CONDITION: ALLERGIC EYE DISEASE (TYPE 1 HYPERSENSITIVITY REACTIONS)

Description

Seasonal allergic conjunctivitis (SAC) is caused by seasonal allergens, especially grass pollen, whereas perennial allergic conjunctivitis (PAC) is caused by environmental allergens such as dust mites or animal dander and is less common and generally less severe. Degranulation of conjunctival mast cells releases histamine and other inflammatory mediators causing hyperaemia, oedema and itch.

Significance

Despite SAC and PAC being relatively common and mild forms of ocular allergy, they can have a significant impact on a patient's quality of life (Meltzer, 2001).

Incidence

It is estimated that 15 to 20% of the population suffers from allergy (Schmid & Schmid, 2000) and up to 8% of patients visiting optometry practices present with Type 1 hypersensitivity reactions. The most common form of ocular allergy is SAC (90% of cases) followed by PAC (5% of cases).

Management category

Optometric management is appropriate for SAC and PAC, but referral to an ophthalmologist may be indicated in severe or non-resolving cases, where vision is affected or where there is corneal involvement. Management of vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) should be in collaboration with an ophthalmologist.

Signs and symptoms

Itch is the pathognomonic ocular symptom associated with seasonal and perennial allergic conjunctivitis. Patients also report redness, watery discharge and associated sneezing and nasal discharge. Signs include mild to moderate lid oedema, bulbar and tarsal conjunctival chemosis, hyperaemia and a diffuse papillary reaction. There should be no corneal involvement or reduction in visual acuity in SAC or PAC.

Differential diagnoses

- Vernal keratoconjunctivitis: Can mimic the signs and symptoms of seasonal allergic conjunctivitis but has the potential for permanent vision loss due to corneal involvement. Patients tend to be young males, with symptoms usually starting before the age of ten years and generally resolving after puberty (Kumar, 2009). Patients present with severe ocular itching, redness and stringy discharge. Patients with VKC often have a personal and/or family history of atopic conditions (e.g. Eczema or asthma).

- Atopic keratoconjunctivitis: Potentially blinding due to corneal involvement. It is commonly observed with concomitant atopic disease (Schmid & Schmid, 2000) (for example, eczema (95%) and asthma (87%)). It is more common in males and has a peak age of incidence of 30 to 50 years. Affected patients present with itchy, watery, burning eyes, accompanied by photophobia, pain and blurred vision.
- Other allergic conjunctivitis:
    - Giant papillary conjunctivitis (GPC): Thought to be an allergic response to contact lenses, deposits on contact lenses, contact lens solutions or the preservatives in contact lens solution (Schmid & Schmid 2000). Signs and symptoms include blurred vision, ocular itch, and enlarged papillae on the superior tarsal conjunctiva.
    - Contact allergic blepharoconjunctivitis: This can be an acute or subacute response to substances instilled onto the eye surface, or used on the eyelids, for example eye drops, contact lens solution or makeup. As the name suggests, there is generally involvement of the lids and conjunctiva. Eyelid skin may be erythematous, with thickening and fissuring in more severe cases. Treatment involves avoiding use of the offending agent, and in some cases a mild topical steroid may be used (Salmon, 2020).
- Dry eye and blepharitis – often exist concurrently with ocular allergy. For further details see the blepharitis oral guidelines.
- Bacterial conjunctivitis.
- Viral conjunctivitis.
- Acne rosacea.
- Chlamydial disease.

Management

1. Non-pharmacological therapy

a. Advice against eye rubbing, as this encourages mast cell degranulation and exacerbation of signs and symptoms
b. Avoidance of allergen (if possible)
c. Cool compresses for symptomatic relief
d. Artificial tears to flush and dilute allergens. For patients requiring frequent dosing, consider non-preserved unit dose vials (single use) to avoid preservative toxicity from multi-dose artificial tears. Both artificial tears and cool compresses, alone or in combination, are effective in reducing bulbar conjunctival hyperaemia and lowering ocular surface temperature (Bilkhu, *et.al*, 2004). Cool compresses can also be used in combination with other management options (see below).

2. Topical Treatment

a. **Topical antihistamine / mast cell stabilisers**: Dual-action treatments are fast and effective and have become the first line of pharmacological management in many cases. Twice daily dosing of these agents also improves patient compliance. Some studies report that olopatadine 0.1% (available as Patanol® or generic olopatadine) controls the signs and symptoms of seasonal allergic conjunctivitis more rapidly and to a greater extent than ketotifen 0.025% (Zaditen®, available in preserved formulation or preservative-free unit dose) (Aguilar, 2000; Berdy, *et.al.,* 2000), although ketotifen is more effective than both placebo and levocabastine (see below) in managing SAC (Kidd, 2003). Effectivity increases over 2 to 4 weeks as the mast cells stabilise. These therapies are generally considered to be safe to prescribe for children (Abelson, 2004; and Lichtenstein, 2007), with the most common adverse effect being transient ocular stinging.

b. **Topical mast cell stabilisers**: Mast cell stabilisers (for example lodoxamide 0.1%) have a slower onset of action (2 to 4 weeks) than antihistamines, require multiple (up to 4 x) daily applications and require initiation before the mast cells degranulate to prevent the allergic inflammatory cascade. They are most useful in the seasonal management of chronic allergic eye disease.

c. **Topical antihistamines**: These may be preferred over oral antihistamines as they are applied directly to the site, act more rapidly and are less likely to cause unwanted side effects. Many antihistamines also inhibit eosinophil activation and migration. Topical antihistamines (eg. Levocabastine 0.05%) require 4 times daily dosing and have a short duration of action (3 to 4 hours only). They are therefore useful for short-term symptomatic relief.

d. **Topical non-steroidal anti-inflammatory drugs (NSAIDs)**: Can be an effective short-term treatment option for instantly relieving the itch and pain associated with allergy-induced inflammation. NSAIDs (for example diclofenac 0.1% or ketorolac 0.5%) relieve itching, but they do not block histamine release and need to be used in combination with antihistamine or dual-acting agents, where they are useful up to 4 x per day for breakthrough itch. Adverse effects of topical NSAIDS include irritation (common), conjunctival hyperaemia and blurred vision. Rarely, NSAIDS can cause corneal thinning and epithelial defects.

e. **Topical corticosteroids:** Tertiary treatment of ocular allergy is indicated when other topically instilled agents are ineffective (Bielory, 2000). Steroids with limited corneal penetration, e.g. fluorometholone 0.1%, can be prescribed. These surface steroids are less likely to cause posterior subcapsular cataract and raised IOP (and subsequent glaucoma) than corticosteroids with better intraocular penetration. Topical corticosteroids can also cause reactivation of viral infection and a number of other potential ocular adverse effects (McGhee, *et.al.,* 2002) and are therefore reserved for treating severe allergic eye disease (Abelson, *et.al.,* 2003). As topical corticosteroids do not treat the early phase allergic reaction (release of histamine), they are best reserved for chronic, allergen-dependent T-cell reactions (Bilkhu *et.al.,* 2015) such as seen in VKC and AKC (Ackerman, *et.al.,* 2016).

f. **Topical calcineurin inhibitors (immunomodulatory agents):** These have been shown to be effective in the treatment of severe ocular allergy (for example: vernal or atopic keratoconjunctivitis) (Jabbehdari *et.al.,* 2019) (Vichyanond & Kosrirukvongs, 2013). Examples of topical calcineurin inhibitors used in the treatment of ocular disease include tacrolimus and cyclosporin. Calcineurin inhibitors are used as an alternative to corticosteroid treatment, or to avoid steroid-related complications such as glaucoma and posterior subcapsular cataract (Chatterjee & Agrawal, 2016; and Erdinest & Solomon, 2014)

   Topical tacrolimus, available as compounded ophthalmic ointment or eye drops (various concentrations), is available on prescription by authorised prescribers, however it is not subsidised. As this medication is used to treat severe ocular allergic conditions that have not responded to conventional treatments, topical tacrolimus is generally prescribed by ophthalmologists. There are a number of published studies detailing efficacy of topical tracrolimus (0.03% or 0.1%) in the treatment of chronic atopic eye disease (Barot, *et.al,* 2016; Chatterjee & Agrawal, 2016; and Samyukta, *et.al,* 2016) A small amount of ointment (approximately 0.5 cm) is applied to the eyelid margin and eyelashes, or instilled into the lower conjunctival fornix, once or twice daily (Shoughy, 2017). Treatment duration varies, but is generally 14 to 30 days, although in some studies, patients are treated for a longer period of time (Al-Amri, 2014; and Erdinest & Solomon, 2014).

Tacrolimus ointment is generally well tolerated and safe, and adverse effects are usually minor (transient ocular surface irritation in approximately 50% of patients (Erdinest & Solomon, 2014). Serious adverse effects are rare. However, a recent European multicentre study (Castellsague, *et.al.,* 2018) found an increase in the incidence of lymphoma in children (and adults, to a lesser extent) treated with topical tacrolimus, with risk increasing with higher cumulative dose. There were smaller associations for melanoma and non-melanoma skin cancer.

Cyclosporin has been shown to be effective in the management of severe allergic conjunctivitis that has not responded to conventional management (topical antihistamines, mast cell stabilisers or corticosteroids) (Ozcan, *et.al.,* 2007) Cyclosporine eye drops can be prepared by a compounding pharmacy (cyclosporine 0.05%), or prescribed as Restasis under Section 29 of the Medicines Act 1981 (medical practitioners only). Section 29 medications cannot be prescribed by optometrists in Aotearoa New Zealand: These medications are not approved for a specific use and can only be prescribed by a medical practitioner. For more information about Section 29 medications, please visit Medsafe's website (https://medsafe.govt.nz).

Although the prescription of compounded cyclosporine 0.05% eye drops is not restricted to medical practitioners, it is unlikely that optometrists will be prescribing these eye drops, as they are reserved for the treatment of severe allergic eye disease.

Please note: Topical vasoconstrictors are not recommended for the treatment of ocular allergy as their cosmetic effects are short-lived, they do not treat the underlying cause, and prolonged use may cause rebound hyperaemia (Bilkhu, *et.al.,* 2015) (Bielory, 2000).

Oral Treatment

Oral antihistamines: Can reduce ocular itching, tearing and conjunctival hyperaemia associated with seasonal allergic rhinoconjunctivitis (Kamegasawa *et.al.,* 2017). However, they can have a slower onset in treating ocular symptoms than topical medications, and may be associated with excessive drying and tear film dysfunction in many patients (Bieloy, 2008). The effects of oral antihistamines are long-lasting and may be useful, in combination with topical treatments, for the treatment of ocular disease. Second generation antihistamines have fewer side effects and are less likely to cause sedation and drying (Schmid & Schmid, 2000).

<u>Second generation antihistamine tablets available in Aotearoa New Zealand include:</u>

- Cetirizine hydrochloride 10 mg (Histaclear®, Razene®, Zista®, Zetop®, Zyrtec® and others – see NZ Formulary for a full and current list)
- Fexofenadine hydrochloride 30 mg to 180 mg (including Telfast® and others – see NZ Formulary)
- Loratadine 10 mg (Lorafix®, Lorfast®, Claratyne®, Lora-Tab® and others – see NZ Formulary).

For relief of the symptoms of hayfever the usual adult dosage of fexofenadine hydrochloride is 60 mg once to twice per day. This dose should be halved for paediatric patients 7 to 12 years of age and is not recommended for children under 2 years of age. For cetirizine hydrochloride and loratadine, the recommended dose for adults and children over 6 years is 10 mg per day.

Oral antihistamines should be used in children only after consultation with the patient's family physician or paediatrician. It is not necessary to adjust the dose for the elderly, or patients with liver impairment. In patients with kidney impairment, a maximum 5 mg daily dose (half dose) of cetirizine

hydrochloride is suggested, with lower doses in more severe impairment. It is contraindicated in patients with creatinine clearance less than 10 mL per minute (NZ Formulary).

Antihistamine tablets are contraindicated in patients with a known hypersensitivity to the active ingredient. The most common side effects are headache, drowsiness, nausea, fatigue and dizziness. All the antihistamines named above come under the category of non-sedating antihistamines.

Liquid antihistamines include:

- Cetirizine hydrochloride 1 mg/mL (Histaclear®, Zyrtec®)
- Loratadine 1mg/mL (Lorfast®, Claratyne®)
- Chlorpheniramine maleate 0.4 mg/mL (Histafen Elixir®).

The typical dosage of chlorpheniramine maleate for adults and children over 6 years of age is 5 mL up to eight times daily. Chlorpheniramine maleate should not be used in children under 6 years old. Cetirizine hydrochloride and loratadine liquids are recommended to be used at a dose of 10 mg (10 mL) per day in adults and children over 6 years (with a reduced dose of 5 mg per day (5 mL) in children 2 to 6 years of age. Patients with renal impairment should have a reduced dose (5 mg per day) of cetirizine hydrochloride.

As cetirizine hydrochloride and loratadine fall under the category of non-sedating antihistamines, sedation is uncommon but some patients can experience drowsiness, lassitude, dizziness and lack of coordination. Patients should be cautioned not to drive or operate heavy machinery if they experience any of these symptoms. Chlorphenamine maleate is a sedating antihistamine and is more likely to lead to drowsiness and psychomotor impairment. Sedation is more likely at higher doses.

Antihistamines have an additive effect with anticholinergics, adrenergic agonists, phenothiazines and monoamine oxidase inhibitors, and should be used in caution with patients already taking any of these medications. Consultation with the patient's family practitioner is recommended in this situation. Antihistamines should not be taken with alcohol or any other central nervous system depressants. Due to their anticholinergic effect, antihistamines should be used with caution in patients at risk of angle closure, patients with urinary retention and patients with prostatic hypertrophy.

Non-sedating oral antihistamines listed above are generally classified as Pregnancy Category B1 or B2, indicating that these drugs have been taken by a limited number of pregnant women, without an increase in the frequency of harmful effects on the human foetus. Available animal studies show no evidence of foetal damage.

Chlorpheniramine maleate (Histafen Elixir®) is listed on MIMS Online as Pregnancy Category A, indicating that it has been taken by a larger number of pregnant women without any documented increase in the frequency of foetal malformations or other direct/indirect harmful effects.

In pregnant patients, before prescribing any medication, it is essential to evaluate the benefits and risks of the therapeutic agent under consideration.

Please note: Contraindications, precautions, interactions and potential adverse effects listed for all medications (both topical and oral) in this document are not exhaustive. If required, the optometrist should seek further clarification from online sources (for example: Medsafe (https://medsafe.govt.nz), NZ Formulary (https://nzformulary.org/), or the patient's other healthcare provider(s) prior to prescribing these medications.

Review

Each patient must be treated, individually, based on subjective complaints and clinical signs. The frequency of follow-up varies with the severity of the condition and the potential for ocular morbidity. Follow-up should be designed to allow for careful monitoring of disease progression and to ensure that the selected treatment regimen is effective. For mild allergic conjunctivitis, follow-up for symptomatic improvement is recommended five to seven days after treatment initiation, whereas patients with moderate to severe signs and symptoms require more careful monitoring (one to four days). As signs and symptoms improve, the frequency of follow-up can be reduced.

Referral criteria

Seasonal and perennial allergic conjunctivitis are rarely referred for further evaluation as there is little to no risk even with continued use of twice daily dosing of dual action drops such as olopatadine 0.1% or ketotifen 0.025%. Referral to an ophthalmologist should occur if the patient experiences changes in vision or they develop corneal involvement. Vernal and atopic keratoconjuncitivitis with corneal involvement should be referred as early as possible for ophthalmological assessment due to their sight-threatening potential.

Informed consent

As with all healthcare interventions, the therapeutic optometrist is responsible for ensuring that the patient has been advised of the possible benefits and risks associated with the prescription medication, in order that the patient can make an informed decision and provide consent to the treatment plan.

References

Abelson, M.B., Ferzola, N.J., McWhirter, C.L., Crampton, H.J. (2004). Efficacy and safety of single- and multiple-dose ketotifen fumarate 0.025% ophthalmic solution in a pediatric population. *Pediatric allergy and immunology*, 15:551-557

Abelson, M.B., Smith, L., Chapin, M. (2003). Ocular allergic disease: mechanisms, disease sub-types, treatment. *Ocular surf,* 1:127-149

Ackerman, S., Smith, L.M., Gomes, P.J. (2016). Ocular itch associated with allergic conjunctivitis: latest evidence and clinical management. *Therapeutic advances in chronic disease*, 7:52-67

Aguilar, A.J. (2000). Comparative study of clinical efficacy and tolerance in seasonal allergic conjunctivitis management with 0.1% olopatadine hydrochloride versus 0.05% ketotifen fumarate. *Acta ophthalmologica Scandinavica supplement*, 230:52-55. https://doi.org/10.1034/j.1600-0420.2000.078s230052.x

Al-Amri, A.M. (2014). Long-term follow-up of tacrolimus ointment for treatment of atopic keratoconjunctivitis. *American journal of ophthalmology,* 157:280-286

Barot, R. K., Shitole, S. C., Bhagat, N., Patil, D., Sawant, P., Patil, K. (2016). Therapeutic effect of 0.1% tacrolimus eye ointment in allergic ocular diseases. *Journal of clinical and diagnostic research,* 10(6), NC05–NC9. https://doi.org/10.7860/JCDR/2016/17847.7978

Berdy, G.J., Spangler, D.L., Bensch, G., Berdy, S.S., Brusatti, R.C. (2000). A comparison of the relative efficacy and clinical performance of olopatadine hydrochloride 0.1% ophthalmic solution and ketotifen fumarate 0.025% ophthalmic solution in the conjunctival antigen challenge model. *Clinical therapeutics,* 22:826-833

Bielory L. (2000). Allergic and immunologic disorders of the eye. Part II: ocular allergy. *Journal of allergy and clinical immunology,* 106:1019-1032.

Bielory L. (2008). Ocular allergy treatment. *Immunology and allergy clinics of North America,* 28(1):189-224, vii. https://doi.org/10.1016/j.iac.2007.12.001

Bilkhu, P.S., Wolffsohn, J.S., Naroo, S.A., Robertson, L., Kennedy, R. (2004). Effectiveness of nonpharmacologic treatments for acute seasonal allergic conjunctivitis. *Ophthalmology,* 121:72-78

Bilkhu, P.S., Naroo, S.A., & Wolffsohn, J.S. (2015). Treatment of ocular allergies: nonpharmacologic, pharmacologic and immunotherapy. *Expert review of ophthalmology*, 10:257-266

Castellsague, J., Kuiper, J.G., Pottegard, A, Berglind, I.A., Dedman, D., Gutierrez, L., Calingaert, B., van Herk-Sukel, M.P., Hallas, J., Sundström, A., Gallagher, A.M., Kaye, J.A., Pardo, C., Rothman, J.J., Perez-Gutthann, S. (2018). A cohort study on the risk of lymphoma and skin cancer in users of topical tacrolimus, pimecrolimus, and corticosteroids (Joint European longitudinal lymphoma and skin cancer evaluation - JOELLE study). *Clinical epidemiology,* 10:299-310. https://doi.org/10.2147/CLEP.S146442

Chatterjee, S., Agrawal, D. (2016) Tacrolimus in corticosteroid-refractory vernal keratoconjunctivitis. *Cornea,* 2016(35): 1444-1448

Erdinest, N, Solomon A. (2014). Topical immunomodulators in the management of allergic eye diseases. *Current opinion in allergy and clinical immunology,*14:457-463

Jabbehdari, S., Starnes, T.W., Kurji, K.H., Eslani, M., Cortina, M.S., Holland,E.J., Djalilian, A.R. (2019). Management of advanced ocular surface disease in patients with severe atopic keratoconjunctivitis. *Ocular surf,* 17(2):303-309. https://doi.org/10.1016/j.jtos.2018.12.002

Kamegasawa, A., Chaoul, M. M., & El Dib, R. (2017). Oral antihistamines for seasonal allergic conjunctivitis. *The Cochrane database of systematic reviews,* 2017(4), CD011172. https://doi.org/10.1002/14651858.CD011172.pub2

Kidd, M., McKenzie, S.H., Steven, I., Cooper, C., Lanz, R., the Australian Ketotifen Study G. (2003). Efficacy and safety of ketotifen eye drops in the treatment of seasonal allergic conjunctivitis. *British journal of ophthalmology,* 87:1206-1211. https://doi.org/10.1136/bjo.87.10.1206

Kumar, S. (2009). Vernal keratoconjunctivitis: a major review. *Acta opthalmologica,* 87:133-147. https://doi.org/10.1111/j.1755-3768.2008.01347.x

Lichtenstein, S.J., Pasquine, T.A., Edwards, M.R., Wells, D.T., Gross, R.D., & Robertson, S.M. (2007). Safety and tolerability of olopatadine 0.2% in children and adolescents. *Journal of ocular pharmacology and therapeutics*, 23:366-371

McGhee, C.N., Dean, S., Danesh-Meyer, H. (2002). Locally administered ocular corticosteroids: benefits and risks. *Drug Safety,* 25:33-55. https://doi.org/10.2165/00002018-200225010-00004

Meltzer, E.O. (2001). Quality of life in adults and children with allergic rhinitis. *Journal of allergy and clinical immunology,* 108:S45-53

Ozcan, A.A., Ersoz, T.R., Dulger, E. (2007). Management of severe allergic conjunctivitis with topical cyclosporin a 0.05% eyedrops. *Cornea,* 26:1035-1038

Schmid, K.L & Schmid, L.M. (2000). Ocular allergy: causes and therapeutic options. *Clinical and experimental optometry,* 83: 257-270. https://doi.org/10.1111/j.1444-0938.2000.tb05014.x

Shoughy S. S. (2017). Topical tacrolimus in anterior segment inflammatory disorders. *Eye and vision (London, England)*, 4,7. https://doi.org/10.1186/s40662-017-0072-z

Salmon, J.F. (2020). Kanski's clinical ophthalmology: a systematic approach (9th ed.): Elsevier. Edinburgh

Samyukta, S.K., Pawar, N., Ravindran, M., Allapitchai, F., & Rengappa, R. (2019). Monotherapy of topical tacrolimus 0.03% in the treatment of vernal keratoconjunctivitis in the pediatric population. *Journal of the American association for pediatric ophthalmology and strabismus (AAPOS),* 23(1):18. https://doi.org/10.1016/j.jaapos.2018.09.010

Vichyanond, P, Kosrirukvongs, P. (2013). Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. *Current allergy and asthma reports,* 13:308-314. https://doi.org/10.1007/s11882-013-0345-0

Please note: These guideline documents are not exhaustive and should be considered 'living' documents that will be added to over time. Conditions outside those described in these guidelines may be deemed out of scope for independent optometric management and require referral to a medical practitioner. If in doubt, please check with the Board for advice.

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