



Act quickly when treating atopic keratoconjunctivitis to avoid adverse outcomes

Adis Medical Writers¹

© Springer Nature Switzerland AG 2019

Abstract

Atopic keratoconjunctivitis (AKC) is the most severe form of allergic conjunctivitis and, if inadequately treated, can cause vision loss. Treatment aims to minimize symptoms, recurrence and consequent eye rubbing, which cause long-term eye damage. First-line treatment generally involves the use of topical ophthalmic formulations of mast-cell stabilizers and/or antihistamines, corticosteroids, calcineurin inhibitors and immunomodulators (used in that order). Systemic formulations of these drugs can be used to treat refractory cases of AKC or when deemed appropriate for the individual.

Atopic keratoconjunctivitis is due to allergies

Atopic keratoconjunctivitis (AKC) is the most serious manifestation of allergic conjunctivitis [1], potentially causing vision loss and severe end-stage dry eye [2]. More prevalent in males, with a peak incidence in individuals aged 30–50 years, severe cases may be associated with sight-threatening complications, such as corneal disease and ocular herpes simplex.

Type I hypersensitivity responses + papillary conjunctivitis are common to both AKC and most less severe forms of allergic conjunctivitis [3]. AKC is generally experienced by people with other atopic conditions, such as eczema or asthma [1] and, in many cases, allergic nasal symptoms. This article summarizes the management options for atopic keratoconjunctivitis (Fig. 1), as reviewed by Ridolo et al. [4].

Leukocyte stimulation likely leads to pathogenesis

A range of cell types appear to be implicated in the pathogenesis of AKC; however, essentially, stimulation of leukocytes and their production of enzymes and proteins appears to cause the corneal involvement, giant papillae formation

and other complications of AKC [4]. Elevated serum immunoglobulin E (IgE) levels are often reported in AKC patients, with a typical IgE-mediated reaction demonstrated via the conjunctival provocation test, which is often used in allergic rhinitis [5]. However, although almost half of AKC patients are not apparently sensitive to common allergens; those who are generally have multiple allergens [6].

T-helper cells not so helpful in this condition

Mast cells, eosinophils, basophils and T-lymphocytes are implicated in the development of AKC [4]. In the tears of people with AKC, increased levels of interferon- γ , tumour necrosis factor- α and interleukins (ILs) confirm the role of T-helper 1 and 2 (T_H1 and T_H2) responses in AKC's pathogenesis [4].

IL-33 signalling has been identified as a significant factor in allergic diseases [7], with an in vitro study demonstrating its role in the regulation of both vascular endothelial cells and giant papillae conjunctival epithelium in patients with AKC [7–9]. Other pro-allergic mediators are also highly expressed in AKC patients' tears and mucus.

Increased activation of eosinophils appears to mediate some corneal complications of AKC, whereas increased quantities of eosinophils in the conjunctiva are found in other allergic eye diseases [10, 11].

✉ Adis Medical Writers
dtp@adis.com

¹ Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

Patient care guidelines

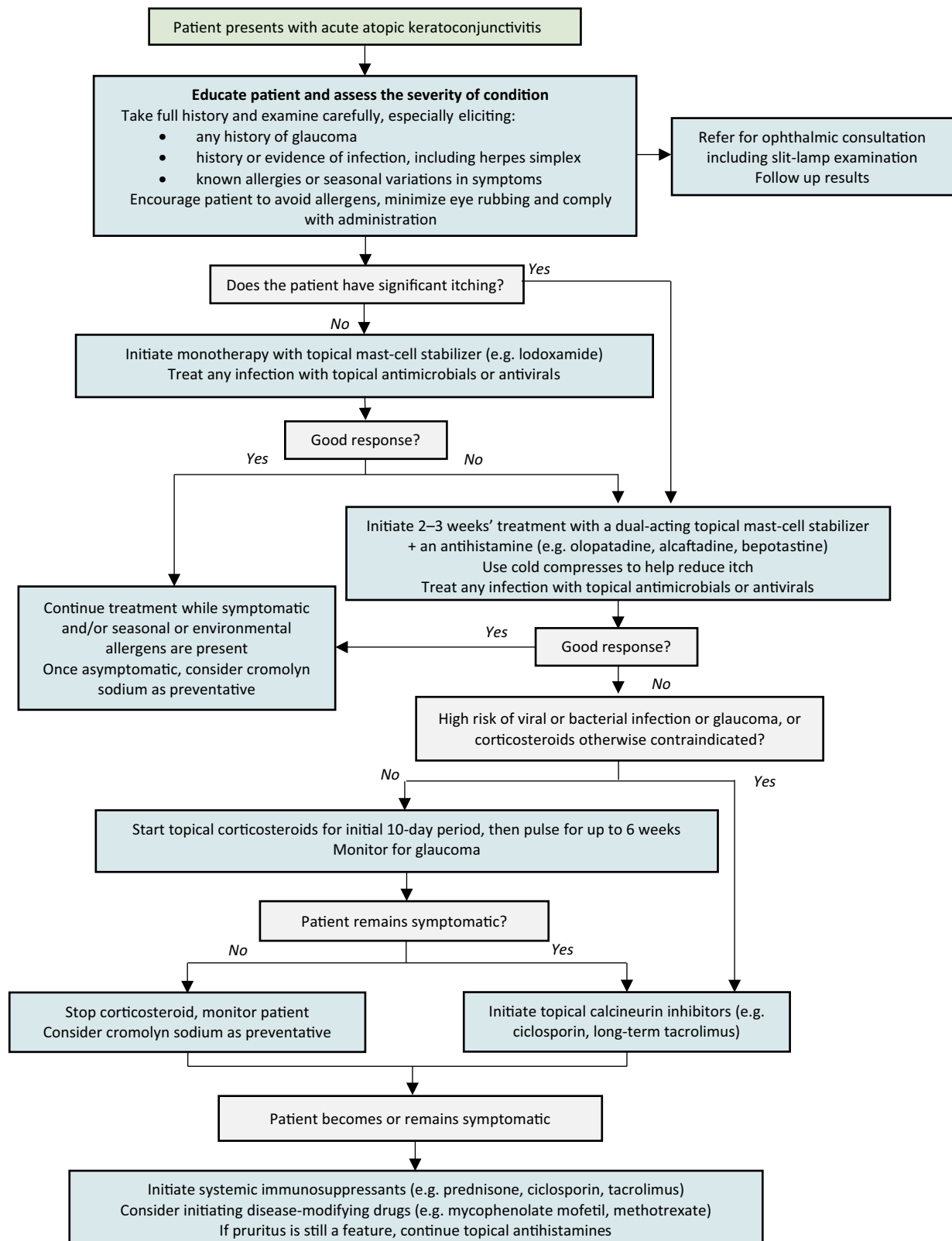


Fig. 1 Management of atopic keratoconjunctivitis as suggested by Ridolo et al. [4]

Table 1 Drug classes used in the topical treatment of atopic keratoconjunctivitis, as reviewed by Ridolo et al. [1]

Examples of topical ophthalmic drugs in drug class	Use of the drug class in AKC
Topical mast cell stabilizers	
Cromolyn sodium 4.0%), lodoxamide (0.1%)	↓ release of proinflammatory mediators, including histamine, from ocular tissue mast cells [2] Lodoxamide: first-line treatment in acute AKC Cromoglycates: more effective in preventing AKC than in its treatment; require frequent daily administration and have a delayed onset of action
Topical antihistamines	
Levocabastine hydrochloride (0.05%), pheniramine maleate(0.3%)	↓ histamine H ₁ -mediated pruritus [13, 15] Efficacy in AKC is unproven [2, 15] Concomitant application of cold compresses may ↑antihistamine effectiveness [21]
Dual-acting antihistamines + mast cell stabilizers	
Olopatidine, alcaftadine, bepotastine, azelastine, epinastine, ketotifen, emedastine	Mast cell stabilization plus H ₁ -receptor blocking properties [22] ↓ inflammation and pruritus Bepotastine: also ↓ eosinophil recruitment and vascular hyperpermeability [23] Use for 2–3 weeks when treatment with a single-acting agent has been ineffective
Corticosteroids	
Loteprednol (0.5%, 0.2%), prednisolone acetate (0.12%, 1.0%), fluorometholone (0.10%), hydrocortisone sodium phosphate (3.35 mg/mL), rimexolone (1%)	Anti-inflammatory, immunomodulatory and anti-mitotic effects, including vasoconstriction, ↓ levels of inflammatory mediators and direct effects on DNA [24] More effective than cromoglycates and antihistamines in AKC Administer as pulse therapy and for a short period (≤6 weeks) [2, 15] Long-term use: ↑ the risk of herpes keratitis and other infections, ocular hypertension and glaucoma [5, 15, 25] Loteprednol 0.2% and fluorometholone 0.10%: have relatively good safety profiles Prednisolone acetate 1.0%: use only for severe AKC
Calcineurin inhibitors	
Ciclosporin A (0.05%), tacrolimus (0.03%, 0.1%)	Block the effects of calcineurin, which is activated by the interaction of antigen-presenting cells and T-cell receptors and which, via its T-cell effects, ↑ interleukin-2 production [15, 21] Use in severe AKC if corticosteroids are contraindicated or therapy is prolonged Ciclosporin 2% instilled 4× day: more effective than placebo in AKC, and ↓ topical corticosteroid use [26]; ciclosporin 1 or 2% can cause stinging and irritation [27, 28] Tacrolimus: more potent immunosuppressant than ciclosporin [21] Continuous tacrolimus significantly ↓ severe AKC, with no adverse drug reactions reported after ≤2 years of therapy [29]

AKC atopic keratoconjunctivitis, ↓ decrease(s), ↑ increase(s)

Look for bilateral itchy and teary eyes...

Itchy, burning and tearing eyes are the most common presenting symptom of AKC [4]. Blurred vision, photophobia and a discharge of stringy mucous are also often reported. Symptoms may be influenced by the season or by environmental allergens [12].

Key areas affected are the eyelids, conjunctiva and cornea [4]. Severe eczema of the eyelid and its surrounds is often accompanied by chronic eyelid inflammation (blepharitis) and staphylococcus infection [13, 14], and sometimes by hyperpigmentation (‘panda eyes’) [15] or infraorbital creases. Bilateral, chronic conjunctival inflammation with papillary hypertrophy is typical, progressing in some cases

to consequent long-term fibrosis and scarring. Patients have low volumes of pre-corneal tear film [12].

... and watch for serious complications

Repeated AKC exacerbations and constant eye rubbing can cause corneal complications. These include punctate keratitis in the early stages and infection-induced corneal ulceration, caused by recurrent herpes simplex and other agents in more advanced AKS; changes in corneal shape (e.g. keratoconus) may also develop. Ultimately, corneal neovascularisation and pannus formation can result in astigmatic changes and permanent marked loss of vision [12].

Table 2 Drug classes used in the systemic treatment of atopic keratoconjunctivitis, as reviewed by Ridolo et al. [1]

Examples of oral drugs in drug class	Use of the drug class in AKC
Antihistamines (second generation)	
Bepotastine, bilastine, cetirizine, ebastine, loratadine, mizolastine, rupatadine and terfenadine	Second-generation histamine H₁-receptor antagonists have better specificity and tolerability than first-generation agents Additional anti-inflammatory properties: rupatadine interacts with platelet activating factor; bepotastine ↓ eosinophil recruitment and vascular hyperpermeability Use oral agents if overall tolerability and compliance is better than with topical agents Bilastine 20 mg/day: improves allergic rhinitis and both nasal and ocular allergy symptoms [30, 31]; has limited CNS adverse effects; is well tolerated in patients including those aged ≥ 65 years, with some reports of somnolence [32] Bepotastine: topical administration is preferred over oral administration, despite its broader anti-inflammatory properties Potential drug interactions: avoid agents mainly metabolized by CYP3A4 (e.g. rupatadine) in patients receiving other potent CYP3A4 inhibitors (e.g. macrolides, protease inhibitors); consider potential interactions in patients receiving moderate CYP3A4 inhibitors (e.g. amiodarone, verapamil, diltiazem) Patients with hepatic dysfunction: consider a ↓ in dosage of agents metabolized by CYP450 (e.g. cetirizine, ebastine, loratadine, rupatadine, terfenadine) [33] Patients with renal dysfunction: consider a ↓ in dosage of agents largely excreted unchanged (e.g. bepotastine, bilastine, mizolastine) [33]
Corticosteroids	
Prednisolone (5–40 mg/day)	Use in severe AKC if topical agents are ineffective within ≤ 6 weeks Adverse drug effects: infection, memory loss, diabetes, depression, psychosis and osteoporosis (all exacerbated with prolonged use)
Calcineurin inhibitors	
Ciclosporin (3–5 mg/kg/day), tacrolimus (0.03–0.08 mg/kg/day)	Effective and well tolerated in severe, refractory AKC (case studies) [34, 35] Use in severe AKC to avoid long-term corticosteroid use, and in AKC with a high risk of complications
Disease-modifying drugs	
Azathioprine, methotrexate, mycophenolate mofetil	Effective therapies for eye inflammation; use in AKC when other agents have been ineffective Mycophenolate mofetil: controlled AKC faster than azathioprine with fewer adverse effects [20]; was corticosteroid-sparing and induced complete and sustained control of AKC [36] Dose-dependent and reversible adverse effects: gastrointestinal intolerance, hepatotoxicity, bone marrow suppression and interstitial pneumonia [37]

AKC atopic keratoconjunctivitis, CYP cytochrome P450, ↓ decrease(s)

AKC has also been associated with retinal detachment and cataracts; subcapsular cataracts may result from oral or topical corticosteroid use [13, 16].

See an ophthalmologist for all suspected cases

If AKC, even of mild severity, is suspected, patients must be referred to an ophthalmologist for slit-lamp examination (Fig. 1) [4]. Slit-lamp examination allows thorough conjunctival examination and may be supplemented by other ophthalmic assessments of inflammation [17]. Allergy testing should also be considered [4], as it may confirm sensitivity even if there is no obvious allergic reaction [18].

Topical medications to start, systemics if needed

Treatment of AKC aims to control immediate symptoms, while minimizing exacerbations and recurrence to decrease the likelihood of vision loss [4]. Mast-cell stabilizers, antihistamines, combinations of the two, corticosteroids and for refractory AKC, calcineurin inhibitors and immunomodulators are all options for AKC treatment (Fig. 1). Ophthalmic drops and ointments (Table 1) are first-line treatments for AKC, as compliance may be better and complications fewer than with systemic treatments (Fig. 1) [4]. However, oral formulations (Table 2) can be used if treatment with ophthalmic

agents fail, or if their use is considered more appropriate for specific patients [4].

If the response to more traditional anti-inflammatory agents is poor, newer immunomodulatory agents should be used without delay (Fig. 1) to prevent severe consequences including the need for surgery [4, 19].

Surgery and disease-modifying drugs may also have a role in AKC treatment. In patients with severe AKC and eye surface disease, surgery may achieve stable or improved vision (vs decreased vision with medication only), based on an analysis of a small sample of 13 people [19]. Disease-modifying drugs have been used successfully in AKC (Table 2) [4, 20], but current data are sparse.

Take home messages

- Treat AKC aggressively as potential long-term consequences include loss of vision.
- Use topical mast cell stabilizers and/or antihistamines as first-line treatment; if the response is not adequate, initiate short-term treatment with corticosteroids, calcineurin inhibitors or immunomodulators without delay.
- Preferably treat with topical agents, but use systemic formulations for refractory AKC.

Compliance with ethical standards

Conflict of interest The article was adapted from *Drugs and Aging* 2019; 36(7) 581–88 [4] by employees of Adis International Ltd./Springer Nature, who are responsible for the article content and declare no conflicts of interest.

Funding The preparation of this review was not supported by any external funding.

References

1. Hogan MJ. Atopic keratoconjunctivitis. *Am J Ophthalmol*. 1953;36(71):937–47.
2. Chen JJ, Applebaum DS, Sun GS, et al. Atopic keratoconjunctivitis: a review. *J Am Acad Dermatol*. 2014;70(3):569–75.
3. Bonini S, Gramiccioni C, Bonini M, et al. Practical approach to diagnosis and treatment of ocular allergy: a 1-year systematic review. *Curr Opin Allergy Clin Immunol*. 2007;7(5):446–9.
4. Ridolo E, Kihlgren P, Pellicelli I, et al. Atopic keratoconjunctivitis: pharmacotherapy for the elderly. *Drugs Aging*. 2019;36(7):581–8.
5. Nivenius E, Van der Ploeg I, Gafvelin G, et al. Conjunctival provocation with airborne allergen in patients with atopic keratoconjunctivitis. *Clin Exp Allergy*. 2012;42(1):58–65.
6. Bonini S. Atopic keratoconjunctivitis. *Allergy*. 2004;59(Suppl 78):71–3.
7. Ding W, Zou GL, Zhang W, et al. Interleukin-33: its emerging role in allergic diseases. *Molecules*. 2018. <https://doi.org/10.3390/molecules23071665>.
8. Lin J, Zhao GQ, Wang Q, et al. Regulation of interleukin 33/ST2 signaling of human corneal epithelium in allergic diseases. *Int J Ophthalmol*. 2013;6:23–9.
9. Leonardi A, Jose PJ, Zhan H, et al. Tear and mucus eotaxin-1 and eotaxin-2 in allergic keratoconjunctivitis. *Ophthalmology*. 2003;110(3):487–92.
10. Oshinskie L, Haine C. Atopic dermatitis and its ophthalmic complications. *J Am Optom Assoc*. 1982;53(11):889–94.
11. Rich LF, Hanifin JM. Ocular complications of atopic dermatitis and other eczemas. *Int Ophthalmol Clin*. 1985;25(1):61–76.
12. Zhan H, Smith L, Calder V, et al. Clinical and immunological features of atopic keratoconjunctivitis. *Int Ophthalmol Clin*. 2003;43(1):59–71.
13. Bielory L. Allergic and immunologic disorders of the eye. Part II: ocular allergy. *J Allergy Clin Immunol*. 2000;106(6):1019–32.
14. Tuft SJ, Ramakrishnan M, Seal DV, et al. Role of *Staphylococcus aureus* in chronic allergic conjunctivitis. *Ophthalmology*. 1992;99(2):180–4.
15. Guglielmetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2010;10(5):478–85.
16. Spergel JM. Immunology and treatment of atopic dermatitis. *Am J Clin Dermatol*. 2008;9(4):233–44.
17. Wakamatsu TH, Okada N, Kojima T, et al. Evaluation of conjunctival inflammatory status by confocal scanning laser microscopy and conjunctival brush cytology in patients with atopic keratoconjunctivitis (AKC). *Mol Vis*. 2009;15:1611–9.
18. Wise SK, Lin SY, Toskala E, et al. International consensus statement on allergy and rhinology: allergic rhinitis. *Int Forum Allergy Rhinol*. 2018;8(2):108–352.
19. Jabbehdari S, Starnes TW, Kurji KH, et al. Management of advanced ocular surface disease in patients with severe atopic keratoconjunctivitis. *Ocul Surf*. 2019;17(2):303–9.
20. Galor A, Jabs DA, Leder HA. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. *Ophthalmology*. 2008;115(10):1826–32.
21. Bielory L, Schoenberg D. Emerging therapeutics for ocular surface disease. *Curr Allergy Asthma Rep*. 2019;19(3):16.
22. Shaker M, Salcone E. An update on ocular allergy. *Curr Opin Allergy Clin Immunol*. 2016;16(5):505–10.
23. Lyseng-Williamson KA. Oral bepotastine: in allergic disorders. *Drugs*. 2010;70(12):1579–91.
24. Coondoo A, Phiske M, Verma S, et al. Side-effects of topical steroids: a long overdue revisit. *Indian Dermatol Online J*. 2014;5(4):416–25.
25. Attas-Fox L, Barkana Y, Iskhakov V, et al. Topical tacrolimus 0.03% ointment for intractable allergic conjunctivitis: an open-label pilot study. *Curr Eye Res*. 2008;33(7):545–9.
26. Hingorani M, Moodaley L, Calder VL, et al. A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. *Ophthalmology*. 1998;105(9):1715–20.
27. Tesse R, Spadavecchia L, Fanelli P, et al. Treatment of severe vernal keratoconjunctivitis with 1% topical cyclosporine in an Italian cohort of 197 children. *Pediatr Allergy Immunol*. 2010;21(2 Pt 1):330–5.
28. Daniell M, Constantinou M, Vu HT, et al. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. *Br J Ophthalmol*. 2006;90(4):461–4.
29. Miyazaki D, Tominaga T, Kakimaru-Hasegawa A, et al. Therapeutic effects of tacrolimus ointment for refractory ocular surface inflammatory diseases. *Ophthalmology*. 2008;115(6):988–92.e5.

-
30. Ridolo E, Montagni M, Bonzano L, et al. Bilastine: new insight into antihistamine treatment. *Clin Mol Allergy*. 2015;13(1):1.
 31. Bousquet J, Ansotegui I, Canonica GW, et al. Establishing the place in therapy of bilastine in the treatment of allergic rhinitis according to ARIA: evidence review. *Curr Med Res Opin*. 2012;28(1):131–9.
 32. Sologuren A, Vinas R, Cordon E, et al. Open-label safety assessment of bilastine in elderly patients with allergic rhinoconjunctivitis and/or urticaria. *Allergy Asthma Proc*. 2018;39(4):299–304.
 33. Simons FE. Comparative pharmacology of H1 antihistamines: clinical relevance. *Am J Med*. 2002;113(Suppl 9A):38s–46s.
 34. Stumpf T, Luqmani N, Sumich P, et al. Systemic tacrolimus in the treatment of severe atopic keratoconjunctivitis. *Cornea*. 2006;25(10):1147–9.
 35. Hoang-Xuan T, Prisant O, Hannouche D, et al. Systemic cyclosporine A in severe atopic keratoconjunctivitis. *Ophthalmology*. 1997;104(8):1300–5.
 36. Daniel E, Thorne JE, Newcomb CW, et al. Mycophenolate mofetil for ocular inflammation. *Am J Ophthalmol*. 2010;149(3):423–32.
 37. Hornbeak DM, Thorne JE. Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention. *Taiwan J Ophthalmol*. 2015;5(4):156–63.