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Allergic conjunctivitis in Asia

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Allergic conjunctivitis (AC), which may be acute or chronic, is associated with rhinitis in 30%–70% of affected individuals, hence the term allergic rhinoconjunctivitis (AR/C). Seasonal and perennial AC is generally milder than the more chronic and persistent atopic and vernal keratoconjunctivitis. Natural allergens like house dust mites (HDM), temperate and subtropical grass and tree pollen are important triggers that drive allergic inflammation in AC in the Asia-Pacific region. Climate change, environmental tobacco smoke, pollutants derived from fuel combustion, Asian dust storms originating from central/north Asia and phthalates may also exacerbate AR/C. The Allergies in Asia Pacific study and International Study of Asthma and Allergies in Childhood provide epidemiological data on regional differences in AR/C within the region. AC significantly impacts the quality of life of both children and adults, and these can be measured by validated quality of life questionnaires on AR/C. Management guidelines for AC involve a stepped approach depending on the severity of disease, similar to that for allergic rhinitis and asthma. Topical calcineurin inhibitors are effective in certain types of persistent AC, and sublingual immunotherapy is emerging as an effective treatment option in AR/C to grass pollen and HDM. Translational research predominantly from Japan and Korea involving animal models are important for the potential development of targeted pharmacotherapies for AC.

Key words: Allergens; Allergen immunotherapy; Epidemiology; Quality of life

INTRODUCTION

Ocular allergies affect 6%–30% of the general population. Allergic conjunctivitis (AC) [1], which may be acute or chronic, is associated with allergic rhinitis (AR) in 30%–70% of affected individuals, where majority have few episodes of mild conjunctivitis annually. Up to 30% of AC sufferers may have frequent episodes with intense and persistent symptoms (especially seasonal AC) [2]. The most common presenting symptoms are red and itchy eyes, followed by burning, stinging sensation, swelling and tearing.

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are usually mild, occurs in atopic individuals, with ocular inflammation driven by IgE-mediated mechanisms. Symptoms are intermittent in SAC and persistent in PAC.

Corneal involvement is a feature of vernal keratoconjunctivitis

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(VKC) and atopic keratoconjunctivitis (AKC) where both IgE and non-IgE mediated allergic inflammation occurs. VKC which may be intermittent or persistent, affects boys aged 5–15 years old, where inflammation of the palpebral conjunctiva can lead to the development of giant papillae on the superior tarsal conjunctiva, copious fibrinous discharge, yellow-white points on the conjunctiva (Trantas dots) which are an aggregation of epithelial cells and eosinophils, lower eyelid creasing (Dennie's lines) and pseudomembrane formation on the upper lid. AKC which is usually chronic, affects late teens and young adults in their early 20s with peak incidence at the age of 30s–50s. It is associated with eye/eyelid involvement in atopic dermatitis (AD) in 20%–43%, and AD in 95% of cases. A personal or family history of atopy is nearly always present.

Contact lens-induced papillary conjunctivitis (CLPC) is a common ocular allergic disease affecting contact lens wearers. In its more severe form, it can cause giant papillary conjunctivitis, resulting in contact lens intolerance and the need to discontinue the use of contact lenses. Refitting patients with silicone hydrogel contact lenses or with daily disposable contact lenses may improve the signs and symptoms of CLPC [3, 4].

EPIDEMIOLOGY IN ASIA

There are few community-based prevalence studies on AC alone. Hospital-based case series tend to be biased towards more severe forms, in particular AKC and VKC. AC is often classified with AR as allergic rhinoconjunctivitis (AR/C) in many studies. The lack of use of validated survey instruments on AC comprising symptom scores (itchy, watery, red eyes), correlation of symptoms in relation to pollen/animal exposure, and lack of doctor diagnosis in various studies also make many studies noncomparable [5].

Most of the studies on VKC in the Asia-Pacific region originate from Japan, Thailand [6], India [7], and Singapore [8]. The age of onset is before the age of 10 years in these studies, with majority outgrowing their VKC at puberty. AKC in the region usually occurs among adults in their 20s to 30s with a history of AD in up to 40%.

The Allergies in Asia Pacific Study (AIAP) [9] was a cross-sectional study across 9 countries comprising 33,378 households screened. Information on nasal allergies, quality of life (QoL), and current treatments was obtained through telephone and in-person interviews. Among the 192 children (aged 4–17 years old) and 1,043 adults (aged 18 years old and above), 9% were diagnosed with AR among whom two-thirds had seasonal symptoms. Nasal congestion was the most common and bothersome symptom. Fifty percent of respondents reported that AR impacted their QoL, school/work performance and productivity. Only two-thirds of patients with AR took medications, of which less than 25% used intranasal corticosteroid, citing inadequate efficacy and bothersome side effects. In the AIAP study, the overall prevalence of ocular symptoms varied from 31% with red, itchy eyes to 41% with watery eyes. Ocular symptoms were present in 20%–30% in most of East and southeast Asia, whereas this was significantly higher with up to 56%–60% in Australia, likely to have been contributed by seasonal allergies. In contrast the overall prevalence was much lower in the International Study of Asthma and Allergies in Childhood studies [10, 11] where nasal and ocular symptoms were present overall in 14% regardless whether in southeast Asia or Australia.

NATURAL ALLERGENS AND POLLUTANTS

Urbanization, industrialization and climate change have led to rapidly occurring changes to both the indoor and outdoor environment. This has significant implications on the prevalence and management of allergic disease, including AC [12]. Rising temperatures, precipitation and more extreme weather have resulted in longer or earlier pollen seasons, thus increasing environmental carbon dioxide and temperature [13, 14].This leads to increased sporulation and antigen production of *Alternaria alternata* [15] and potential increase in house dust mite burden.

Outdoor air pollution is a major risk factor for rhinoconjunctivitis where key contributors are fuel combustion and dust storms because of changes in land-use and development. Relevant air pollutants exacerbating rhinoconjunctivitis include environmental tobacco smoke, pollutants derived from fuel combustion, Asian dust storms originating from Central/North Asia and phthalates. Phthalates are plasticizers used in plastic products (e.g., toys, food containers, paints) which may aerosolize and settle in dust especially affecting children. Air pollutants may be allergenic, irritant or a combination of both. Common pollutants include nitrogen dioxide, carbon monoxide, ozone, sulphur dioxide, and particulate matter [16]. Asian dust storms affect much of East Asia during spring where dust blown from the deserts of Mongolia, China and Kazakhstan is carried eastwards to Korea, Japan, Russia and even the United States. An

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increase in rhinitis visits in Taipei following an Asian dust storm has been reported [17].

QUALITY OF LIFE

Symptoms of AR/C impair the health related QoL of AC patients in Asia by adversely impacting sleep, daily activities, physical and mental status and social functioning. QoL is usually measured with the generic Short Form-36; or disease-specific Rhinitis Quality of Life Questionnaire (RQLQ), mini-RQLQ and Pediatric RQLQ (PRQLQ). Impairment of QoL is similar to that demonstrated in studies on AR/C patients in Europe and the United States. Overall control of AR/C should encompass objective nasal and ocular symptoms, QoL, comorbid conditions and effect on patients' cognition [18].

The Japanese Allergic Conjunctival Disease (ACD) QoL questionnaire [19] is a specific QoL questionnaire. This was administered to 521 ACD patients and 127 healthy volunteers. It was developed by modifying the Japanese rhino-conjunctivitis QoL questionnaire. The items were grouped into 4 subscales after factor analysis, daily activity, psychological well-being, eye symptoms and nasal symptoms. Good item-internal consistency (Cronbach alpha, 0.846–0.934) was found, and QoL scores were correlated with eye itching, eye irritation and tearing. This questionnaire has not been validated outside of Japan: it would need to be validated if used in other Asian populations, with translation and back-translations done.

MANAGEMENT

Several practice guidelines on the management of AC have been published including those from Europe [3], Latin America [20], Japan [21] and Spain [22]. Principles of management include [23, 24]:

First line: allergen identification and avoidance, avoidance of eye rubbing and contact lens wear during symptomatic periods, treatment of tear film dysfunction, cool compress, topical dual-acting antihistamine/mast cell stabilizers, oral nonsedating anti-H_1 antihistamines, treatment of coexisting AR;

Second line: consider preservative-free topical therapy, topical steroids (short course), oral steroids (short course), subcutaneous or sublingual allergen immunotherapy (AIT);

Third line: topical immunomodulators e.g., calcineurin inhibitors, Omalizumab anti-IgE monoclonal antibody in severe VKC/AKC, especially in the presence of concurrent asthma or chronic urticaria.

Management guidelines for AC involve a stepped approach depending on the severity of disease, similar to that for AR (Allergic Rhinitis and its Impact on Asthma, ARIA 2010) and asthma (Global Initiative for Asthma, GINA 2017). Although one of the most common ocular disorders in pediatric patients, AC is frequently overlooked, misdiagnosed, and undertreated in children. There is a paucity of best practice guidelines for the treatment of paediatric AC [25].

TOPICAL CALCINEURIN INHIBITORS

The topical calcineurin inhibitor Ciclosporin (CsA) (Restasis, Allergan, Parsippany-Troy Hills, NJ, USA) 0.05%–0.1% has been shown to be of variable efficacy in VKC and AKC; and 1.00% and 1.25% has been used for severe forms. This is supported by data from case series [26, 27] and systematic reviews [28] published from the region. Adverse drug reactions include mild and transient burning (2%). A case series from Hong Kong [29] comprising 14 children with AC, VKC, AKC with mean age 10.8 ± 3.2 years showed that topical CsA 0.05% Restasis reduced symptoms, signs, and itch severity scores compared with baseline ($p \leq 0.001$) and 78.6% of subjects successfully tapered off steroid eye drops. A placebo-controlled, randomized prospective study from Turkey [30] on 62 subjects with VKC over 4 weeks showed a reduction in mean posttreatment scores in the CsA vs placebo group ($p < 0.001$); with no adverse effects. A prospective observational postmarketing study from Japan [31] on 594 patients with VKC or AKC using 0.1% aqueous ophthalmic CsA demonstrated reduction in scores for symptoms and signs from month 1–6, and 30% discontinuation of topical steroids. Adverse drug reactions which occurred in 12% comprised eye irritation (4.4%) and corneal infections (5 AKC) (bacterial ulcer, 2; herpetic keratitis, 3) where all patients were concomitantly receiving topical steroids.

Topical Tacrolimus (Protopic, Astellas Pharma Tech Co., Ltd., Toyama, Japan) is 100 fold more potent than Ciclosporin. Topical 0.005% is used for steroid resistant refractory VKC, and 0.03% [32] and 0.1% [33] ointments have been demonstrated to be effective over 4–48 weeks. The 0.1% [34] ophthalmic suspension (Senju

Pharmaceutical Co., Osaka, Japan) are effective within 4 weeks. Tear periostin is a potential biomarker of response to topical Tacrolimus [35]. In a prospective observational study of 1,436 patients with refractory AC and poor response to antiallergic drugs with/without topical steroids with/without topical cyclosporine, 0.1% Tacrolimus eye drops was found to reduce signs and symptoms of AC in 1 month, and 50% of the patients were taken off topical steroids.

ALLERGEN IMMUNOTHERAPY

AIT improves ocular symptoms and signs using both subcutaneous immunotherapy (SCIT) (more for polysensitized individuals) and sublingual immunotherapy (SLIT) [36, 37]. The duration of effect persists for up to 5 years after termination of SCIT. Clinical trials have shown 2–3 times improvement in visual analog scale and ocular symptom scores; and conjunctival surface challenge required 10–100 times more allergen to provoke a response. Combined symptom and medication score are recommended as the primary outcome measure in all AIT clinical trials [38], with AIT reducing total (nasal plus ocular) symptom/medication score 27%–28% in adults and children [39].

GRASS POLLEN ALLERGEN IMMUNOTHERAPY

Ragwitek SLIT tablet (Catalent Pharma Solutions Ltd., Wiltshire, UK) containing short ragweed pollen allergen extract approved for use in 18–65 year olds, has been found to improve short ragweed-induced AR/C in 784 adults who participated in a randomized, double-blind multinational trial in North America and Europe [40]. Oralair SLIT (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue) (Catalent Pharma Solutions Ltd.) 5-grass mixed pollens allergen extract is approved for children and adults aged 10–65 years old. It improved symptom scores in 473 adults in the United States with grass pollen AR/C who received preseasonal and coseasonal treatment with the 300IR 5-grass pollen sublingual tablets [41]. A prolonged effect of 5-grass SLIT up to 2 years after treatment cessation was also observed [42]. Grazax/Grastek Timothy grass pollen SLIT tablet (Catalent Pharma Solutions Ltd.) is the only approved therapy for children as young as 5 years old with Timothy grass pollen AR/C [43].

Grass pollens of the temperate (Pooideae) subfamily and subtropical subfamilies of grasses are major aeroallergens worldwide. The subtropical Chloridoideae (e.g., *Cynodon dactylon;* Bermuda grass) and Panicoideae (e.g., *Paspalum notatum;* Bahia grass) species are abundant in parts of Africa, India, Asia, Australia, and the Americas, often more so than temperate grasses [44]. This knowledge of regional differences in aerospora is important in understanding the appropriateness of various grass pollen AIT products which would be more likely to be effective in patients from the Asia-Pacific region. There have been no studies on grass pollen AIT on AR/C in the region.

HOUSE DUST MITE ALLERGEN IMMUNOTHERAPY

HDM are an important cause of perennial AR/C, where HDM sensitization due to *Dermatophagoides pteronyssinus, Dermatophagoides farinae, and Blomia tropicalis* (the latter in tropical regions of Southeast Asia) is prevalent. SCIT to HDM and weed pollen extract manufactured in China has been shown to improve the QoL in adults with AR/C over 1 year [45]. SLIT to HDM has also been shown to be effective in HDM AR/C by improving nasal and ocular symptoms, which exceeded World Allergy Organization-established clinical efficacy criteria (≥20% improvement versus placebo) by 8 weeks [46]. In a Singapore study, SLIT to all 3 HDM species was found to be effective following pooled analysis in both children and adults [47]. SQ ALK-Abello HDM SLIT tablet has been approved in 11 European countries and Japan for patients with HDM-induced respiratory allergic disease. A randomized, double-blind, placebo-controlled trial [48] comprising 946 Japanese adults and adolescents (12–64 years) with moderate to severe HDM AR showed statistically significant reductions in total combined rhinitis score compared with the placebo group evident from 12 weeks of treatment. Symptom improvement in AR/C which were secondary end points, were statistically significant in favor of active treatment compared with placebo, with *post hoc* analysis of TCRSs in adolescents showing the same efficacy as in adults.

TRANSLATIONAL RESEARCH USING ANIMAL MODELS OF ALLERGIC CONJUNCTIVITIS

Much of the translational research done in the Asia-Pacific region on potential treatments in AC come from Japan and Korea.

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Tacrolimus 0.01%–1% eye drops have been shown to inhibit T cell and eosinophil infiltration in the late responses in ocular allergy models in rats and guinea pigs [49]. Topical Tacrolimus has also been showed to reduce allergic inflammation in conjunctiva by reducing eosinophil and lymphocyte infiltration into subconjunctival tissue in the Balb/c mice of the ovalbumin sensitized experimental allergic conjunctivitis (OVA-EAC) model [50].

Toll-like receptor 2 (TLR2) activation also occurs in AC. A designed small peptide ZY12 was found to contain therapeutic potential in staphylococcal enterotoxin B-induced AC model, where treatment with ZY12 significantly inhibited TLR2 expression in conjunctival tissue, with remission of clinical signs, plasma total IgE levels, number of mast cells and the proportion of degranulated mast cell in mice with AC [51].

Topical application of IL-28A to OVA-EAC reduced clinical symptoms, serum OVA-specific IgE, and the infiltration of eosinophils in the conjunctiva; suppressed the expression of interleukin (IL)-4, IL-5, and IL-13 (Th2-type cytokine) but promoted the expression of interferon-γ (Th1-type cytokine) by splenocytes and cervical lymph node cells in EAC mice. Thus topical IL-28A has a potential therapeutic role in AC [52].

Transient receptor potential vanilloid-1 (TRPV1) has been implicated as a mediator of itch in AR. TRPV1 antagonist was shown in murine models to attenuate the clinical signs of AC and OVA-specific IgE in sera, and inhibited the infiltration of inflammatory cells into conjunctiva and the production of Th2 cytokines in lymph nodes [53].

IgG1 monoclonal antibody (mAb) Fabs targeting Japanese cedar pollen (JCP) Cry j1 have been shown to regulate JCP-induced AC in mice. It was effective in suppressing JCP-induced AC in mice, suggesting the possibility that some epitopes recognized by Fabs could be used as a tool to regulate AC [54].

Topical application of β-1,3-glucan (BG), a cell wall component of a variety of fungi, yeasts, and bacteria attenuates AC in BALB/c mice sensitized to intraperitoneal OVA by stimulating IL-10-producing CD4+ T cells and suppressing both the Th2 response in draining lymph nodes and conjunctival eosinophil infiltration. This suggests a therapeutic potential of topical BG administration in AC [55].

Curcumin is a yellow pigment isolated from *Curcuma longa L* (turmeric), a powerful anti-inflammatory agent. Curcumin administration in a OVA-EAC mouse model markedly suppressed IgE-mediated and eosinophil-dependent conjunctival inflammation. Mice administered curcumin had less IL-4 and IL-5 (Th2 type cytokine) production in the conjunctiva, spleen, and cervical lymph nodes than mice in the non–curcumin-administered group. OVA challenge resulted in activation of the production of inducible nitric oxide (iNOS), and curcumin treatment inhibited iNOS production in the conjunctiva [56].

CONCLUSION

AC comprises a spectrum of conditions across different age-groups, both acute and chronic. In the Asia-Pacific region, persistent AR/C from house dust mite allergy is more common than intermittent seasonal AR/C. Much work has been done in Japan and Korea (epidemiology, basic science, drug development) and Thailand (epidemiology, clinical). Topical calcineurin inhibitors are effective for severe, chronic AC. AIT has a definitive/ adjunctive role in refractory cases or mild seasonal/ perennial cases. There is great potential for studies on HDM-AIT in Asian AR/C.

REFERENCES

1. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol 2004;113:832-6.
2. Leonardi A, Castegnaro A, Valerio AL, Lazzarini D. Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study. Curr Opin Allergy Clin Immunol 2015;15:482-8.
3. Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, Doan S, Marmouz F, Demoly P, Delgado L. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. Allergy 2012;67:1327-37.
4. Solomon A. Allergic manifestations of contact lens wearing. Curr Opin Allergy Clin Immunol 2016;16:492-7.
5. Katelaris CH. Ocular allergy in the Asia Pacific region. Asia Pac Allergy 2011;1:108-14.
6. Uthaisangsook S. Prevalence of asthma, rhinitis, and eczema in the university population of Phitsanulok, Thailand. Asian Pac J Allergy Immunol 2007;25:127-32.

7. Yadav SP, Goel HC, Chanda R, Ranga R, Gupta KB. A clinical profile of allergic rhinitis in Haryana. Indian J Allergy Asthma Immunol 2001;15:13-5.
8. Choi H, Lee SB. Nonseasonal allergic conjunctivitis in the tropics: experience in a tertiary care institution. Ocul Immunol Inflamm 2008;16:141-5.
9. Katelaris CH, Lai CK, Rhee CS, Lee SH, Yun WD, Lim-Varona L, Quang VT, Hwang J, Singh H, Kim J, Boyle JM, Dhong HJ, Narayanan P, Vicente G, Blaiss M, Sacks R. Nasal allergies in the Asian-Pacific population: results from the Allergies in Asia-Pacific Survey. Am J Rhinol Allergy 2011;25 Suppl 1:S3-15.
10. Aït-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J; ISAAC Phase Three Study Group. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy 2009;64:123-48.
11. Fok AO, Wong GW. What have we learnt from ISAAC phase III in the Asia-Pacific rim? Curr Opin Allergy Clin Immunol 2009;9:116-22.
12. Jalbert I, Golebiowski B. Environmental aeroallergens and allergic rhino-conjunctivitis. Curr Opin Allergy Clin Immunol 2015;15:476-81.
13. van Vliet AJ, Overeem A, De Groot R, Jacobs AF, Spieksma FT. The influence of temperature and climate change on the timing of pollen release in the Netherlands. Int J Climatol 2002;22:1757-67.
14. Ziska L, Knowlton K, Rogers C, Dalan D, Tierney N, Elder MA, Filley W, Shropshire J, Ford LB, Hedberg C, Fleetwood P, Hovanky KT, Kavanaugh T, Fulford G, Vrtis RF, Patz JA, Portnoy J, Coates F, Bielory L, Frenz D. Recent warming by latitude associated with increased length of ragweed pollen season in central North America. Proc Natl Acad Sci U S A. 2011;108:4248-51.
15. Wolf J, O'Neill NR, Rogers CA, Muilenberg ML, Ziska LH. Elevated atmospheric carbon dioxide concentrations amplify Alternaria alternata sporulation and total antigen production. Environ Health Perspect 2010;118:1223-8.
16. Mimura T, Ichinose T, Yamagami S, Fujishima H, Kamei Y, Goto M, Takada S, Matsubara M. Airborne particulate matter (PM2.5) and the prevalence of allergic conjunctivitis in Japan. Sci Total Environ 2014;487:493-9.
17. Chang CC, Lee IM, Tsai SS, Yang CY. Correlation of Asian dust storm events with daily clinic visits for allergic rhinitis in Taipei, Taiwan. J Toxicol Environ Health A 2006;69:229-35.
18. Maspero J, Lee BW, Katelaris CH, Potter PC, Cingi C, Lopatin A, Saffer M, Nadeau G, Walters RD. Quality of life and control of allergic rhinitis in patients from regions beyond western Europe and the United States. Clin Exp Allergy 2012;42:1684-96.
19. Fukagawa K, Fujishima H, Fukushima A, Sumi T, Okamoto S, Shoji J, Satake Y, Ohno S, Namba K, Kitaichi N, Ebihara N, Takahashi H, Kumagai N, Uchino Y, Uchino M, Murayama K, Sakata M, Uchio E, Takamura E, Ohashi Y, Ohkubo K, Satoh T. A quality of life questionnaire for Japanese allergic conjunctival disease. Nippon Ganka Gakkai Zasshi 2012;116:494-502.
20. Santos MS, Alves MR, Freitas Dd, Sousa LB, Wainsztein R, Kandelman S, Lozano M, Beltrán F, Lozada OB, Santacruz C, Guzzo G, Zaccarelli Filho CA, Gomes JÁ. Ocular allergy Latin American consensus. Arq Bras Oftalmol 2011;74:452-6.
21. Takamura E, Uchio E, Ebihara N, Ohno S, Ohashi Y, Okamoto S, Kumagai N, Satake Y, Shoji J, Nakagawa Y, Namba K, Fukagawa K, Fukushima A, Fujishima H; Japanese Society of Allergology. Japanese guidelines for allergic conjunctival diseases 2017. Allergol Int 2017;66:220-9.
22. Sánchez-Hernández MC, Montero J, Rondon C, Benitez del Castillo JM, Velázquez E, Herreras JM, Fernández-Parra B, Merayo-Lloves J, Del Cuvillo A, Vega F, Valero A, Panizo C, Montoro J, Matheu V, Lluch-Bernal M, González ML, González R, Dordal MT, Dávila I, Colás C, Campo P, Antón E, Navarro A; SEAIC 2010 Rhinoconjunctivitis Committee; Spanish Group Ocular Surface-GESOC. Consensus document on allergic conjunctivitis (DECA). J Investig Allergol Clin Immunol 2015;25:94-106.
23. Bielory L, Meltzer EO, Nichols KK, Melton R, Thomas RK, Bartlett JD. An algorithm for the management of allergic conjunctivitis. Allergy Asthma Proc 2013;34:408-20.
24. Shaker M, Salcone E. An update on ocular allergy. Curr Opin Allergy Clin Immunol 2016;16:505-10.
25. Berger WE, Granet DB, Kabat AG. Diagnosis and management of allergic conjunctivitis in pediatric patients. Allergy Asthma Proc 2017;38:16-27.
26. Vichyanond P, Kosrirukvongs P. Use of cyclosporine A and tacrolimus in treatment of vernal keratoconjunctivitis. Curr Allergy Asthma Rep 2013;13:308-14.
27. Labcharoenwongs P, Jirapongsananuruk O, Visitsunthorn N, Kosrirukvongs P, Saengin P, Vichyanond P. A double-masked comparison of 0.1% tacrolimus ointment and 2% cyclosporine eye drops in the treatment of vernal keratoconjunctivitis in children. Asian Pac J Allergy Immunol 2012;30:177-84.
28. Wan KH, Chen LJ, Rong SS, Pang CP, Young AL. Topical cyclosporine in the treatment of allergic conjunctivitis: a meta-analysis. Ophthalmology 2013;120:2197-203.
29. Wu MM, Yau GS, Lee JW, Wong AL, Tam VT, Yuen CY. Retrospective review on the use of topical cyclosporin a 0.05% for paediatric

https://doi.org/10.5415/apallergy.2017.7.2.57

allergic conjunctivitis in Hong Kong Chinese. ScientificWorldJournal 2014;2014:396987.
30. Keklikci U, Dursun B, Cingu AK. Topical cyclosporine a 0.05% eyedrops in the treatment of vernal keratoconjunctivitis - randomized placebo-controlled trial. Adv Clin Exp Med 2014;23:455-61.
31. Ebihara N, Ohashi Y, Uchio E, Okamoto S, Kumagai N, Shoji J, Takamura E, Nakagawa Y, Nanba K, Fukushima A, Fujishima H. A large prospective observational study of novel cyclosporine 0.1% aqueous ophthalmic solution in the treatment of severe allergic conjunctivitis. J Ocul Pharmacol Ther 2009;25:365-72.
32. Hazarika AK, Singh PK. Efficacy of topical application of 0.03% tacrolimus eye ointment in the management of allergic conjunctivitis. J Nat Sci Biol Med 2015;6(Suppl 1):S10-2.
33. Al-Amri AM. Long-term follow-up of tacrolimus ointment for treatment of atopic keratoconjunctivitis. Am J Ophthalmol 2014;157:280-6.
34. Fukushima A, Ohashi Y, Ebihara N, Uchio E, Okamoto S, Kumagai N, Shoji J, Takamura E, Nakagawa Y, Namba K, Fujishima H, Miyazaki D. Therapeutic effects of 0.1% tacrolimus eye drops for refractory allergic ocular diseases with proliferative lesion or corneal involvement. Br J Ophthalmol 2014;98:1023-7.
35. Fujishima H, Okada N, Matsumoto K, Fukagawa K, Igarashi A, Matsuda A, Ono J, Ohta S, Mukai H, Yoshikawa M, Izuhara K. The usefulness of measuring tear periostin for the diagnosis and management of ocular allergic diseases. J Allergy Clin Immunol 2016;138:459-67.e2.
36. Tabatabaian F, Casale TB. Selection of patients for sublingual immunotherapy (SLIT) versus subcutaneous immunotherapy (SCIT). Allergy Asthma Proc 2015;36:100-4.
37. Calderon MA, Penagos M, Sheikh A, Canonica GW, Durham S. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev 2011;(7):CD007685.
38. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, Durham SR, Jacobsen L, Malling HJ, Mösges R, Papadopoulos NG, Rak S, Rodriguez del Rio P, Valovirta E, Wahn U, Calderon MA; European Academy of Allergy and Clinical Immunology. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy 2014;69:854-67.
39. Li JT, Bernstein DI, Calderon MA, Casale TB, Cox L, Passalacqua G, Pfaar O, Papadopoulos NG. Sublingual grass and ragweed immunotherapy: Clinical considerations-a PRACTALL consensus report. J Allergy Clin Immunol 2016;137:369-76.
40. Creticos PS, Maloney J, Bernstein DI, Casale T, Kaur A, Fisher R, Liu N, Murphy K, Nékám K, Nolte H. Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European adults. J Allergy Clin Immunol 2013;131:1342-9.e6.
41. Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. J Allergy Clin Immunol 2012;130:1327-34.e1.
42. Didier A, Malling HJ, Worm M, Horak F, Sussman GL. Prolonged efficacy of the 300IR 5-grass pollen tablet up to 2 years after treatment cessation, as measured by a recommended daily combined score. Clin Transl Allergy 2015;5:12.
43. Dahl R, Roberts G, de Blic J, Canonica GW, Kleine-Tebbe J, Nolte H, Lawton S, Nelson HS. SQ grass sublingual allergy immunotherapy tablet for disease-modifying treatment of grass pollen allergic rhinoconjunctivitis. Allergy Asthma Proc 2016;37:92-104.
44. Davies JM. Grass pollen allergens globally: the contribution of subtropical grasses to burden of allergic respiratory diseases. Clin Exp Allergy 2014;44:790-801.
45. Li L, Guan K. Effect on quality of life of the mixed house dust mite/weed pollen extract immunotherapy. Asia Pac Allergy 2016;6:168-73.
46. Nolte H, Maloney J, Nelson HS, Bernstein DI, Lu S, Li Z, Kaur A, Zieglmayer P, Zieglmayer R, Lemell P, Horak F. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. J Allergy Clin Immunol 2015;135:1494-501.e6.
47. Soh JY, Thalayasingam M, Ong S, Loo EX, Shek LP, Chao SS. Sublingual immunotherapy in patients with house dust mite allergic rhinitis: prospective study of clinical outcomes over a two-year period. J Laryngol Otol 2016;130:272-7.
48. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, Konno A. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. J Allergy Clin Immunol 2016 Nov 15 [Epub]. pii: S0091-6749(16)31294-5. https://doi.org/10.1016/j.jaci.2016.09.043.
49. Fukushima A, Yamaguchi T, Ishida W, Fukata K, Liu FT, Ueno H. Cyclosporin A inhibits eosinophilic infiltration into the conjunctiva mediated by type IV allergic reactions. Clin Exp Ophthalmol 2006;34:347-53.
50. Shoji J, Sakimoto T, Muromoto K, Inada N, Sawa M, Ra C. Comparison of topical dexamethasone and topical FK506 treatment for the experimental allergic conjunctivitis model in BALB/c mice. Jpn J Ophthalmol 2005;49:205-10.
51. Xu C, He X, Liu W, Chen Y, Zhou C, Duan Z, Lu Q, Yan X, Zhang Z, Zheng R. An inhibitor peptide of toll-like receptor 2 shows therapeutic

potential for allergic conjunctivitis. Int Immunopharmacol 2017;46:9-15.

52. Chen J, Zhang J, Zhao R, Jin J, Yu Y, Li W, Wang W, Zhou H, Su SB. Topical application of interleukin-28A attenuates allergic conjunctivitis in an ovalbumin-induced mouse model. Invest Ophthalmol Vis Sci 2016;57:604-10.
53. Kwon JY, Lee HS, Joo CK. TRPV1 antagonist suppresses allergic conjunctivitis in a murine model. Ocul Immunol Inflamm 2016 Oct 11:1-9 [Epub]. https://doi.org/10.1080/09273948.2016.1231330.
54. Mizutani N, Nabe T, Yoshino S. Topical ocular treatment with monoclonal antibody Fab fragments targeting Japanese cedar pollen Cry j 1 inhibits Japanese cedar pollen-induced allergic conjunctivitis in mice. Eur J Pharmacol 2017;798:105-12.
55. Lee HS, Kwon JY, Joo CK. Topical administration of β-1,3-glucan to modulate allergic conjunctivitis in a murine model. Invest Ophthalmol Vis Sci 2016;57:1352-60.
56. Chung SH, Choi SH, Choi JA, Chuck RS, Joo CK. Curcumin suppresses ovalbumin-induced allergic conjunctivitis. Mol Vis 2012;18:1966-72.