

INVITED REVIEW

Presentation, diagnosis, and the role of subcutaneous and sublingual immunotherapy in the management of ocular allergy

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Allergic eye disease or ocular allergy is a debilitating condition with a significant impact on quality of life and productivity. As atopy continues to be on the rise, primary care providers are likely to encounter increasing numbers of patients with allergic eye disease. This review outlines the classification and pathophysiology of allergic eye disease and its clinical presentation. This paper does not detail traditional first-line therapies of allergic eye disease but describes the interdisciplinary management between the eye-care provider and allergist. It is recommended that patients with ongoing signs and symptoms of ocular allergy despite first-line therapies be referred for allergen immunotherapy, as it is highly effective for treatment of allergic eye disease. Through induction of immune tolerance, allergen immunotherapy is a disease-modifying therapy that can result in long-term improvement of ocular allergy. A thorough literature review was conducted on the efficacy and safety of allergen immunotherapy, including subcutaneous immunotherapy and sublingual immunotherapy, and its role in allergic eye disease.

Key words: allergic conjunctivitis, allergic eye disease, immunotherapy, ocular allergy, subcutaneous sublingual

Allergic eye disease represents one of the most common ocular conditions encountered by primary care providers, particularly as the global prevalence of atopy continues to increase.¹ Allergic eye disease has a profound negative impact on patient quality of life² and contributes to the national economic burden together with its associated atopic co-morbidities.³ These co-morbidities include allergic rhinitis, atopic dermatitis, asthma, food allergy, and eosinophilic oesophagitis.^{4,5}

The terms 'allergic eye disease' and 'ocular allergy' encompass a group of immune-mediated, inflammatory ocular surface disorders that affect the eyelid and conjunctiva. These include hypersensitivity conditions such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis.⁶ Additional conditions that result in very similar signs and symptoms of ocular allergic inflammation include giant papillary conjunctivitis, also known as contact lens papillary conjunctivitis, and contact blepharoconjunctivitis, which were traditionally considered within the group of allergic eye diseases, but have since been discovered to be secondary to non-immune tissue

damage due to repetitive micro-trauma, usually in chronic contact lens wearers.⁷

Allergic conjunctivitis affects 10–20 per cent of patients globally,⁸ with a reported prevalence of 40 per cent in the USA,⁹ with likely similar representations in other developed nations with high incidence of atopic disease.

Symptoms of allergic eye disease can become severely debilitating, and include pruritus, tearing, redness, foreign body sensation, discharge, and swelling.¹⁰ Despite the associated morbidity, up to one-third of patients are undiagnosed and undertreated,¹¹ and often self-medicate with topical saline or with over-the-counter medications. Some of these drugs have limited efficacy, and their overuse can lead to undesirable side effects.¹² Primary care providers therefore face a diagnostic and management challenge, as patients often delay professional assessment.

The aim of treatment in allergic eye disease is to minimise the immune-mediated inflammatory cascade associated with the allergic response, to relieve symptoms, and to prevent complications of chronic inflammation. Initial therapies are empiric, and include allergen avoidance, intranasal

corticosteroids, oral and topical second-generation antihistamines, leukotriene receptor antagonists, topical vasoconstrictors and mast cell stabilisers. Allergic eye disease refractory to these measures can be referred for topical corticosteroids and topical immunomodulator therapies, although the former are associated with ocular adverse effects and therefore appropriate for short courses only.¹³ Allergen immunotherapy is well-established as the only disease-modifying treatment available that may provide long-term benefit in the control of moderate-severe allergic eye disease that is refractory to initial therapies.¹⁴

This paper summarises the pertinent features of allergic eye disease and the role of interprofessional collaboration between eye-care providers and immunologists/allergists for patients with persistent signs and symptoms of allergic eye disease. Traditional first-line therapies for allergic eye disease are not detailed, but particular attention is focused on the role of allergen immunotherapy, the types of immunotherapy available, the appropriate prescription of immunotherapy, and expected outcomes of immunotherapy in the management of the patient with ocular allergy.

Immunopathology of allergic eye disease and the role of allergens

Over the last decade, there has been significant progress in understanding the immunopathogenesis of allergic eye disease, leading to progressively more targeted therapies. The ocular surface of the human eye is immunologically active, unlike the internal structure, which has immune privilege. The ocular surface consists of the conjunctiva and cornea, together with elements such as the lacrimal gland, lacrimal drainage apparatus, and associated eyelid structures. Given that this ocular surface is constantly in contact with the environment, allergic eye disease involves anterior ocular surface inflammation, mediated primarily by environmental allergens that stimulate specific immunoglobulin E (IgE)-mediated mast cell activation, degranulation, and subsequent release of inflammatory mediators.¹⁵ However, allergic conjunctivitis (seasonal and

perennial) is the only ocular disease to involve solely immediate type I hypersensitivity, while vernal and atopic keratoconjunctivitis have a more complex immunological mechanism with a chronic inflammatory component^{10,16,17} (Figure 1).

Immunopathogenesis of seasonal and perennial allergic conjunctivitis

Experimental allergic conjunctival models and clinical research studies have shown that T-helper type 2-related mechanisms are involved in the sensitisation phase of ocular allergy, and that both T-helper type 1 and type 2 cytokines are overexpressed in active disease, resulting in ocular inflammation.^{17–19} Sensitisation occurs when very small (picograms) quantities of environmental allergens (including pollen, dust mite faecal particles, and animal dander) reach the conjunctival mucosa. These particles are then processed by antigen-presenting cells (Figure 1). The antigens are carried by antigen-presenting cells to

native lymphocytes that express antigen-specific receptors and recognise the antigenic peptides. In these sensitised patients, T-helper 2 cells release pro-inflammatory cytokines (interleukins 3, 4, 5, 13) that stimulate IgE production by B lymphocytes.

Subsequent exposure to environmental allergens in these sensitised patients causes cross-linking of IgE bound to the membrane of mast cells, with subsequent degranulation of mast cells, with release of histamine, tryptase, prostaglandins, and leukotrienes. These mediators trigger the clinical manifestations of the acute (or early) phase of the disease, with symptoms including pruritus, tearing, redness (hyperaemia due to conjunctival vasodilatation), conjunctival injection, chemosis, periorcular swelling, and a papillary reaction (Figure 1). Mast cell degranulation also activates vascular endothelial cells, causing an upregulation of expression of chemokine and adhesion molecules, resulting in recruitment of activated inflammatory cells into the conjunctiva. The early phase begins within seconds to minutes after exposure and clinically persists for up to 30 minutes.

This is followed by the late-phase reaction, which occurs hours after allergen exposure. Mast cell degranulation also induces activation of vascular endothelial cells, with release of chemokines and adhesion molecules that increase recruitment of inflammatory cells in the conjunctival mucosa. This is characterised by the recurrence or prolongation of symptoms due to infiltration of eosinophils, neutrophils, and T lymphocytes into the mucosa (Figure 1). This late phase reaction also leads to the processes responsible for chronic severe allergic eye disease, including vernal and atopic keratoconjunctivitis, with increased risk of corneal damage and visual impairment.¹²

Immunopathogenesis of vernal and atopic keratoconjunctivitis

Specific allergen sensitisation is not found in all patients with vernal and atopic keratoconjunctivitis, suggesting that type IV hypersensitivity, in addition to the typical immediate type I hypersensitivity, contributes to the pathogenesis of conjunctival inflammation.²⁰ In these patients, there is increased T-helper-2 prevalence, IgE production, and persistent mast cell and eosinophilic function, leading to remodelling of the ocular surface environment, corneal opacity, and visual impairment.^{21,22} In vernal keratoconjunctivitis, eosinophils are markedly increased in the substantia propria of the

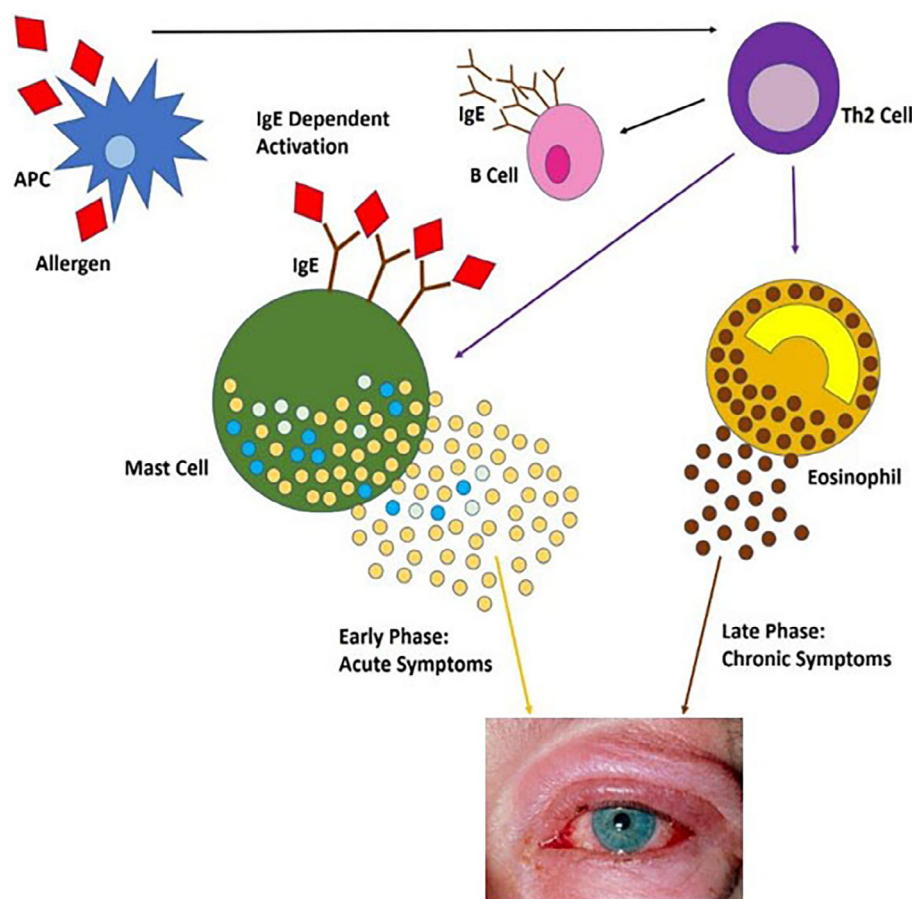


Figure 1. Pathogenesis of allergic eye disease. Adapted from Bonini et al.¹⁴⁶

conjunctiva, and infiltrate the conjunctival epithelium, releasing cytotoxic enzymes that increase tear fluid production and exacerbate corneal damage.²³

Clinical overview of allergic eye disease

Allergic conjunctivitis

Seasonal and perennial allergic conjunctivitis are the most common forms of allergic eye disease, affecting at least 15–20 per cent of the global population,²⁴ and representing 25–50 per cent of all cases of ocular allergy.²⁰ Allergic conjunctivitis is associated with childhood atopic conditions, including atopic dermatitis, food allergy, and allergic rhinitis. Their hallmark feature is the presence of specific IgE antibodies to a seasonal or perennial allergen, and this can be documented in almost all cases of allergic conjunctivitis. Signs and symptoms of the two conditions are the same, but the difference is the specific allergens to which the patient is sensitised.

Seasonal allergic conjunctivitis is associated with hypersensitivity to aeroallergens such as tree pollen, weed pollen, and grasses, and hence seasonal allergic conjunctivitis symptoms are most severe in the spring and summer,

when the pollen count is high. In contrast, the allergens that trigger perennial allergic conjunctivitis are often indoor antigens, including dust mites, animal dander, and moulds. Patients with perennial allergic conjunctivitis have more persistent, low-grade symptoms that do not follow a seasonal pattern.²⁵

Seasonal and perennial allergic conjunctivitis is bilateral, with involvement of the eyelids and conjunctiva. The predominant symptom is itch, followed by burning sensation, tearing, chemosis (Figure 2A), conjunctival injection, and photophobia. Burning sensation may also reflect dry eye syndrome, with allergic conjunctivitis and dry eye syndrome sharing several similar characteristics.²⁶ Fine papillary reaction of the superior tarsal conjunctiva may be seen in perennial allergic conjunctivitis (Figure 2B), and dry eye syndromes may exacerbate the condition. Corneal involvement is rare in both seasonal and perennial allergic conjunctivitis.²⁷

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis represents 0.5 per cent of allergic eye disease, affects mainly children and young adolescents, has a male predominance, and occurs more commonly in warm climates.^{28,29} Vernal keratoconjunctivitis is characterised by the presence of

corneal epithelial stromal lesions, as well as conjunctival proliferative changes, with giant papillae in the upper conjunctiva, giving it a cobblestone appearance on the surface of the everted eyelid (Figure 2C). Additionally, patients can develop gelatinous eosinophilic and neutrophilic mounds (Trantas dots) (Figure 2D-E). These changes cause intense itch, tearing, mucous discharge, ocular pain due to corneal involvement, severe photophobia, and intense foreign body sensation due to the irregularity of the conjunctival surface and copious mucous production.¹⁸ The massive eosinophilic infiltration and activation in the conjunctiva is responsible for corneal complications. Chronic eye rubbing contributes to keratoconus and other corneal ectasias, and corneal ulcers may form in severe cases.³⁰ If left untreated, corneal involvement causes permanent scarring and visual impairment.

Atopic keratoconjunctivitis

Atopic keratoconjunctivitis is severe, chronic, bilateral inflammation of the ocular surface. It is more common in adulthood, and up to 95 per cent of patients have a personal or family history of allergic disease. Atopic dermatitis is the most common associated condition,³¹ and atopic keratoconjunctivitis is

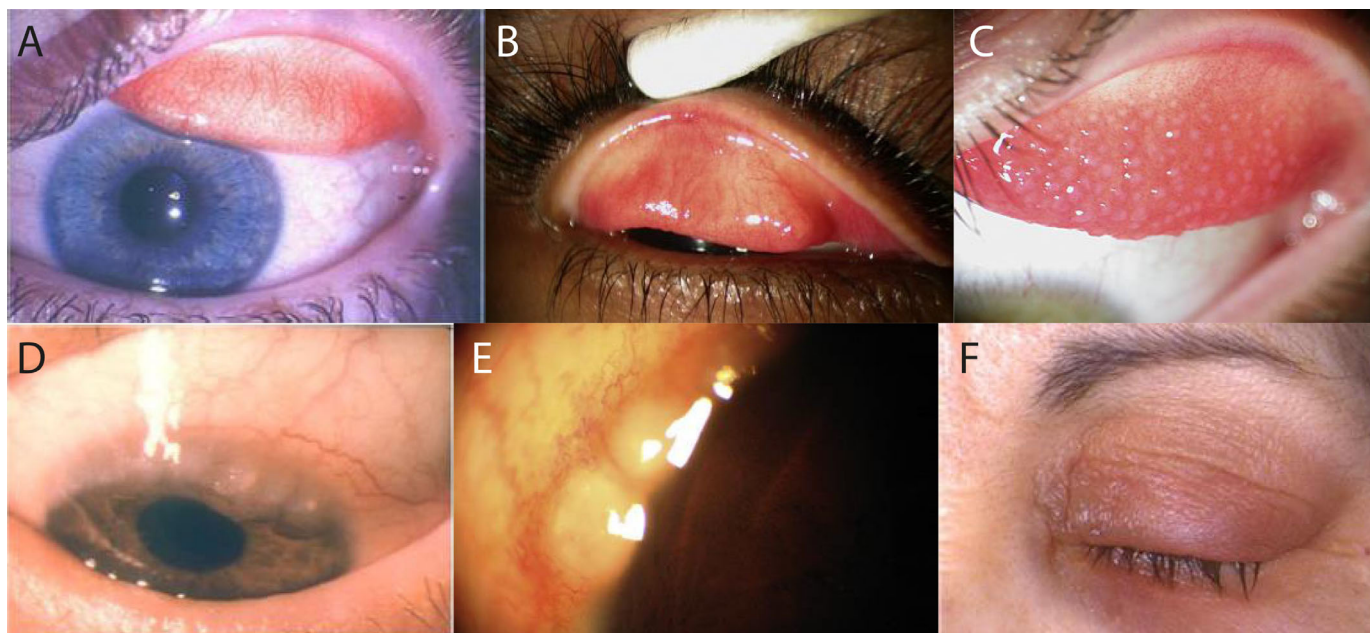


Figure 2. Signs of allergic conjunctivitis. A: Allergic conjunctivitis with mild conjunctival injection and moderate chemosis. B: Fine papillary reaction of superior tarsal conjunctiva in perennial allergic conjunctivitis. C: Giant papillae of the superior palpebral conjunctiva in vernal keratoconjunctivitis. D: Trantas dots of vernal keratoconjunctivitis. E: Trantas dots of limbal vernal keratoconjunctivitis. F: Eyelid eczema in atopic keratoconjunctivitis. Adapted from La Rosa et al.¹³ and Miraldi Utz et al.²⁰

considered the 'ocular counterpart' of atopic dermatitis. The eyelids have an eczematous appearance (Figure 2F), and madarosis or loss of eyelashes is often present. Other ocular findings include chemosis of the eyelid skin, with fine sandpaper-like texture, conjunctival injection, and conjunctival scarring.³² Similar to vernal keratoconjunctivitis, small Trantas dots and papillae may be present. Patients may also develop atopic cataracts and may require cataract surgery at a young age.¹³ Corneal complications are common, and risk of vision-threatening herpetic keratitis also increases.²⁰ As seen in allergic conjunctivitis, many patients with atopic keratoconjunctivitis also test positive to aeroallergen sensitivity.

Differential diagnoses

Giant papillary conjunctivitis or contact lens papillary conjunctivitis is an inflammatory eye disease that is typically caused by mechanical trauma from irritative stimuli, such as contact lenses or ocular prosthesis. An allergic component may be involved when protein deposits on the contact lenses or prostheses, which can either create a type I or type IV hypersensitivity response, either serving as allergens or haptens, respectively.³³

Contact blepharoconjunctivitis or allergic contact dermatitis of the eye is a type IV hypersensitivity reaction which occurs secondary to re-exposure to cosmetics, chemicals, antimicrobials, plants and certain ophthalmic medications (including atropine and tropicamide).²⁰ Treatment involves withdrawing the allergen and avoiding subsequent contact.

Given that these conditions lack specific allergen sensitisation, allergen immunotherapy is not indicated or beneficial. However, giant papillary conjunctivitis and contact blepharoconjunctivitis remain important differential diagnoses in the assessment of a patient with allergic eye disease.

Diagnosis of allergic eye disease

Despite its significant negative impact on patient quality of life, allergic eye disease continues to be underdiagnosed and undertreated due to a combination of factors. These include patient self-diagnosis and self-treatment with over-the-counter medications, with delayed presentation to the primary care physician or eye-care provider. Early diagnosis and appropriate treatment

commencement are essential to reduce the frequency of relapses and to avoid potentially sight-threatening complications. Table 1 summarises the signs and symptoms for the different types of allergic eye disease.

History and clinical presentation

A thorough patient history is the first crucial step in the diagnosis of allergic eye disease, particularly due to the 'red eye' being a common presentation for primary care providers. The hallmark of ocular allergy is itching, redness, and watering of the eyes. Less common symptoms of ocular allergy include burning, photophobia, blurry vision, and pain. The history also covers whether there is unilateral or bilateral eye involvement, the age of onset and duration of symptoms, season of onset, exacerbation or relieving factors, previous episodes, trial of any therapies, and the duration of that therapy. History of atopic co-morbidities or known allergies, systemic illnesses, environmental or occupational exposures (such as pets, moulds, pollen, or smoke), recent relocations, use of contact lenses, or previous ocular surgery are identified.⁶ Finally, the functional impact of symptoms on patient quality of life are noted, and can be assessed via quality of life questionnaires. Symptom severity can be assessed via ocular severity scores and concomitant medication use.

A history of bilateral red, watery, itchy eyes recurring in the spring and summer is highly suspicious for allergic eye disease. Nasal symptoms are often present. Conjunctival symptoms are present in 30–70 per cent of patients with allergic rhinitis.³⁴ Atopic keratoconjunctivitis is present in up to 40 per cent of patients with atopic dermatitis, and 40–75 per cent of vernal keratoconjunctivitis patients suffer from other atopic conditions.⁸ In children, a diagnosis of attention deficit hyperactivity disorder is associated with a higher likelihood of suffering from allergic conjunctivitis.³⁵ Ocular pain and visual loss are very unusual in simple allergic conjunctivitis and suggest the more severe vernal or atopic keratoconjunctivitis. The use of eyedrops, eye cosmetics, and contact lenses may increase suspicion of giant papillary conjunctivitis, contact blepharoconjunctivitis, or infection.

Physical examination

Physical examination for the primary care provider includes observation of the eye for hyperaemia or chemosis which may be

marked in the lower eyelid due to gravity³⁶ (Figure 2A). When severe, the conjunctiva may appear gelatinous and thickened. Watery or mucinous discharge may be visible, and stringy mucus threads can indicate chronic conjunctivitis. Eczema-like dermatitis may be present on the eyelids, particularly in cases of atopic keratoconjunctivitis (Figure 2F). Eversion of the upper and lower eyelids is performed for any foreign bodies or specific signs, including superior tarsal conjunctival giant papillae and Trantas dots (Figure 2C-E).

Visual acuity measurement via Snellen chart, pupil examination for any afferent pupillary defect or asymmetry, and examination of extraocular eye movements is usually performed. The opacity of the cornea is evaluated for severity assessment. Topical fluorescein application and examination with appropriate blue light can stain corneal involvement and may be used in primary care for the evaluation of any red eye associated with pain, vision impairment, or photophobia.²² Finally, examination also includes evaluation for co-morbid allergic disease.

Multidisciplinary approach to diagnosis and investigation

Eye-related presentations comprise two to four per cent of primary care consultations.³⁷ The role of the primary care provider is core and includes assessment of the symptoms and signs via a thorough history and physical examination, as well as commencement of first-line therapy. A multidisciplinary approach with open communication is recommended between primary care physicians, eye-care providers, and allergists for holistic care in patients with ocular allergy. Referral to an allergist is recommended for skin prick testing for allergen identification (which is the generally preferred method for testing for specific IgE antibodies) and for potential allergen immunotherapy, particularly if symptoms remain uncontrolled despite first-line therapies.

Supportive diagnostic tools and investigations for allergic eye disease

The diagnosis of ocular allergy is primarily clinical, but certain tests can be useful in supporting the diagnosis, including ocular surface evaluation and tear sampling,³⁸ which are beyond the scope of this paper. Allergy testing is relevant for immunotherapy for treatment of ocular allergy.

	SAC	PAC	VKC	AKC	GPC	CBC
Onset and occurrence	Childhood. Can diminish with age. Recurrent. Seasonal. Equal M:F. Hx of atopy.	Childhood. Can diminish with age. Continuous. Equal M:F. Hx of atopy.	Childhood. Adolescence. 3–25 years. Can diminish over years. Chronic. Acute seasonal flares. M > F.	Late adolescence or adulthood. M > F. Chronic, with acute flares. Strong Hx of atopy.	All ages. Equal M:F. Chronic. Resolves post-removal of trigger.	All ages. Equal M:F. Chronic. Resolves post-removal of trigger.
Triggers	Grass pollens. Tree pollens. Weed pollens.	Dust mites. Animal dander. Moulds.	As per SAC and PAC. Atopy in 50% of patients. Warm and dry climates.	As per SAC and PAC. Perennial, flares in winter. Always associated with atopy.	Contact lens (soft > hard). Poor lens hygiene. Infrequent lens replacement. Foreign body. Ocular prostheses. Sutures.	Eye drops. Cosmetics. Soaps. Inert chemicals.
Pathogenesis	Atopic. IgE-mediated. Type I hypersensitivity.	Atopic. IgE-mediated. Type I hypersensitivity.	Childhood +/- atopic. IgE and non-IgE mediated. Type I and IV hypersensitivity.	Adult atopic. IgE and non-IgE mediated. Type I and IV hypersensitivity.	Atopic or non-atopic. Non-IgE mediated. Type I and IV hypersensitivity.	Non-atopic. Non-IgE mediated. Type IV hypersensitivity.
Skin prick test	Positive	Positive	Positive	Positive	Variable	Variable
Symptoms	Itching. Tearing. Photophobia.	Itching. Tearing. Photophobia.	Itching. Copious mucous. Tearing. Photophobia.	Severe itching. Burning. Photophobia.	Itching. Burning. Photophobia.	Itching. Tearing. Photophobia.
Clinical signs	Bilateral. Conjunctival redness and swelling. Watery discharge.	Bilateral. Conjunctival redness and swelling. Watery discharge.	Bilateral. Giant papillae upper lid conjunctiva. Conjunctival injection. Mucoid discharge. Trantas dots. Limbic papillae. Corneal erosions.	Bilateral. Atopic dermatitis of eyelid. Blepharitis. Conjunctival scarring. Eyelid oedema. Corneal erosions. Infiltration of limbus and cornea.	Localised to site of foreign body. Giant papillary hypertrophy. Mucoid discharge. Excessive movement of contact lenses.	Lid dermatitis. Periocular oedema and erythema.
Eyelids	Nil affect.	Nil affect +/- palpebral oedema.	Eyelid oedema.	Eczema. Blepharitis.	Nil affect.	Erythema. Eczema.
Conjunctiva	Follicles +/- papillae.	Follicles +/- papillae.	Giant papillae.	Papillae +/- fibrosis.	Giant papillae.	Hyperaemia. +/- follicles.
Limbus	Nil affect.	Nil affect.	Thickened. Trantas dots.	Thickened. +/- Trantas dots.	Hyperaemia.	Nil affect.
Cornea	Nil affect.	Nil affect.	SPK. Ulcer. Vernal plaque.	SPK. Ulcer. Opacity. Neovascularisation.	Rare.	Nil affect.

Table 1. Characteristics of different types of allergic eye disease. Adapted from Miraldi Utz et al.,²⁰ Leonardi et al.,³⁸ Patel et al.,²⁵ and Dupuis et al.¹²

	SAC	PAC	VKC	AKC	GPC	CBC
Complications	Minimal.	Minimal.	Eyelid thickening. Ptosis. Corneal ulceration, scarring, ulcer, neovascularisation, keratoconus.	Eyelid tightening. Loss of lashes. Corneal ulceration, scarring, neovascularisation, keratoconus, Cataract.	Ptosis. Lid swelling.	Minimal.
Visual impairment	+/-	+/-	++	+++	+/-	+/-
AKC: atopic keratoconjunctivitis, CBC: contact blepharoconjunctivitis, GPC: giant papillary conjunctivitis, Hx: history, M:F: male-to-female ratio, PAC: perennial allergic conjunctivitis, SAC: seasonal allergic conjunctivitis, SPK: superficial punctate keratitis, VKC: vernal keratoconjunctivitis.						

Table 1. Continued

ALLERGY TESTING

Allergy testing can be helpful to confirm allergic eye disease, but it is most useful in identifying sensitisation to a specific allergen, to subsequently allow allergen minimisation and allergen immunotherapy.

Epicutaneous or skin prick tests are considered the gold standard first-line method of identifying IgE-mediated sensitisation, as they are efficient in both performance and result, safe, and relatively cost-effective. Skin prick tests should be performed as per current guidelines, with a positive wheal-and-flare reaction confirming specific allergen sensitisation.³⁹

Serum-specific-IgE measurements to specific allergens should be considered if the skin prick test result is unexpected (for example, discordance with the medical history), as both specific IgE and skin prick tests have different sensitivity and specificity distinct for each allergen.⁴⁰

Patients with allergic conjunctivitis may have polysensitisation, with sensitisation to two or more allergens, confirmed on allergy testing. Once this is demonstrated, the relevance of the allergen to the patient's allergic eye disease can be tested via the conjunctival provocation test. This test involves applying known quantities of a specific allergen to the ocular surface and assessing the reproduction of signs and symptoms of the allergic response (itching, tearing, hyperaemia, chemosis) at 15–30 minutes post-exposure. This can also be used if the clinical history suggests allergic eye disease, but the skin prick test or specific IgE tests are negative or inconclusive.⁴¹

Management of allergic eye disease

The aim of treatment in allergic eye disease is to alleviate symptoms to improve quality of life, reduce recurrence to slow down chronic inflammation, and prevent complications. Management involves a stepwise approach with non-pharmacological interventions such as allergen avoidance and/or minimisation first. Pharmacological therapies are then utilised, including lubricants, topical and oral antihistamines, topical vasoconstrictors, mast cell stabilisers, corticosteroids and immunomodulators. These treatment options are reviewed thoroughly in the medical literature,^{42–51} and the current topical therapies are summarised in Table 2.

Allergen immunotherapy

Allergic ocular symptoms represent an important co-morbidity of allergic rhinitis. Allergen-specific immunotherapy is an additional treatment option with established efficacy in patients with inadequately controlled allergic rhinoconjunctivitis. Immunotherapy is an effective, disease-modifying, long-acting therapy for patients with identified allergen-specific IgE antibodies. It involves regular allergen administration at set intervals to modulate the immune response and induce a clinical tolerance to the specific allergen, thereby altering the natural history of allergic rhinoconjunctivitis. Immune tolerance achieved in successful allergen immunotherapy involves a myriad of cellular and molecular events that ultimately inhibit both the early- and late phase immune response to allergen exposure. The effectiveness of immunotherapy is measured through control of symptoms and reduction in concomitant medication use.

The general proposed mechanism of action of allergen immunotherapy and induction of immune tolerance is shown in Figure 3. Immunotherapy or desensitisation leads to induction of regulatory T cells, which release interleukin-10 and transforming growth factor beta, which then cause early suppression of mast cells, basophils, and eosinophils, thereby reducing release of their pro-inflammatory mediators following aeroallergen exposure. Interleukin-10 and transforming growth factor beta also suppress T-helper-2 cells, which are critically involved in allergic diseases, and also suppress inflammatory dendritic cells, while inducing tolerogenic dendritic cells. Finally, interleukin-10 and transforming growth factor beta promote immunoglobulin class switching, by promoting production of IgG4 and IgA, which compete with IgE for allergen binding, thereby limiting the IgE mediated activation and degranulation of mast cells and basophils that cause the allergic response.

The long-term effect of immunotherapy includes overall reduced IgE-to-IgG4 ratio, as well as a reduction in mast cell and eosinophil numbers, thereby resulting in reduction of the mediators released during the allergic response.⁵² Hence, immunotherapy induces interleukin-10 secreting inducible Treg cells, specific for the same allergic epitope.⁵³ The immunologic response to immunotherapy is characterised by reduction in end-organ response with decreased early and late

Drug class	Example agents	Indications	Adverse effects	Comments
Lubricants	Artificial tears. Hydroxypropyl cellulose. Carboxymethyl cellulose.	Irrigation of allergens from ocular surface. Relief of dryness.	Well tolerated.	Insufficient as sole therapy. Short duration of action.
Second-generation antihistamines	Emedatine. Levocabastine. Can be used concomitantly with oral antihistamines.	Relief of pruritus. Reduction in symptoms.	Well tolerated. Transient sting on application with prolonged use. Bitter aftertaste.	Insufficient as sole therapy. Short duration of action. High doses can have anti-cholinergic side effects. Synergistic with intranasal corticosteroids in allergic rhinitis (naso-ocular reflex).
Mast cell stabilisers	Cromolyn. Lodoxamide. Nedocromil. Pemirolast.	Stabilise mast cell to reduce degranulation. Reduction in symptoms. Long-term prophylaxis once symptoms controlled.	Transient sting on application. 4x/day dosing, potential for poor compliance. Well tolerated otherwise.	May not treat acute symptoms. Loading period of application weeks prior to antigen exposure. Can take several weeks for efficacy, slow onset of action. Long-term usage.
Dual-acting agents (antihistamine + mast cell stabiliser)	Azelastine. Epinastine. Ketotifen. Olopatadine. Bepotastine.	Dual action in single agent, clinically superior than either agent alone. Immediate and prophylactic action.	Bitter taste. Transient sting. Conjunctival injection. Overall well tolerated.	2x/day dosing increases compliance. Considered first-line therapy in allergic conjunctivitis. Preservative-free drops preferred.
Decongestants/ vasoconstrictors	Naphazoline. Pheniramine. Xylometazoline. Brimonidine.	Vasoconstriction reduces erythema, chemosis and oedema. Relief of episodic pruritus.	Tachyphylaxis. Mydriasis. Rebound hyperaemia upon cessation. Ocular irritation. Hypersensitivity.	Rapid onset, short duration of action. Possible paradox effect. Use for short duration only. Avoid in patients with hypertension and cardiovascular disease.
Dual-acting agents (antihistamine + decongestants)	Antazoline-naphazoline. Pheniramine-naphazoline. Znatazoline-tetryzoline.	Antihistamine reduces pruritus. Vasoconstrictor relieves injection.	As above. Risk of overuse.	Rapid onset. More effective than systemic antihistamines. Limited duration of action.
NSAIDs	Ketorolac. Topical prostaglandin.	Reduces ocular pruritus and redness.	Burning common on application.	Can cause ocular and systemic side effects.
Corticosteroids	Prednisolone. Dexamethasone. Loteprednol. Fluorometholone. Rimexolone.	Reduction in inflammation, with reduction in symptoms. Use in moderate-severe cases.	Cataract. Elevated intraocular pressure and glaucoma. Viral infection.	Effective anti-inflammatory action but risk of toxicity. Close monitoring required. Potential for inappropriate patient use. Contraindicated in viral eye infections or fungal keratitis. Short-term use only. Initial pulse therapy (3–4 drops per day for 3–5 days) followed by prolonged therapy with gradual taper.
Calcineurin Inhibitors	Cyclosporin A (0.05% – 2%). Tacrolimus (off-label use for severe VKC and AKC refractory to cyclosporin).	Severe VKC and AKC not responding to above. Steroid-sparing agent to reduce dependence on topical corticosteroids.	Transient sting. Local erythema. Conjunctival hyperaemia. Blurred vision. Theoretical risk of infection.	Steroid sparing agent. Eyes to be kept closed to 2 mins post instillation to increase action and reduce systemic absorption.

AKC: atopic keratoconjunctivitis, NSAIDs: non-steroidal anti-inflammatory drugs, VKC: vernal keratoconjunctivitis.

Table 2. Topical therapies for allergic eye disease. Adapted from Leonardi et al.,⁴⁷ Bielory et al.⁴⁶ and Patel et al.²⁵

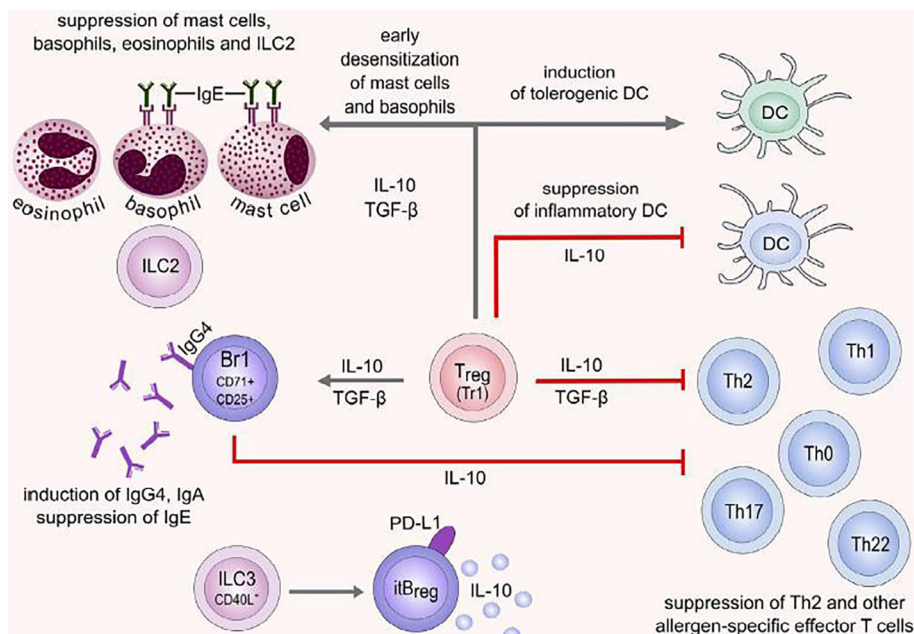


Figure 3. Mechanism of action of allergen immunotherapy and induction of immune tolerance. DC: dendritic cell, IL-10: interleukin-10, ILC2: innate lymphoid cell 2, ILC3: innate lymphoid cell 3, iTreg: innate transitional regulatory B cell, TGF-β: transforming growth factor beta, Th0: naïve T cell, Th1: T-helper-1 cell, Th2: T-helper-2 cell, Th17: T-helper-17 cell, Th22: T-helper-22 cell, Treg: regulator T cell. Adapted from Globinska et al.⁵²

allergic responses of the skin, conjunctiva, nasal mucosa, and bronchi to allergen challenge.^{54,55}

As per the European Academy of Allergy and Clinical Immunology guidelines, allergen immunotherapy is indicated in patients who meet the following criteria: (a) those who have clinical symptoms of allergic rhinoconjunctivitis, including watery, red or itchy eyes, sneezing, nasal congestion, or watery nasal discharge; (b) those who have moderate-to-severe symptoms that interfere with activities of daily living, refractory to appropriate pharmacotherapy and avoidance strategies; and (c) those who have recurrent clinical symptoms upon specific aeroallergen exposure, with evidence of allergen-specific IgE sensitisation, either via skin prick testing or serum-specific IgE testing, to ensure the correct standardised allergen formulation is used for the desensitisation process.¹⁴

Skin prick testing with standardised extracts to aeroallergens is the preferred diagnostic tool and has been shown to be more sensitive than specific IgE testing, although this depends on the potency of the allergen being tested.⁵⁶ Major guidelines recommend that allergen immunotherapy should be prescribed and monitored by qualified allergists/immunologists following

identification of the relevant sensitising allergen(s).^{14,56,57}

There are two main forms of immunotherapy that are currently available: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SCIT involves administration of small but increasing amounts of allergen via subcutaneous injection and can include either pre-seasonal or continuous therapy. SLIT involves administration of allergens via drops or tablets under the tongue on a daily basis. A recent systematic review and meta-analysis showed that both SCIT and SLIT are effective for allergic rhinoconjunctivitis, with both therapies resulting in a reduction in symptoms and use of concomitant pharmacotherapy.⁵⁸

Subcutaneous immunotherapy

SCIT has traditionally been the gold standard administration route for allergen immunotherapy. It appears that the regulatory T cell response occurs very early in the early course of SCIT;⁵⁹ however, the clearest demonstration of immune deviation was in patients who had received high-dose SCIT for three to five years.

There is extensive experience with SCIT, although trials did not initially report on

ocular symptoms. In the last two decades, multiple systematic reviews and meta-analyses of randomised controlled trials have confirmed significant reductions in conjunctival symptoms in patients with seasonal allergic rhinoconjunctivitis due to grasses and pollens, and perennial allergic rhinoconjunctivitis due to house dust mites and animal dander.^{60,61} There is strong evidence that SCIT to grass mix, timothy grass, cat, *Parietaria* and *Alternaria*, improves symptoms of conjunctivitis.^{60,62–65} These trials confirm the improvement in allergic rhinoconjunctivitis symptoms, quality of life, and concomitant medication score with SCIT over placebo.⁶⁶

All common allergens are standardised and available for continuous therapy, and three of these allergens (trees, ragweed, grass) are also available as pre-seasonal injections. Pre-seasonal SCIT is effective for pollen allergy. A trial comparing pre-seasonal SCIT with perennial SCIT found that both groups had significant reduction in ocular symptoms compared to baseline, but there was no statistically significant difference between the pre-seasonal and continuous arms, although total allergic rhinoconjunctivitis symptoms and concomitant medication score were lower in the continuous SCIT group.⁶⁷

AVAILABILITIES AND ADMINISTRATION

Traditional immunotherapy with native, unmodified allergen extracts is successful, but has several limitations that cannot be controlled in the manufacturing process. These include increased risk of adverse systemic reactions, higher production costs, and limitations in the availability, consistency, and potency of the individual allergen molecules.⁶⁸ Advances in allergen immunotherapy production have allowed the development of chemically modified, depigmented polymerised extracts, known as allergoids, which can overcome the traditional drawbacks of SCIT. Allergoids provide safer, more consistent, readily available and effective extracts that increase immunogenicity while reducing risk of adverse reactions compared to native extracts, thereby allowing higher dosing with shorter courses and greater safety.^{61,69,70} There have been several double-blind placebo-controlled trials conducted with allergoid immunotherapy, which all support their efficacy in SCIT.^{71–75}

DOSING

The build-up phase involves receiving SCIT injections with increasing amounts of

allergen. This usually requires weekly up-dosing regimens, followed by four to six weekly maintenance injections for three to five years.⁷⁶ Clinical improvement can be demonstrated very shortly after the patient reaches a maintenance dose,^{77–79} and patients should be followed up every six months to monitor this. However, reasons that improvement may not be observed include: (a) failure to remove significant allergenic exposures from the household; (b) ongoing exposure to high levels of allergen; (c) ongoing exposure to non-allergenic triggers; (d) incomplete identification and treatment of clinically relevant allergens; or (e) failure to comply with adequate doses of each allergen.⁵⁶

SAFETY

Only standardised and regulated allergen extracts with evidence of safety and efficacy should be prescribed.⁸⁰ Extracts should be stored at 4–8°C to reduce the rate of potency loss.

Local reactions to SCIT injections are common, manifesting as erythema, pruritus, and swelling at the injection site. These can be managed with cool compresses, antihistamines, or topical corticosteroids, and do not require dose adjustment.⁸¹ Traditionally, there has been concern that pre-injection antihistamines may mask a minor reaction that may otherwise alert a physician to an impending systemic reaction. However, a randomised controlled trial demonstrated that premedication reduced the frequency of severe systemic reactions caused by conventional immunotherapy and increased the proportion of patients who achieved the target maintenance dose.⁸² Hence, premedication with antihistamines can be considered in patients who recurrently have significant local reactions. Of note, the size of a local reaction does not predict the occurrence of a systemic reaction with the next injection.⁸³

There is a very small but real risk of systemic allergic reactions or anaphylaxis with allergen immunotherapy, and the risk associated with SCIT appears to be greater than that for SLIT.⁸⁴ SCIT should therefore be administered in a medical facility experienced in immunotherapy administration that allows prompt recognition and management of adverse reactions. A review of SCIT systemic reaction rates found that the rate of a systemic reaction (including sneezing, nasal congestion, urticaria) is 1.9 per cent, and the rate of anaphylaxis is 0.02 per

cent.⁸⁵ Anaphylaxis can develop within minutes after the SCIT injection and should be treated with appropriate resuscitation including intramuscular adrenaline, corticosteroids, supplemental oxygen and intravenous fluids.⁸⁶

Delayed systemic reactions, including biphasic reactions, can occur up to 30 minutes post-SCIT injection, and can occur without any preceding symptoms. It is recommended that patients remain in the physician's office or medical clinic for 30 minutes after the SCIT injection.¹⁴ After a SCIT-induced systemic reaction, the risk versus benefit of ongoing immunotherapy should be evaluated and the next maintenance dose should be appropriately reduced.⁸⁷

To reduce the risk of systemic reactions, the following practices may be conducted: pre-injection health assessments, asthma peak flow, clear documentation, dose reduction late injections, and dose reduction by 50–90 per cent with manufacturer lot changes.^{56,87} Of note, most patients tolerate SCIT without seasonal adjustments, although highly sensitive patients may have a systemic reaction during high pollen season and may require individual dose titration.⁸⁷

Sublingual immunotherapy

SLIT is shown to be an effective and safe alternative for the treatment of allergic rhinoconjunctivitis due to grass pollen, ragweed, and house dust mite allergens.^{88–97} During SLIT, allergen is captured via the oral mucosa by dendritic cells, which mature and migrate to the proximal draining specialised micro-environment lymph nodes that favour the induction of mucosal tolerance through the production of IgG antibodies and induction of regulatory T cells.^{98,99}

Many high-quality trials over the last decade have demonstrated that SLIT is clinically effective, with improvement in ocular symptoms, conjunctival sensitivity, concomitant rescue medication requirements and quality of life questionnaire scores in patients with allergic rhinoconjunctivitis.^{100–104} A systematic review with 63 studies and 5,131 patients found SLIT reduced conjunctivitis symptoms and concomitant medication scores.¹⁰⁵ A Cochrane systematic review that evaluated 42 trials found that SLIT significantly reduced the total and individual ocular symptom scores for red eyes,

itchy eyes, and watery eyes in patients with seasonal allergic conjunctivitis compared with placebo.¹⁰⁶

A recent meta-analysis with 13 trials and 1,592 patients concluded that symptoms of pollen-induced allergic conjunctivitis improved significantly with SLIT compared with dust-mite induced allergic conjunctivitis, reducing total ocular symptom scores, ocular redness, itch and tearing, but not concomitant medication use.¹⁰⁷ Another meta-analysis found a reduction in ocular symptoms and concomitant medication score, including eyedrop use.¹⁰⁸ However, a meta-analysis evaluating 13 trials and 4,659 patients for symptom score, and 12 trials and 4,558 patients for medication score, found only a small treatment benefit in symptom scores and concomitant medication scores (antihistamines and corticosteroids) with grass pollen SLIT in patients with seasonal allergic conjunctivitis.¹⁰⁹

Additional data over the last decade from double-blind placebo-controlled trials have shown that high-dose aqueous SLIT to pollen was effective in reducing concomitant medication scores in children.¹¹⁰ *Alternaria* SLIT was shown to be effective in significantly reducing the concomitant medication score.¹¹¹ Multi-allergen SCIT has been tested in a single-centre trial with timothy grass monotherapy, timothy grass and nine other pollen allergens, or placebo. Only the timothy grass monotherapy group showed statistically significant improvement.¹¹² Additional study on multi-allergen SLIT is needed.

For perennial allergic rhinoconjunctivitis, SLIT with house dust mite tablets is more effective than any first-line pharmacotherapies¹¹³ with dose-related reduction in concomitant medication use.^{114,115} For seasonal allergic conjunctivitis, grass and ragweed SLIT is almost as effective as intranasal corticosteroids, and more effective than other pharmacotherapies, while the five-grass SLIT was superior over all pharmacotherapy treatments.¹¹⁶

DOSING AND ADMINISTRATION

SLIT can be delivered both as dissolvable tablets or extract solution, retained under the tongue for at least one minute and then swallowed. There is greater evidence for SLIT tablets than drops, particularly for house dust mite.^{114,117,118} SLIT can be taken continuously or pre-seasonally, commencing ideally four months prior to the start of the pollen season. SLIT therapy is

Uncontrolled asthma.
History of prior SCIT injection-related systemic reactions.
High degree of sensitisation.
SCIT injection during peak pollen season/high allergen exposure.
Mast cell disease.
Active infections.
Dosing or administration errors of therapeutic allergens, such as overdose.
Excess dose escalation during initiation.
Concurrent use of beta blocker therapy.
Recent high-intensity physical exercise.
SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy.

Table 3. Risk factors for systemic reactions during allergen immunotherapy. Adapted from Roberts et al.¹⁴ and Sanchez-Borges et al.⁸⁷

usually initiated with a full dose, or a very short dose escalation schedule. Dosing continues once daily and is self-administered by the patient at home.

SLIT is recommended for grass pollen for at least three years,^{119–122} and for house dust mite for at least one year.^{114,117,123,124}

SAFETY

SLIT is a safe and well tolerated treatment,¹²⁵ with a more favourable safety profile than SCIT^{58,84} and can be administered at home after the first dose is administered under the supervision of a physician in a medical centre that can manage anaphylaxis.

Common local reactions with SLIT include oral-mucosal pruritus and lip angioedema, but these usually occur during the initial phase of the treatment course, are self-limiting, and generally do not persist with continued treatment.^{126,127} While some patients have ceased treatment due to these local reactions, oral antihistamines given prior to SLIT initiation, and for the initial weeks of therapy, can reduce local irritation.⁷⁶ Systemic reactions can occur, and notably, patients who did not tolerate SCIT also had anaphylaxis to SLIT.¹²⁸ A 2012 review estimating the anaphylaxis rate of SLIT to be one per 100 million doses, or one per 526,000 treatment years.¹²⁹ No treatment-related anaphylaxis has occurred in diverse large-scale randomised controlled trials

using SLIT,¹³⁰ although some countries require patients be prescribed an adrenaline pen prior to SLIT commencement, and the first dose should be given in the physician's office.

Temporary cessation of SLIT may be advised for seven days in certain situations, such as post-dental extraction, oral surgery, oral ulcer, or acute asthma exacerbation.¹⁴

Practical points of allergen immunotherapy

Before immunotherapy is commenced, a careful explanation must be given to the patient, outlining the details and commitment required as it is a long-term program involving frequent injections of allergenic extracts for at least three years. Patients should understand the benefits, risks, and costs of allergen immunotherapy, and counselling should also include the expected onset of efficacy and duration of treatment and importance of adhering to the dosing schedule.

Absolute contraindications to immunotherapy include uncontrolled or severe asthma, active systemic autoimmune disease that is

Grade A and B recommendations for SCIT

Continuous SCIT is recommended for adults (A) and children (B) with SAC for short-term benefit in those with moderate-to-severe disease.

Pre-seasonal or co-seasonal SCIT is recommended for adults (A) and children (B) with SAC for short-term benefit.

Both allergoids and unmodified allergen SCIT extracts are recommended for adults (A) and children (B) with ARC for short-term benefit.

Continuous grass pollen SCIT is recommended for adults (A) and children (B) with ARC for short-term and long-term benefit.

Grade A recommendations for SLIT

Pre-seasonal or co-seasonal or continuous SLIT is recommended for seasonal ARC for short-term benefit.

SLIT with tablets for pollens or house dust mite is recommended for ARC for short-term benefit.

SLIT aqueous solutions for pollens is recommended for children (A) and adults (B) with ARC for short-term benefit.

SLIT aqueous solutions for house dust mite cannot be recommended for ARC for short-term benefit.

Continuous grass pollen SLIT tablets or SLIT solution is recommended for ARC for long-term benefit.

SLIT tablet for house dust mite is recommended for ARC for long-term benefit in adults (B).

General Grade A and B recommendations for allergen immunotherapy in ARC

Polysensitised patients who are polyallergic for taxonomically related homologous allergens can receive either a single allergen or a mixture of homologous allergens from that biological family that covers all the major allergens.

AIT can be recommended in otherwise healthy elderly patients with ARC whose symptoms are not adequately controlled by pharmacotherapy (Grade A for SLIT, Grade B for SCIT).

To achieve long-term efficacy, it is recommended that a minimum of three years of therapy is used.

Premedication with an antihistamine is recommended as it reduces the frequency and severity of local and systemic cutaneous reactions. It does not eliminate the risk of other systemic adverse reactions including anaphylaxis.

ARC: allergic rhinoconjunctivitis, PAC: perennial allergic conjunctivitis, SAC: seasonal allergic conjunctivitis, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy.

Table 4. Summary of Grade A and B recommendations for allergen immunotherapy in allergic rhinoconjunctivitis. Adapted from Roberts et al.¹⁴

unresponsive to treatment, and initiation during pregnancy.¹⁴ Relative contraindications that require caution, detailed risk versus benefit analysis, and close monitoring, include patients with partially controlled asthma, local or systemic beta blockade,

severe cardiovascular disease or ischaemic heart disease, systemic autoimmune disease in remission, severe psychiatric disorders, poor adherence, primary or secondary immunodeficiency, or a history of serious systemic reactions to

immunotherapy. The risk factors for systemic reactions during immunotherapy are summarised in Table 3. Dose reductions of 25–50 per cent should be conducted for intercurrent illness or delayed injections for SCIT, while dose interruptions for oral

	SCIT	SLIT
Benefits/pros	Improvement in symptoms. Reduced need for rescue medication. Reduced likelihood of progression from ARC to bronchial asthma. Pre-seasonal, co-seasonal, and continuous SCIT effective in short-term for SAC and PAC. Persistent benefit for years after completion of 3–5 years of SCIT. Highest evidence of grass pollen SCIT. Benefit higher than single-drug pharmacotherapy.	Improvement in symptom scores, on top of rescue medication. Reduced need for concomitant pharmacotherapy. Benefit higher than single-drug pharmacotherapy. Pre-seasonal, co-seasonal, and continuous SLIT tablets or drops effective in short-term for SAC. Continuous SLIT tablets effective in short-term for PAC. Continuous SLIT for 3 years is effective in long-term for grass pollen (tablet or drop) and house dust mite (tablet only) for ARC. No injections. Able to dose at home after first dose.
Risks/cons	Inconvenience due to regular clinic visits (usually monthly on maintenance, more on up-dosing). Frequent minor, local reactions. Potential for systemic reactions. 1:2,000 risk of moderate–severe systemic reactions per SCIT injection. Less with allergoids. Potential for anaphylaxis. Must be observed for 30 min in clinic after each SCIT injection. SCIT overall has higher risk of systemic reactions than SLIT.	Minimal harm. Very frequent, but mild, local adverse events, usually self-limited. Very rare systemic events. Must observe in clinic for 30 min after first dose. Rare moderate-to-severe systemic reactions (< 1:500 risk over 3 years therapy). SLIT overall seems safer than SCIT. Must remember to take daily doses at home.
Cost	Cost of allergen extract SCIT treatment. Cost of visit to medical clinic to receive SCIT. Regular loss of productivity to receive SCIT. Data on SCIT versus SLIT is variable.	SLIT is cost-effective compared to pharmacotherapy after several years of administration. Data on cost of SLIT versus SCIT is variable.
Risk versus benefit assessment	Benefit > harm for patients who have refractory ARC despite pharmacotherapies. Benefit > harm for patients who have chronic and persistent symptoms.	Benefit of treatment seen beyond that with rescue medications. Lasting effect at least 2 years off treatment. Minimal harm with SLIT.
Patient preference	Decision regarding requirement for AIT based on adequate relief of symptoms with pharmacotherapies versus cost and inconvenience of SCIT. This can be compensated by long-term clinical benefit and relief from as-required medication. SCIT can be cost-effective over persistent symptomatic therapy in the long term.	SLIT improved symptoms with low risk for adverse events. Definite improvement with SLIT with grass pollen tablet, ragweed tablet, house dust mite tablet, tree pollen aqueous solution. Improvement with dual SLIT in bi-allergic patients. Less evidence for improvement with <i>Alternaria</i> and <i>Epithelia</i> SLIT.
Recommendation	Strong recommendation for SCIT in patients with ARC symptoms for significant periods of time each year, refractory to pharmacotherapies for adequate symptomatic relief. Strong recommendation for patients who would benefit from secondary disease-modifying effects of SCIT (prevention of asthma or new sensitisation), especially in children.	Strong recommendation for high-dose tablet SLIT for grass pollen, ragweed, house dust mite in patients with SAC and PAC who wish to reduce their symptoms and concomitant medication use.

AIT: allergen immunotherapy, ARC: allergic rhinoconjunctivitis, PAC: perennial allergic conjunctivitis, SAC: seasonal allergic conjunctivitis, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy.

Table 5. Evidence-based decision-making points for SCIT and SLIT in allergic rhinitis and allergic rhinoconjunctivitis. Adapted from Wise et al.⁶⁸ and Roberts et al.¹⁴

lesions should be conducted for SLIT as described earlier.

Immunotherapy should be commenced two to four months prior to pollen season in patients with seasonal allergic conjunctivitis, and when allergen exposure is lowest in patients with perennial allergic conjunctivitis. A minimum of three years of allergen immunotherapy is recommended to achieve long-term efficacy after treatment discontinuation,¹⁴ although improvement in symptoms can occur within 12 months.¹³¹

There is no specific upper or lower age limit for initiating allergen immunotherapy if appropriate indications are present.¹⁴

Allergen immunotherapy is not usually initiated during pregnancy due to risk of adverse effects of systemic reactions on the foetus, mother, or both. If pregnancy occurs in the build-up phase and the dose is unlikely to be therapeutic, discontinuation of allergen immunotherapy should be considered. However, allergen immunotherapy can be continued during pregnancy if it is well tolerated, and retrospective studies suggest there is no greater risk of prematurity, foetal abnormality, or other adverse pregnancy outcome in patients receiving allergen immunotherapy during pregnancy.¹³²

Immunotherapy for children with allergic rhinoconjunctivitis has been shown to be

safe and effective, with additional improvement in asthma symptom control and reduction of progression to asthma.^{133,134} Asthma must be well-controlled at the time of SCIT injection, and SCIT should be withheld if there is an acute asthma exacerbation. Similarly, concomitant uncontrolled asthma is associated with severe systemic reactions after SLIT.¹²⁹

Adherence to immunotherapy is crucial for its efficacy. SCIT requires regular visits to the clinic, while SLIT can be performed at home daily. The range of reported adherence varies between 18 per cent to 90 per cent, with overlapping ranges for SCIT and SLIT. Non-adherence to the immunotherapy schedule and premature discontinuation are common problems and reasons for limited success. The main causes of poor adherence are side effects, inconvenience, lack of efficacy, or forgetting to use.¹³⁵ Factors such as age and patient education play a role, and patients should be informed fully regarding importance of regular doses and completion of the course of immunotherapy. Reminders to take SLIT are recommended for increased adherence.¹³⁶ Adherence may also be better with three-monthly follow-up appointments rather than six- or 12-monthly.¹³⁷ Evidence-based communication, patient-preferred administration, motivational interviewing and shared

decision-making are all important for allergen immunotherapy commencement that increases successful reduction in symptoms of allergic eye disease.¹³⁸

One of the main disadvantages of allergen immunotherapy is the associated cost. Cost is determined by the brand or company utilised, the type of allergen immunotherapy (SCIT versus SLIT), the particular allergen and number of allergen extracts required, and whether they are able to be mixed in the same kit (and therefore potentially diluted) or whether multiple separate extracts are required. Allergen immunotherapy can be administered for three to five years with likely continuing relief of symptoms for years after discontinuation. However, pharmacotherapy must be continued indefinitely, since it has no disease-modifying activity. Hence, the overall higher cost of allergen immunotherapy may be offset by the continuing benefit after it is ceased, and may be comparable to cost of prolonged first-line therapies and productivity lost with inadequate control of symptoms.

A meta-analysis of costs showed that SCIT and SLIT may be cost-effective compared with standard pharmacotherapy for six years, but the investigators were not able to establish a clear difference between SCIT and SLIT in cost-effectiveness.¹³⁹ Generally with most allergen immunotherapy companies, SCIT is less expensive than SLIT, with allergoid injectable extracts costing less than sublingual tablets or sprays.

Polysensitised patients and allergen mixtures

Most patients with allergic conjunctivitis are sensitised to a diversity of aeroallergens. Not all these sensitisations will be clinically relevant, hence it is prudent to identify whether the patient is: (a) polysensitised and clinically monoallergic (where only one allergen is driving symptoms); (b) polysensitised and polyallergic (with symptoms on exposure to multiple different allergens). There is evidence that immunotherapy to single extracts is clinically effective in polysensitised patients who are monoallergic,^{112,140} and hence polysensitised patients who are monoallergic are recommended to receive immunotherapy for the specific allergen driving their symptoms. It is recommended that mixed allergen immunotherapy is only given to polyallergic patients with homologous (taxonomically related) allergens.^{14,59} For polyallergic patients with non-homologous allergens, it

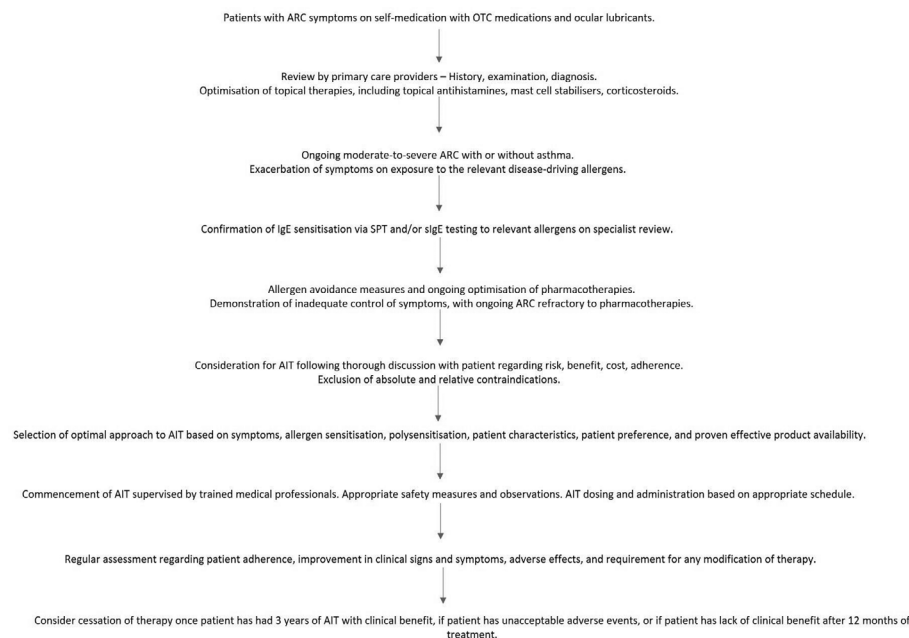


Figure 4. Approach to the patient with allergic eye disease who may be a candidate for allergen immunotherapy. Adapted from Bousquet et al.,⁵⁷ Cox et al.⁵⁶ and Roberts et al.¹⁴

is recommended that separate immunotherapy preparations for one or two of the clinically most important allergens are applied separately.¹⁴¹

Table 4 outlines the Grade A evidence-based recommendations for allergen immunotherapy in allergic rhinoconjunctivitis, as per the most recent guidelines.¹⁴ Grade A evidence refers to consistent Level I studies, which include systematic reviews, meta-analyses and randomised controlled trials.

SLIT versus SCIT

Comparison of the clinical efficacy of SCIT versus SLIT should only be assessed by head-to-head comparisons. There are few studies conducted accordingly,^{142,143} with no conclusive evidence of any statistically significant difference between the two routes. A recent meta-analysis of 37 studies for symptom scores and 31 studies for medication scores showed comparative reductions in allergic rhinoconjunctivitis symptoms with both SCIT and SLIT during the pollen season, with no significant differences between the two modes of allergen immunotherapy.¹⁴⁴ A recent prospective comparative case series on 100 patients also found no significant difference between SCIT or SLIT in achieving clinical improvement in patients with allergic conjunctivitis, with improvement with both routes in all follow-up parameters including ocular symptom scores, medication scores, and total serum IgE levels.¹³¹

The choice between SCIT and SLIT therefore does not rely solely on proof of efficacy, which appears to be equivalent for both, but on individual patient preferences, cost, compliance, risk of adverse events and polysensitisation, all of which play a role in the allergen immunotherapy prescribed.¹⁴⁵ This decision is made by the allergist in consultation with the patient, and includes considerations such as burden of monthly injections with SCIT versus the generally increased cost of SLIT. Table 5 outlines the recommendations based on current evidence for SCIT and SLIT in patients with allergic rhinitis and allergic rhinoconjunctivitis. Figure 3 depicts a basic approach to the patient with allergic conjunctivitis.

Conclusion

The extensive literature review covered in this paper confirms that allergen immunotherapy

is a highly effective treatment in patients with moderate-to-severe allergic eye disease. Allergen immunotherapy is recommended for patients who have demonstrated sensitisation to a specific allergen and have allergic eye disease that is refractory to first-line and second-line pharmacotherapies. Allergen immunotherapy should be prescribed as per evidence-based guidelines to ensure optimisation of efficacy, as well as optimisation of safety with consideration of risks and benefits of therapy (Figure 4).

While there is significant demonstration of the efficacy of allergen immunotherapy, further large definitive trials and head-to-head comparative studies are required in the medical literature, as well as pharmacoeconomic evaluations that can clarify the place of allergen immunotherapy in comparison with other treatment options. Overall, allergen immunotherapy is a safe and highly effective treatment for allergic eye disease, and we recommend it as an essential part of the management strategy in patients with ocular allergy.

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