Systemic effects of allergen exposure on blood basophil IL-13 secretion and FcεpsilonRIβ. *J Allergy Clin Immunol* 2004;114:768–74.
 48. Denburg JA, Sehmi R, Saito H, et al. Systemic aspects of allergic disease: bone marrow responses. *J Allergy Clin Immunol* 2000;106(5 Suppl):S242–46.
 49. Naclerio R. Intranasal corticosteroids reduce ocular symptoms associated with allergic rhinitis. *Otolaryngol Head Neck Surg* 2008;38:129–39.
 50. Yáñez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2002;89:479–84.
 51. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998;317:1624–29.
 52. Kaszuba SM, Baroody FM, deTineo M, et al. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. *Arch Intern Med* 2001;161:2581–87.
 53. Condemni J, Schulz R, Lim J. Triamcinolone acetone aqueous nasal spray versus loratadine in seasonal allergic rhinitis: efficacy and quality of life. *Ann Allergy Asthma Immunol* 2000;84:533–8.
 54. Kaliner MA, Storms W, Tilles S, et al. Comparison of olopatadine 0.6% nasal spray versus fluticasone propionate 50 mcg in the treatment of seasonal allergic rhinitis. *Allergy Asthma Proc* 2009;30:255–62.
 55. Shah SR, Nayak A, Ratner P, et al. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. *Clin Ther* 2009;31:99–107.
 56. Bousquet J, Khaltaev N, Cruz AA, et al.; the World Health Organization, GA(2)LEN, AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN, and AllerGen). *Allergy* 2008;63(Suppl 86):8–160.
 57. • Bernstein JA, Prenner B, Ferguson BJ, et al. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. *Am J Rhinol Allergy* 2009;23:512–7. *This was a randomized clinical trial comparing*

- a new sucralose-containing formulation of intranasal azelastine with the original formulation. Improvements in nasal symptoms were comparable between the two formulations.*
58. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. *J Allergy Clin Immunol* 1999;104:150–58.
 59. Rosenwasser LJ, Mahr T, Abelson MB, et al. A comparison of olopatadine 0.2% ophthalmic solution versus fluticasone furoate nasal spray for the treatment of allergic conjunctivitis. *Allergy Asthma Proc* 2008;29:644–53.
 60. Andrews CP, Martin BG, Jacobs RL, et al. Fluticasone furoate nasal spray is more effective than fexofenadine for nighttime symptoms of seasonal allergy. *Allergy Asthma Proc* 2009;30:128–38. *This article reports the results of two similarly designed clinical studies comparing the INS fluticasone furoate and the oral antihistamine fexofenadine as therapies for the nocturnal symptoms of seasonal allergy. Fluticasone furoate demonstrated superiority to fexofenadine and placebo on measures of nasal and ocular symptomatology.*
 61. Anolik R, Pearlman D, Teper A, Gates D. Mometasone furoate improves nasal and ocular symptoms of seasonal allergic rhinitis in adolescents. *Allergy Asthma Proc* 2009;30:406–412. *This was a post hoc analysis of data on adolescents who participated in a prospective study of the INS mometasone furoate in SAR. Mometasone furoate demonstrated superiority to placebo in the treatment of nasal and ocular allergic symptoms.*
 62. Bachert C, Kuna P, Sanquer F, et al.; Bilastine International Working Group. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy* 2009;64:158–65.
 63. Kuna P, Bachert C, Nowacki Z, et al.; the Bilastine International Working Group. Efficacy and safety of bilastine 20 mg compared with cetirizine 10 mg and placebo for the symptomatic treatment of seasonal allergic rhinitis: a randomized, double-blind, parallel-group study. *Clin Exp Allergy* 2009;39:1338–47.
 64. Abelson MB, Torkildsen GL, Williams JL, et al. Time to onset and duration of action of the antihistamine bepotastine besilate ophthalmic solutions 1.0% and 1.5% in allergic conjunctivitis: a phase III, single-center, prospective, randomized, double-masked, placebo-controlled, conjunctival allergen challenge assessment in adults and children. *Clin Ther* 2009;31:1908–21.
 65. Hashiguchi K, Tang H, Fujita T, et al. Bepotastine besilate OD tablets suppress nasal symptoms caused by Japanese cedar pollen exposure in an artificial exposure chamber (OHIO Chamber). *Expert Opin Pharmacother* 2009;10:523–9.
 66. LaForce C. Use of nasal steroids in managing allergic rhinitis. *J Allergy Clin Immunol* 1999;103:S388–94.
 67. Daley-Yates PT, Kunka RL, Yin Y, et al. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. *Eur J Clin Pharmacol* 2004;60:265–8.
 68. Allen A, Down G, Newland A, et al. Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin Ther* 2007;29:1415–20.
 69. Bross-Soriano D, Hanenberg-Milner C, Schimelmitz-Idi J, et al. Effects of three nasal topical steroids in the intraocular pressure compartment. *Otolaryngol Head Neck Surg* 2004;130:187–91.
 70. Banov CH, Woehler TR, LaForce CF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. *Ann Allergy* 1994;73:240–46.
 71. van As A, Bronsky EA, Dockhorn RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate. *J Allergy Clin Immunol* 1993;91:1146–54.
 72. Dibildox J. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. *J Allergy Clin Immunol* 2001;108(1 Suppl):S54–8.
 73. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. *Int J Pediatr Otorhinolaryngol* 2009;73:651–7.
 74. Maspero JF, Rosenblut A, Finn A Jr, et al. Safety and efficacy of fluticasone furoate in pediatric patients with perennial allergic rhinitis. *Otolaryngol Head Neck Surg* 2008;138:30–37.
 75. Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2005;95:600–606.
 76. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Safety* 2003;26:863–93.
 77. Pipkorn U, Proud D, Lichtenstein LM, et al. Inhibition of mediator release in allergic rhinitis by pre-treatment with topical glucocorticosteroids. *N Engl J Med* 1987;316:1506–510.
 78. Stelmach R, do Patrocinio M, Nunes M, et al. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest* 2005;128:3140–47.
 79. Reinartz SM, Overbeek SE, KleinJan A, et al. Desloratadine reduces systemic allergic inflammation following nasal provocation in allergic rhinitis and asthma patients. *Allergy* 2005;60:1301–307.
 80. DeWester J, Philpot EE, Westlund RE, et al. The efficacy of intranasal fluticasone propionate in the relief of ocular symptoms associated with seasonal allergic rhinitis. *Allergy Asthma Proc* 2003;24:331–7.
 81. Bielory L. Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal corticosteroid mometasone furoate. *Ann Allergy Asthma Immunol* 2008;100:272–9.
 82. Settupane G, Korenblat PE, Winder J, et al. Triamcinolone acetonide aqueous nasal spray in patients with seasonal ragweed allergic rhinitis: a placebo-controlled, double-blind study. *Clin Ther* 1995;17:252–63.
 83. Tinkelman D, Falliers C, Gross G, et al. Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis. *Ann Allergy* 1990;64:234–40.
 84. Ciprandi G, Canonica WG, Grosclaude M, et al. Effects of budesonide and fluticasone propionate in a placebo-controlled study on symptoms and quality of life in seasonal allergic rhinitis. *Allergy* 2002;57:586–91.
 85. Scadding GK, Keith PK. Fluticasone furoate nasal spray consistently and significantly improves both the nasal and ocular symptoms of seasonal allergic rhinitis: a review of the clinical data. *Expert Opin Pharmacother* 2008;9:2707–715.
 86. Keith PK, Scadding GK. Are intranasal corticosteroids all equally consistent in managing ocular symptoms of seasonal allergic rhinitis? *Curr Med Res Opin* 2009;258:2021–41.
 87. Katelaris CH, Bielory L. Evidence-based study design in ocular allergy trials. *Curr Opin Allergy Clin Immunol* 2008;8:484–8.
 88. Vasar M, Houle PA, Douglass JA, et al. Fluticasone furoate nasal spray: effective monotherapy for symptoms of perennial allergic rhinitis in adults/adolescents. *Allergy Asthma Proc* 2008;29:313–21.
 89. Bielory L. A meta-analysis of the impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis [poster P511]. Poster presented at the 2009 American Academy of Allergy, Asthma & Immunology Annual Meeting. Washington, DC; March 13–17, 2009.
 90. Nathan RA, Berger W, Yang W, et al. Effect of once-daily fluticasone furoate nasal spray on nasal symptoms in adults and adolescents with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2008;100:497–505.
 91. Mandl M, Nolop K, Lutsky BN; the 194-079 Study Group. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. *Ann Allergy Asthma Immunol* 1997;79:370–78.

92. Abelson MB, Gomes PJ, Vogelsson CT, et al. Effects of a new formulation of olopatadine ophthalmic solution on nasal symptoms relative to placebo in two studies involving subjects with allergic conjunctivitis or rhinoconjunctivitis. *Curr Med Res Opin* 2005;21:683–91.
93. Horak F, Berger UE, Menapace R, et al. Dose-dependent protection by azelastine eye drops against pollen-induced allergic conjunctivitis. a double-blind, placebo-controlled study. *Arzneimittelforschung* 1998;48:379–84.
94. Gow JA, Williams JI, McNamara TR, Gomes PJ, Abelson MB. Bepreve™ 1.5% Reduces nasal congestion for at least 16 hours: an analysis of integrated data from two phase 3 conjunctival allergen challenge (CAC) clinical trials. *J Allergy Clin Immunol* 2010;125(2):AB38.
95. Schatz M. A survey of the burden of allergic rhinitis in the USA. *Allergy* 2007;62(Suppl 85):9–16.
96. Canonica GW, Bousquet J, Mullol J, et al. A survey of the burden of allergic rhinitis in Europe. *Allergy* 2007;62(Suppl 85):17–25.
97. Calderon MA, Alves B, Jacobson M, et al. Allergen injection immunotherapy for seasonal allergic rhinitis. *Cochrane Database Syst Rev* 2007;1:CD001936.
98. Patel P, Roland PS, Marple BF, et al. An assessment of the onset and duration of action of olopatadine nasal spray. *Otolaryngol Head Neck Surg* 2007;137:918–24.
99. Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. *Ann Allergy Asthma Immunol* 2005;95:474–9.
100. Lee TA, Pickard S. Meta-analysis of azelastine nasal spray for the treatment of allergic rhinitis. *Pharmacotherapy* 2007;27:852–9.
101. Berlin JM, Golden SJ, Teets S, et al. Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis. *J Am Osteopath Assoc* 2000;100(7 Suppl):S8–13.
102. Charpin D, Godard P, Garay RP, et al. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. *Eur Arch Otorhinolaryngol* 1995;252:455–8.
103. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. *Ann Allergy Asthma Immunol* 1996;76:181–8.
104. Storms WW, Pearlman DS, Chervinsky P, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. *Ear Nose Throat J* 1994;73:382–94.
105. Ratner PH, Ehrlich PM, Fineman SM, et al. Use of intranasal cromolyn sodium for allergic rhinitis. *Mayo Clin Proc* 2002;77:350–54.
106. Handelman NI, Friday GA, Schwartz HJ, et al. Cromolyn sodium nasal solution in the prophylactic treatment of pollen-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 1977;59:237–42.
107. Meltzer EO; for the NasalCrom Study Group. Efficacy and patient satisfaction in the treatment of seasonal allergic rhinitis: a placebo-controlled study. *Clin Ther* 2002;24:942–52.
108. Fokkens WJ, Jogi R, Reinartz S, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. *Allergy* 2007;62:1078–84.
109. Martin BG, Ratner PH, Hampel FC, et al. Optimal dose selection of fluticasone furoate nasal spray for the treatment of seasonal allergic rhinitis in adults and adolescents. *Allergy Asthma Proc* 2007;28:216–25.
110. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: a single treatment option for the symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007;119:1430–37.
111. Penagos M, Compalati E, Tarantini F, et al. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. *Allergy* 2008;63:1280–91.
112. Schenkel E, LaForce C, Gates D. Mometasone furoate nasal spray in seasonal allergic rhinitis: effective in relieving ocular symptoms. *Allergy Clin Immunol Int J World Allergy Org* 2007;19:50–53.
113. Lumry W, Hampel F, LaForce C, et al. A comparison of once-daily triamcinolone acetonide aqueous and twice-daily beclomethasone dipropionate. *Allergy Asthma Proc* 2003;24:203–210.
114. Gross G, Jacobs RL, Woodworth TH, et al. Comparative efficacy, safety, and effect on quality of life of triamcinolone acetonide and fluticasone propionate aqueous nasal sprays in patients with fall seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2002;89:56–62.
115. Berger WE, Kaiser H, Gawchik SM, et al. Triamcinolone acetonide aqueous nasal spray and fluticasone propionate are equally effective for relief of nasal symptoms in patients with seasonal allergic rhinitis. *Otolaryngol Head Neck Surg* 2003;129:16–23.
116. Schoenwetter W, Lim J. Comparison of intranasal triamcinolone acetonide with oral loratadine for the treatment of patients with seasonal allergic rhinitis. *Clin Ther* 1995;17:479–92.
117. LaForce C, van Bavel J, Meltzer EO, Wingertzahn MA. Efficacy and safety of ciclesonide hydrofluoroalkane nasal aerosol once daily for the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2009;103:166–73.
118. Chervinsky P, Kunjibettu S, Miller DL, et al. Long-term safety and efficacy of intranasal ciclesonide in adult and adolescent patients with perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2007;99:69–76.
119. Ratner PH, Wingertzahn MA, van Bavel JH, et al. Effectiveness of ciclesonide nasal spray in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;97:657–63.
120. Meltzer EO, Kunjibettu S, Hall N, et al. Efficacy and safety of ciclesonide, 200 microg once daily, for the treatment of perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2007;98:175–81.
121. Ratner PH, Wingertzahn MA, van Bavel JH, et al. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;118:1142–48.
122. Morgan MM, Khan DA, Nathan RA. Treatment for allergic rhinitis and chronic idiopathic urticaria: focus on oral antihistamines. *Ann Pharmacother* 2005;39:2056–64.
123. Meltzer EO, Prenner BM, Nayak A; Desloratadine Study Group. Efficacy and tolerability of once-daily 5 mg desloratadine, an H1-receptor antagonist, in patients with seasonal allergic rhinitis: assessment during the spring and fall allergy seasons. *Clin Drug Invest* 2001;21:25–32.
124. Goodhue K, Depelteau D, Welch D, et al. Evaluation of the anti-allergic and anti-inflammatory effects of multiple doses of desloratadine on conjunctival allergen challenge-induced ocular signs and symptoms [poster]. Poster presented at the 2006 Association for Research in Vision and Ophthalmology Annual Meeting. Fort Lauderdale, FL; April 30–May 4, 2006.
125. Casale TB, Andrade C, Qu R. Safety and efficacy of once-daily fexofenadine HCl in the treatment of autumn seasonal allergic rhinitis. *Allergy Asthma Proc* 1999;20:193–8.
126. Leynadier F, Mees K, Arendt C, Pinelli ME. Efficacy and safety of levocetirizine in seasonal allergic rhinitis. *Acta Otorhinolaryngol Belg* 2001;55:305–12.
127. Joint Task Force on Practice Parameters. Attaining optimal asthma control: a practice parameter. *J Allergy Clin Immunol* 2005;116:S3–11.
128. Wallace DV, Dykewicz MS. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol* 2008;122:S1–84.