

Should Intranasal Corticosteroids Be Used for the Treatment of Ocular Symptoms of Allergic Rhinoconjunctivitis? A Review of Their Efficacy and Safety Profile

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Key Words

Allergic rhinitis • Cataract • Corticosteroids • Fluticasone furoate • Glaucoma • Intranasal corticosteroids • Intraocular pressure • Nasal spray • Ocular allergy • Ophthalmic safety profile

Abstract

Allergic rhinoconjunctivitis (ARC) presents as nasal symptoms, eye watering and additional signs of ocular allergy (e.g. itchy/burning eyes). Intranasal corticosteroids (INSs) are the most effective treatment for the nasal symptoms of seasonal allergic rhinitis (SAR; based on 4 meta-analyses) and are considered first-line therapy when nasal congestion forms a substantial component of the patient's rhinitis symptoms. Clinical trial evidence shows that INSs also provide some relief from ocular symptoms of SAR and seasonal ARC in adults. INSs probably alleviate eye watering, the main ocular symptom of SAR, by relieving nasal congestion. Other ocular symptoms also improve with INSs. The mechanism for this effect is unknown, but might relate to naso-ocular reflex reduction. There are limited data on ocular safety with INSs. However, the literature supports the use of INSs over several months as there appears to be no considerable increase in the risk of ocular hypertension or glaucoma.

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Introduction

Allergic rhinitis (AR) is highly prevalent, affecting approximately 500 million people worldwide [1]. AR presents as nasal symptoms (congestion, sneezing, itching and rhinorrhea) and eye watering; allergic rhinoconjunctivitis (ARC) presents with additional signs of ocular allergy (e.g. itchy/burning eyes) [2]. Seasonal and perennial allergic nasal symptoms often co-exist with allergic conjunctivitis (AC) [3, 4]. Most (71.4%) patients with AR experience both nasal and ocular symptoms of either AR or ARC, with itchy/red eyes considered to be a bothersome symptom [5]. However, physicians tend to underestimate the prevalence of ocular symptoms compared with patients (37 vs. 57%, respectively) and overestimate nasal symptoms (86 vs. 67%, respectively) [5, 6]. These data suggest that physicians may be more inclined to prescribe treatments that target nasal rather than ocular symptoms.

However, ocular symptoms are associated with reduced quality of life for patients [7–13], as well as substantial economic costs [14]. Indeed, data from a recent observational cross-sectional study in France, Germany, Italy and Spain, which included 1,009 patient records, showed that in patients suffering from nasal symptoms, the presence of ocular symptoms reduced quality of life and work productivity, and increased healthcare resource utilization [15]. Based on this evidence, the relief of ocular symptoms remains a key unmet need [2, 5, 15].

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A number of treatment options are currently available for the management of AR. The Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines, which are used globally to inform the treatment of patients with AR, have recently been updated and are the only guidelines to have been developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [1]. The guidelines include recommendations for the management of AR, covering the potential use of oral and topical pharmacologic treatments, allergen-specific immunotherapy, as well as complementary and alternative therapies (which were not recommended by the panel for the treatment of AR).

Intranasal corticosteroids (INs) were suggested by the ARIA guidelines for the treatment of adults and children with AR, in preference to oral H₁-antihistamines were the disease was more than mild and intermittent (based on the efficacy of INs) [1]. Subcutaneous, sublingual or local nasal allergen-specific immunotherapies were suggested as treatments for adults or children with AR without concomitant asthma, depending on whether the AR was caused by pollen or house dust mites [1].

The ARIA guidelines suggested intraocular H₁-antihistamines or intraocular chromones could be used for patients with AR and symptoms of conjunctivitis (on the basis of low- or very-low-quality evidence, respectively, as assessed by the GRADE approach). However, the guidelines did not specifically address whether INs or oral antihistamines have a role in treating the ocular symptoms of AR and ARC [1]. A systematic review, which supported the use of INs over oral antihistamines as first-line treatment for AR, showed that INs were as effective as oral antihistamines in reducing the ocular symptoms of AR, although the results varied considerably between different studies [16, 17]. Evidence obtained more recently increasingly suggests that INs may be effective in alleviating ocular symptoms (e.g. eye watering) [18–35].

In light of the potential for increased use of INs to alleviate ocular symptoms of AR and ARC, this review examines how INs achieve their effects on the eyes, describes their safety profiles, and considers whether INs should be used for the treatment of the ocular symptoms of AR.

Why Do Ocular Symptoms Occur?

Nasal symptoms of AR are initiated by an IgE-mediated hypersensitivity reaction following direct exposure of the nasal mucosal membranes to allergen(s) [36]. Similarly, seasonal allergic rhinoconjunctivitis (SAC) and pe-

rennial AC (PAC) follow hypersensitivity reactions due to direct allergen exposure in the eye [4, 37]. During the early phase of this response, the release of inflammatory mediators (histamine, prostaglandins, leukotrienes, tryptase and cytokines) is triggered by allergen binding to IgE on conjunctival mast cells. Histamine is primarily responsible for causing itching, redness and swelling, whereas prostaglandins and leukotrienes increase mucus secretion and vascular permeability [4, 37, 38].

During the early phase, neutrophils concentrate in conjunctival scrapings or tears [39]. Eosinophils are recruited during the late phase, within 6–10 h after allergen exposure, followed by lymphocytes and monocytes for up to 24 h. A diagnosis of AC is strongly supported by the presence of eosinophils in the conjunctival scrapings, and eosinophils are one of the predominant cell types associated with red eye in AC. Eye redness and the sensation of foreign body in the eye, along with itching and tearing, can persist long after allergen exposure [4, 37, 39, 40].

In addition, various studies have suggested a naso-ocular neurogenic reflex mediated by inflammatory mediators, such as histamine [37, 40–42]. In a placebo-controlled crossover study involving 20 patients with seasonal AR (SAR), an extra-seasonal challenge with grass or ragweed in one nostril induced the release of histamine at the site of the challenge, followed by an increase in nasal vascular permeability and a bilateral increase in itchy eye symptoms and lacrimation. Intranasal application of H₁-antihistamine inhibited both nasal and ocular symptoms [41]. Similarly, nasal provocation with grass pollen extra-seasonally in patients with allergies induced conjunctival inflammation and eye watering in a recent study. Substance P and histamine were detected in the tear fluid obtained from 9/11 patients included in the study and were correlated with the scores for ocular pruritus (15 min after provocation) and lacrimation (24 h after provocation), respectively [43].

Taken together, these studies support the hypothesis that histamine produced locally at the site of allergen provocation may initiate a reflex by irritating sensory nerves, producing a signal that travels to and stimulates the midbrain, activating parasympathetic nerves inducing rhinorrhea and nasal congestion plus tearing and watering of the eye via neurotransmitter release [42].

The relative contributions of direct allergen contact and naso-ocular reflex to eye symptoms are unknown.

INs: Effect on Ocular Symptoms

The favorable effect of INs on ocular symptoms [44] was supported by recent studies which included treat-

ment with INs agents: mometasone furoate (MF) [18–21], fluticasone furoate (FF) [22–28], fluticasone propionate (FP) [29, 30], budesonide [31], and (to some degree) triamcinolone acetonide (TA) [32] and beclomethasone dipropionate (BDP) aqueous nasal spray [33, 34]. However, the effects of INs on ocular symptoms were inconsistent across some separate studies [37, 40].

A comprehensive assessment of all available data in the public domain (including government- and regulatory institution-registered trials) was performed to determine the consistency of INs in treating the ocular symptoms of AR [45]. This review examined 35 randomized, double-blind, placebo-controlled clinical trials that investigated the effects of BDP, budesonide, ciclesonide, flunisolide, FF nasal spray (FFNS), FP, MF or TA in patients with SAR [45]. Studies had a ≥ 2 -week duration; patients were ≥ 6 years of age (the majority were ≥ 12 years of age). All studies assessed ocular symptom scores and non-nasal symptom (eye itching, eye tearing, eye redness, and ear/palate itching) scores – either as a primary/secondary endpoint or as a component of the total symptom score. Overall, approximately half of the trials were inconclusive or suggested that INs may have no efficacy at improving ocular symptoms in patients with SAR (BDP: 1/2 trials, budesonide: 3/6 trials, ciclesonide: 1/1 trial, FFNS: 0/6 trials, FP: 4/10 trials, MF: 8/11 trials and TA: 1/2 trials); indeed, conflicting, inconsistent or negative effects were observed with most INs examined (except FFNS) as part of this review.

However, these findings differed from 2 pooled analyses, and, more recently, a meta-analysis of 10 randomized placebo-controlled trials, in which MF showed a reliable positive effect on ocular symptoms, including tearing, itching and redness [18, 19, 21]. FFNS provided consistent positive effects on the ocular symptoms of SAR, compared with placebo, across the 6 prospective trials [22–28, 45]. These effects were consistent across different allergy seasons and geographic locations, and were considered to be robust owing to the consistent use of ocular symptom scores to determine ocular efficacy [45]. The consistent efficacy of FFNS in relieving the ocular symptoms in patients with AR was further confirmed by a systematic review of 16 trials and an integrated analysis of 4 randomized placebo-controlled trials in patients with SAR [35, 46].

How Do INs Alleviate Ocular Symptoms?

In patients with SAR, INs inhibit both early- and late-phase allergic reactions, and relieve nasal symptoms. The mechanism by which INs alleviate the ocular symptoms

of SAR is probably partly linked to relief of nasal congestion [37, 40].

Theoretically, one mechanism could involve systemic absorption of INs leading to a direct anti-inflammatory effect within the eye. Corticosteroids (CSs) have potent anti-inflammatory effects, but systemic absorption of INs (with high binding affinities and low bioavailability) is below the level expected to produce localized ocular effects. Therefore, it is unlikely that INs act systemically, but they could have indirect systemic effects that reduce inflammatory cells in other tissues, including the eyes [40].

Several potential mechanisms have been proposed:

- (1) INs could enter the eye via the nasolacrimal duct and have a direct anti-inflammatory effect on the conjunctiva. This is considered unlikely owing to the low prevalence of steroidal side effects [such as raised intraocular pressure (IOP), glaucoma, and cataracts] associated with INs [40]. Furthermore, the nasolacrimal duct has valves preventing fluid movement from the nose to the eye [40].
- (2) INs could reduce inflammation at the base of the nasolacrimal duct, improving drainage and reducing exposure of the conjunctiva to allergens and inflammatory mediators. This mechanism is considered unlikely because duct patency is maintained in patients with a symptomatic allergic response after ocular challenge [40].
- (3) By decreasing nasal inflammation, INs may modulate or normalize the excess stimulation of reflex neural activity that occurs during allergic reactions and reduce ocular symptoms [40].

Indeed, an intranasally applied H_1 -receptor antagonist (azelastine) blocked both nasal and ocular symptoms suggesting that the naso-ocular reflex was augmented by allergic inflammation. This indicates that INs treatment could reduce nasal inflammation and decrease mediator release within the nose, and so reduce the naso-ocular neurogenic reflex believed to be partly responsible for the ocular symptoms of AR [41, 47–49]. This was investigated in a study of 17 patients with SAR who received nasal allergen challenge (for 3 consecutive days) after undergoing 1 week of treatment with FFNS or placebo [47]. Patients given placebo experienced priming of sneezing, nasoset secretory reflex and an increase in ocular symptoms. In contrast, treatment with FFNS inhibited all of the allergen-induced responses and the ocular symptoms. These findings confirmed the presence of a naso-ocular reflex contributing to ocular symptoms.

INSS: Ocular Safety Profile

Relatively few adverse reactions have been observed in patients on INSS during years of extensive use [50–53]. The most common local side effects include dry nose, crusting and bleeding. There has been little evidence for systemic effects with INSS. However, recently the Pharmacovigilance Working Party of the European Medicines Agency reviewed the risk of systemic adverse events (AEs) associated with inhaled or intranasal CSs and concluded that there is a risk of psychiatric and behavioural reactions with the use of these agents [54]. In addition, there are concerns that these agents could compromise ocular safety, particularly during long-term use.

Ocular safety is assessed by examining the lens of the eye for cataract development and measuring IOP. A cataract is an opacity in the intra-ocular lens of the eye and can reduce vision. When IOP is consistently raised above the normal level of up to 21 mm Hg, it denotes ocular hypertension (OHT) [55], which can progress to glaucoma if the pressure remains elevated. Glaucoma occurs in this setting when the raised IOP causes damage to the optic nerve and changes occur in the visual field as a consequence of the neuronal damage.

Concerns around the ocular safety of INSS are based on the safety profile of oral and inhaled CSs. AEs, such as an increased risk of cataract development and raised IOP/glaucoma, are associated with long-term oral CSs, and have been reported with inhaled CSs [36, 56–64] and with steroids administered via eye drops [60]. Indeed, the summary of product characteristics for some INSS warn of the risk of glaucoma and/or cataract development and recommend close monitoring of patients with a change in vision or with a history of increased intra-ocular pressure, glaucoma and/or cataracts [65]. The type of cataract caused by steroids is the posterior subcapsular cataract. It is often present in the visual axis and can have a marked effect on vision; treatment involves removal of the lens and replacement with a clear plastic lens.

Ocular AEs are generally related to the dose and duration of treatment [56–64], although with steroid eye drops the IOP rise can occur rapidly in some people ('steroid responders'). Increased IOP is believed to involve an alteration in the resistance to aqueous humor outflow. IOP also shows diurnal variation and certain drugs (alcohol and caffeine) can cause transient IOP changes [55], although these changes are not indicative of a problem. When oral or inhaled CSs are the cause of high IOP, both eyes are usually affected and CS treatment is stopped, if possible. Alternatively, treatments that lower IOP are provided – this often necessitates several different types of

drops (e.g. β -blockers, prostaglandins, carbonic anhydrase inhibitors or α_2 -selective adrenergic agonists). Progression of optic nerve changes and increasing visual field loss (despite these drops) would be an indication for considering surgical treatment [55].

While oral or inhaled CSs are associated with increased risk of ocular AEs, the ocular safety risk appears to be dependent on the dose of CS and route of administration [66]. The published data currently available for INSS indicate that they do not appear to increase the incidence of ocular conditions, including OHT, glaucoma and cataracts, in patients with rhinitis (tables 1, 2) [50, 63, 67–75].

No cataracts or significant changes in IOP were observed in adolescent patients with perennial AR (PAR) treated with MF nasal spray (MFNS) over 1 year. Similarly, FFNS was well tolerated, with no clinically significant differences in ophthalmic parameters compared with placebo over 1 year (tables 1, 2). Some reports indicate an increased risk of developing ocular conditions with INSS in 'at-risk' individuals (patients with glaucoma or OHT) [67]; however, this is not corroborated by other studies (table 1) [63]. Taken together, study data showed that ocular AEs with INSS are rare (tables 1, 2).

A retrospective examination of 286,078 patient records in the UK General Practice Research Database has shown that the incidence rate of cataract among INSS users was similar to the rate among non-users of CSs (1/1,000 person years), whereas oral CSs users were at increased risk of cataract (incidence rate 2.2/1,000 person years; table 2) [74]. A recent meta-analysis (4 studies: 46,638 cases and 146,378 controls) showed that the risk of cataracts also increased in patients treated with inhaled CS; the risk increased by approximately 25% with each dose increase (1,000 $\mu\text{g/day}$) of inhaled CS (BDP or equivalent) [76]. The increase might partly be due to systemic absorption of BDP, which is readily absorbed from the lungs [77]. In contrast, while some INSS do have high bioavailability, the newer compounds such as FF, MF and FP have very low absolute bioavailability (<1%), which may explain why the occurrence of ocular AEs with INSS is rare [49, 53, 78–80]. Of note, patients included in the 4 studies appeared to be from the same databases, although the selection criteria were possibly different [61–64]. Therefore, the studies might not provide fully independent estimates.

Other AEs that may occur with CS use include central serous retinopathy and herpes simplex (HS) corneal infection (HS keratitis). Central serous retinopathy, a condition characterized by monofocal or multifocal serous retinal detachments, causes blurring of vision but usu-

Table 1. Studies showing no increased incidence of OHT/glaucoma with INSs

Study	Study population		Treatment	Outcome
	patients, n	condition/population		
Bui et al. [67]	12 (adults)	glaucoma/OHT	FP, budenoside, TA, MF (16 months)	reduction in IOP following INS discontinuation (after discontinuation, many patients met their target IOP and avoided/delayed additional glaucoma therapy)
Garbe et al. [63]	48,118 (≥66 years of age)	glaucoma/OHT (new diagnosis of borderline glaucoma/OHT); vs. controls (no cases with ophthalmologist visits)	INSs or ICSs (≥3 months)	INSs/ICSs: no increase in risk of OHT/open-angle glaucoma ICSs (high dose: 1,600 mg/day): increased risk of OHT/open-angle glaucoma
Spiliotopoulos et al. [68]	54	AR	INSs (27–35 days)	no evidence for IOP increase
Bernstein [69]	490 (≥12 years of age)	PAR ≥2 years	MFNS, BDP, placebo (12 weeks)	no significant changes in IOP from baseline with MFNS vs. placebo
Ozturk et al. [70]	26	patients who had undergone endoscopic sinus surgery	budesonide, BDP 100 µg b.d. (≥3 months)	no evidence of OHT
Bross-Soriano et al. [71]	360	rhinitis	FP, BDP, MF (1 year)	no significant increase in IOP
Bernstein [69]	293 (≥12 years of age)	PAR ≥2 years	MFNS 200 or 100–400 µg o.d. (1 year)	no clinically significant change from baseline in IOP
Rosenblut et al. [50]	806 (≥12 years of age)	PAR ≥2 years	FFNS (1 year)	similar mean changes from baseline in IOP vs. with placebo; elevated IOP (≥21 mm Hg) was observed in 12 patients receiving FFNS, but glaucoma was not detected
Chervinsky et al. [72]	663 (≥12 years of age)	PAR	ciclesonide 200 µg or placebo (1 year)	no clinically relevant differences in IOP with ciclesonide 200 µg vs. placebo
Ratner et al. [73]	255 (6–11 years of age)	PAR ≥1 year	MF (1 year)	no significant change in IOP

b.d. = Twice daily; BDP = beclomethasone dipropionate; FFNS = fluticasone furoate nasal spray; FP = fluticasone propionate; ICSs = inhaled corticosteroids; INSs = intranasal corticosteroids; IOP = intraocular pressure; MF = mometasone furoate; MFNS = mometasone furoate nasal spray; o.d. = once daily; OHT = ocular hypertension; PAR = perennial allergic rhinitis.

ally settles spontaneously within a few months. The pathogenesis is unclear, but CSs and stress may be triggers. Indeed, it has been reported following systemic and topical skin steroids, as well as inhaled steroids and INSs [81], which should be discontinued if possible.

HS keratitis is a serious but rare AE. There appears to be an increased risk of HS keratitis with CS use, but it is probably not a major issue with short-term use [82, 83].

In addition, studies have demonstrated that CS use (either systemically or via topical application to the eye) is not a risk factor for atopic patients to develop HS virus eye infections [82, 83].

In clinical practice, it is not advisable to use INSs in any patient who is known to have had HS keratitis, who has steroid-related glaucoma, or who has had central serous retinopathy, which may be steroid related.

Table 2. Studies showing no increased incidence of cataract with INSs

Study	Study population		Treatment	Outcome
	patients, n	condition/population		
Derby and Maier [74]	286,078 (retrospective examination of patient records in the UK General Practice Research Database)	INS and OCS users, corticosteroid non-users	INSs, OCSs	similar incidence of cataract for INS users and corticosteroid non-users (1/1,000 person years); increased incidence for OCS users (2.2/1,000 person years)
Ozturk et al. [70]	26	patients who had undergone endoscopic sinus surgery	budesonide, BDP 100 µg b.d. (≥3 months)	no evidence of PSC
Banov et al. [75]	365	PAR	FP (24 weeks)	no changes in ophthalmic examinations suggestive of FP-induced PSC
Bernstein [69]	490 (≥12 years of age)	PAR ≥2 years	MFNS 200 µg o.d. (12 weeks)	no cataracts observed
Bernstein [69]	293 (≥12 years of age)	PAR ≥2 years	MFNS 200 or 100–400 µg o.d. (1 year)	no PSC observed
Rosenblut et al. [50]	806 (≥12 years of age)	PAR ≥2 years	FFNS (1 year)	PSC reported in 2/605 (0.33%) patients receiving FFNS vs. 1/201 (0.5%) patients receiving placebo
Chervinsky et al. [72]	663 (≥12 years of age)	PAR	ciclesonide 200 µg or placebo (1 year)	no clinically relevant differences in LOC III system or unrefracted or refracted visual acuity

b.d. = Twice daily; BDP = beclomethasone dipropionate; FFNS = fluticasone furoate nasal spray; FP = fluticasone propionate; INSs = intranasal corticosteroids; LOC = lens opacification classification; MFNS = mometasone furoate nasal spray; OCSs = oral corticosteroids; o.d. = once daily; PAR = perennial allergic rhinitis; PSC = posterior subcapsular cataract.

Discussion

Increased use of INSs for AR management reflects their good efficacy, tolerability and safety. Individuals with both nasal and ocular symptoms may benefit from INSs treatment. Indeed, recent clinical trial evidence in adults showed that INSs provided relief from the ocular symptoms of SAR/SAC [20, 21, 84–87]. However, few INSs have demonstrated this effect consistently in well-controlled clinical studies. A recent meta-analysis of 10 randomized, placebo-controlled trials showed that MFNS improved the instantaneous total ocular symptom score in patients with SAR/PAR, and FFNS has demonstrated consistent ocular efficacy in patients with AR across clinical trials [21, 45, 88]. Thus, the potential for increased use of INSs has raised interest in the ophthalmic safety profile of these agents.

The ocular safety risk of CSs appears to be dose and administration route dependent. However, ocular safety data for INSs are limited. Available literature supports the assertion that therapeutic doses of INSs can be used without OHT (i.e. continuous use of INSs for ≥3 months does not seem to be associated with any considerable increased risk of OHT or glaucoma). However ‘at-risk’ patients (i.e. with co-existing ocular conditions or using steroids by other routes) should be monitored.

Several mechanisms have been proposed to explain how INSs alleviate ocular symptoms, especially those of SAC, but the exact mechanism remains unknown. Certain INSs (e.g. FF and MF) exhibit high receptor binding and low bioavailability [78–80]. This may minimize systemic exposure and contribute to the low incidence of systemic and ocular AEs in clinical studies to date. While these INSs probably improve eye watering of SAR by alleviating nasal congestion, they might also treat the ocu-

lar allergy component through inhibition of the naso-ocular neurogenic reflex, not through systemic absorption or direct contact with the eye.

Conclusion

The ocular symptoms of ARC tend to be underestimated by physicians. However, ocular symptoms are associated with reduced quality of life for patients. Clinical trial evidence shows that INSs provide some relief from ocular symptoms of AR as well as nasal congestion. Indeed, the updated ARIA guidelines support the use of INSs for the treatment of AR, which are very effective for AR and probably for ARC too.

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