Lirentelimab for severe and chronic forms of allergic conjunctivitis

Stephen D. Anesi, MD,[a] Joseph Tauber, MD,[b] Quan Dong Nguyen, MD, MSc,[c] Peter Chang, MD,[a] Gregg J. Berdy, MD,[d] Charles C. Lin, MD,[c] David S. Chu, MD,[e] H. Terry Levine, MD,[f] Andrew D. Fernandez, MD,[g] Neeta Roy, PhD,[g]* Penny A. Asbell, MD,[g] Andrea M. Kantor, BS,[h] Alan T. Chang, BS,[h] Bhupinder Singh, MD,[h] Bradford A. Youngblood, PhD,[h] Bennie H. Jeng, MD,[i] Vishal Jhanji, MD,[j] Henrik S. Rasmussen, MD, PhD,[h]* and C. Stephen Foster, MD[a] *Waltham, Mass; Kansas City and St Louis, Mo; Palo Alto and San Carlos, Calif; Palisades Park, NJ; Overland Park, Kan; Memphis, Tenn; Baltimore, Md; and Pittsburgh, Pa*

Background: Allergic conjunctivitis (AC) is an ocular inflammatory disease with symptoms driven by eosinophils and mast cells. Allergic comorbidities are common. Current treatments are often ineffective in severe AC and limited by potential side effects. Lirentelimab is an anti–sialic acid–binding immunoglobulin-like lectin-8 mAb that depletes eosinophils and inhibits mast cells.

Objective: We sought to determine safety and preliminary efficacy of lirentelimab in an open-label, phase 1b study.

Methods: Patients with chronic, severely symptomatic atopic keratoconjunctivitis, vernal keratoconjunctivitis, and perennial AC, and who had history of topical or systemic corticosteroid use, were enrolled to receive up to 6 monthly lirentelimab infusions (dose 1: 0.3 mg/kg, dose 2: 1 mg/kg, subsequent doses: 1 or 3 mg/kg). Changes from baseline in peripheral blood eosinophils, changes in patient-reported symptoms (measured by daily Allergic Conjunctivitis Symptom Questionnaire, including atopic comorbidities), changes in investigator-reported ocular signs and symptoms (Ocular Symptom Scores), changes in quality of life, and changes in tear cytokine and chemokine levels were assessed.

Results: Thirty patients were enrolled (atopic keratoconjunctivitis n = 13, vernal keratoconjunctivitis n = 1, perennial AC n = 16), 87% of whom had atopic comorbidities. After lirentelimab treatment, mean improvement was observed in Allergic Conjunctivitis Symptom Questionnaire score (−61%; 95% CI, −75% to −48%) and Ocular Symptom Scores (−53%; 95% CI, −76% to −31%), consistent across atopic keratoconjunctivitis, vernal keratoconjunctivitis, and perennial AC groups. There was substantial improvement in atopic comorbidities, with −55% (95% CI, −78% to −31%), −50% (95% CI, −82% to −19%), and −63% (95% CI, −87% and −38%) reduction in symptoms of atopic dermatitis, asthma, and rhinitis, respectively. Levels of key mediators of inflammation were reduced in patient tears after lirentelimab treatment. The most common adverse effects were mild to moderate infusion-related reactions.

Conclusions: Lirentelimab was well tolerated, improved severe AC and concomitant atopic symptoms, and reduced inflammatory mediators in patient tears. (J Allergy Clin Immunol 2022;150:631-9.)

Key words: *AK002, sialic acid–binding immunoglobulin-like lectin-8, perennial allergic conjunctivitis, atopic keratoconjunctivitis, vernal keratoconjunctivitis, allergic conjunctival diseases, ocular allergy*

From [a]Massachusetts Eye Research & Surgery Institution, Waltham; [b]Tauber Eye Center, Kansas City; [c]Byers Eye Institute, Stanford University, Palo Alto; [d]Ophthalmology Associates, St Louis; [e]Metropolitan Eye Research & Surgery Institute, Palisades Park; [f]Allergy & Asthma Care, PA, Overland Park; [g]University of Tennessee Health Sciences Center, Memphis; [h]Allakos Inc, San Carlos; [i]University of Maryland School of Medicine, Baltimore; and [j]University of Pittsburgh, Pittsburgh.

*Author is no longer at the listed affiliation.

Data sharing: Data available on reasonable request to the sponsor.

This research did not receive any specific grant from funding agencies. The study was sponsored by Allakos Inc (Allakos), San Carlos, Calif. The sponsor participated in the design of the study, conducting the study, data collection, data management, data analysis, interpretation of the data, and preparation and review of the manuscript.

Disclosure of potential conflict of interest: S. D. Anesi has received speaker fees from Abbvie, has received speaker and consultant fees from Mallincrodt and Eyepoint Pharmaceuticals, and has been a consultant for Allakos. J. Tauber reports grants from Tauber Eye Center during the conduct of the study. D. S. Chu is a consultant for Aldeyra and has received a writing grant for Mallinckrodt. C. S. Foster has consultancies with Aldeyra Therapeutics (Lexington, Mass), Allakos (San Carlos, Calif), Bausch & Lomb Surgical, Inc (Rancho Cucamonga, Calif), Eyegate Pharma (Waltham, Mass), Genentech (South San Francisco, Calif), Novartis (Cambridge, Mass), and pSivida (Watertown, Mass), grants or grants pending with Aciont (Salt Lake City, Utah), Alcon (Aliso Viejo, Calif), Aldeyra Therapeutics (Lexington, Mass), Bausch & Lomb (Rochester, NY), Clearside Biomedical (Alpharetta, Ga), Dompé Pharmaceutical (Milan, Italy), Eyegate Pharma (Waltham, Mass), Mallinckrodt Pharmaceuticals (Staines-upon-Thames, UK), Novartis Pharmaceuticals (Cambridge, Mass), pSivida (Watertown, Mass), and Santen (Osaka, Japan), payment for lectures including service on speaking bureaus: Alcon (Aliso Viejo, Calif), Allergan (Dublin, Ireland), Mallinckrodt Pharmaceuticals (Staines-upon-Thames, UK), and stock or stock options of Eyegate Pharma (Waltham, Mass). A. D. Fernandez, N. Roy, and P. A. Asbell are employees of the University of Tennessee Health Sciences Center. A. T. Chang, B. Singh, and B. A. Youngblood are employees of Allakos and hold stock options in the company. A. M. Kantor and H.S. Rasmussen are past employees of Allakos and may own stock; H. S. Rasmussen is named on patents for Allakos. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 13, 2021; revised March 18, 2022; accepted for publication March 24, 2022.

Available online April 4, 2022.

Corresponding author: C. Stephen Foster, MD, Massachusetts Eye Research & Surgery Institution, 1440 Main St #201, Waltham, MA 02451. E-mail: sfoster@mersi.com.

0091-6749

https://doi.org/10.1016/j.jaci.2022.03.021

Abbreviations used

AC: Allergic conjunctivitis
ACS: Allergic Conjunctivitis Symptom
AE: Adverse event
AKC: Atopic keratoconjunctivitis
IRR: Infusion-related reaction
NEI VFQ 25: National Eye Institute Visual Functioning Questionnaire-25
OSS: Ocular Symptom Scores
PAC: Perennial allergic conjunctivitis
PD: Pharmacodynamics
QOL: Quality of life
VKC: Vernal keratoconjunctivitis

Allergic conjunctivitis (AC) is a chronic, ocular inflammatory disease driven by eosinophils and mast cells often characterized by very severe itching, pain and burning in both eyes, watering or mucous discharge, and redness and swelling of the conjunctiva. Severe forms of AC include atopic keratoconjunctivitis (AKC), vernal keratoconjunctivitis (VKC), and perennial allergic conjunctivitis (PAC). In severe cases, patients with AKC and VKC can also develop corneal damage and ulceration, which can lead to photophobia and permanent vision loss.[1,2]

Ocular allergy is estimated to affect at least 20% of the population, with some studies reporting rates up to 40%.[3,4] Allergic comorbidities, such as atopic dermatitis, asthma, and rhinitis, are strongly associated with AC, with 30% to 71% of patients with allergic rhinitis having concomitant AC.[5-7] The disease burden is significant, with approximately 7.4 million diagnosed with AC in the United States, and an estimated 120,000 patients receiving chronic ocular corticosteroids.[4,8] There have been no curative treatments identified for AC, and local corticosteroid use is common in antihistamine-refractory patients.[4,8] Ocular topical corticosteroid use is associated with adverse effects such as cataracts and glaucoma, as well as increased risk of irreversible vision loss with chronic, long-term use. It has been reported that two-thirds of patients with AKC eventually developed significant keratopathy and vision loss when managed with combinations of oral antihistamine, topical mast cell stabilizer, and intermittent topical corticosteroids.[9,10] Physicians may resort to systemic corticosteroids for patients with chronic and aggressive symptoms, but their use is associated with adverse effects, especially with long-term use. There clearly remains a substantial need for a targeted treatment that can be safely used in a chronic setting for AC.

The disease mechanisms of AC involve an inflammatory response, with participation of eosinophils and mast cells as key effector cells.[11] Mast cell activation plays a role in triggering an early-phase type I hypersensitivity reaction and subsequent recruitment of inflammatory cells.[12] Severe symptoms and poor outcomes are thought to result from mast cell– and eosinophil-driven ocular surface inflammation.[13,14]

Sialic acid–binding immunoglobulin-like lectin-8 is an inhibitory receptor selectively expressed on mature eosinophils and mast cells.[15-17] Lirentelimab (AK002), an investigational medicine, is a first-in-class, humanized nonfucosylated IgG_1 mAb directed against sialic acid–binding immunoglobulin-like lectin-8 that depletes eosinophils in blood and tissues and broadly inhibits mast cell activation.[16-19] Lirentelimab has been evaluated in a phase 2, randomized, double-blind, placebo-controlled trial in patients with eosinophilic gastritis and eosinophilic duodenitis,[20] as well as several open-label clinical studies in chronic urticaria (ClinicalTrials.gov NCT03436797) and indolent systemic mastocytosis (ClinicalTrials.govNCT02808793).

Herein, we report the results of a phase 1b, open-label study to investigate the safety, tolerability, preliminary efficacy, and pharmacodynamics (PD) of up to 6 monthly doses of lirentelimab in patients with severe and chronic AC.

METHODS

Trial design and oversight

The index study was a phase 1b, multidose, dose escalation clinical trial to evaluate the safety and tolerability of lirentelimab in patients with AKC, VKC, and PAC from centers in the United States (clinicaltrials.gov: NCT03379311). The study was conducted in accordance with the Declaration of Helsinki, all applicable laws and regulations, and Good Clinical Practice Guidelines. Institutional review board approval was obtained. All patients gave written informed consent before entry. The trial was designed by Allakos (the commercial sponsor) in collaboration with investigators, the investigators collected the data, and the commercial sponsor analyzed the data. The academic authors had access to all data. The first draft of the manuscript was prepared by a medical writer, with direction and content driven by the first and senior authors. The manuscript was reviewed and approved by all the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were adults aged 18 to 80 years with diagnosed AKC, VKC, or PAC (as classically described[21]; Table I) and an average total Allergic Conjunctivitis Symptom (ACS) Questionnaire score of 15 or more (from ≥14 daily questionnaires during 4-week screening). The ACS Questionnaire assessed daily severity of itching, light sensitivity, eye pain, foreign body sensation, and watering on a 0 to 10 scale (0 = no symptom, 10 = most severe) for each symptom (total maximum score = 50). Patients had to have a medical history of topical or systemic corticosteroid use for the treatment of AC. Patients were excluded if they had known hypersensitivity to study drug or constituents, were pregnant or breast-feeding, had abnormal lab values or clinically significant conditions, had a history of malignancy, or use during the 30 days before day 1 of topical decongestants, topical vasoconstrictors, topical calcineurin inhibitors, topical corticosteroids (except for atopic comorbidities), omalizumab, dupilumab, systemic immunosuppressive drugs, or more than 10 mg/d prednisone or equivalent.

Study procedures

Patients received up to 6 monthly intravenous infusions of lirentelimab (0.3 mg/kg for the first infusion, 1 mg/kg for the second infusion, and 1 mg/kg or 3 mg/kg for the subsequent 4 infusions; infusions were given over ~5 hours for the first infusion and 2-4 hours for subsequent infusions). Intrapatient dose escalations up to 3 mg/kg of lirentelimab were allowed after the second infusion if the patient did not experience adequate symptom improvement per judgment of the investigator/medical monitor. Acetaminophen, antihistamines, and, if needed, a glucocorticoid (eg, 125 mg methylprednisolone intravenous) were allowed if the patient experienced infusion-related reactions (IRRs). Both systemic and topical steroids were prohibited for the treatment of AKC, VKC, and PAC. Ocular corticosteroids, eye drops with antiredness, decongestants, or vasoconstrictors were prohibited for the duration of the study. Antihistamines or mast cell stabilizers were allowed.

Expected total study duration was approximately 48 weeks (11 months), with study day 1 being the day of the first infusion. After the treatment period (up to 24 weeks), follow-up assessments continued every 4 weeks over 20 weeks after the final lirentelimab dose.

TABLE I. Patient characteristics at baseline*†

Characteristic	AKC (n = 13)	VKC (n = 1)	PAC (n = 16)	Total (n = 30)
Age (y), median (range)	50 (23-72)	25	55 (29-79)	52 (23-79)
Sex: female, n (%)	5 (38)	0	10 (63)	15 (50)
Race or ethnic group, n (%)				
White	11 (85)	1	16 (100)	28 (93)
Asian	2 (15)	0	0	2 (7)
Weight (kg), median (range)	81 (50-107)	68	82 (52-108)	80 (50-108)
Body mass index, median (range)	26 (20-43)	21	29 (19-40)	27 (19-43)
Age of AC onset (y), median (range)	36 (7-72)	12	46 (19-69)	43 (7-72)
Duration with AC (y), median (range)	6 (<1-38)	13	4 (<1-19)	6 (<1-38)
Atopic comorbidity diagnosis, n (%)				
≥1 comorbidity	11 (85)	1	14 (88)	26 (87)
≥2 comorbidities	10 (77)	1	7 (44)	18 (60)
Atopic dermatitis	11 (85)	0	7 (44)	18 (60)
Asthma	7 (54)	1	4 (25)	12 (40)
Rhinitis	7 (54)	1	12 (75)	20 (67)
Blood absolute eosinophil count/mm^3	234 ± 341	520	122 ± 114	186 ± 252
Total ACS Questionnaire score*	25 ± 7	26	20 ± 8	23 ± 8
Total OSS*	7 ± 2	7	5 ± 3	6 ± 3

*Plus-minus values are mean ± SD.

†Diagnosis was made before entering this study as indicated in patient's medical history. Diagnosis of AKC was determined by the observation of characteristic severe AC with corneal involvement (including signs of significant conjunctival thickening and hyperemia along with current or previously seen corneal changes including perilimbal infiltrate, epitheliopathy, corneal neovascularization, and stromal scarring), along with the presence or history of typically persistent eczematous dermatitis as well as other possible associated allergic disease including asthma, hay fever, and/or eosinophilia and family history of atopy. VKC was diagnosed using many of the same ocular clinical features of AKC, with additional classic findings of large pedunculated papillae and thick ropy mucous discharge, and typical diagnosis includes presentation at a much earlier age, with disease often being seasonally active, particularly in warmer climates and months.

End points

The primary study objective was the safety and tolerability assessment of lirentelimab. Secondary and exploratory end points are summarized in Table E1 in this article's Online Repository at www.jacionline.org and included PD evaluation of changes in baseline in peripheral blood counts of eosinophils, preliminary efficacy evaluation of changes in symptoms associated with AKC, VKC, or PAC as measured daily by the electronic patient ACS Questionnaire, changes in signs and symptoms via the Ocular Symptom Scores (OSS) tool as assessed by the investigator (see Table E2 in this article's Online Repository at www.jacionline.org), and changes in quality of life (QOL) as measured by the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ 25). Ophthalmic examinations were performed in accordance with standard of care. Slit lamp color photography, including punctate corneal staining, was an optional assessment performed only at select sites electing to participate.

Blood samples for complete blood cell and peripheral blood cell counts were obtained on days −1, 1, 8, 15, 28, 29, 36, 44, 56, 57, 84, 85, 112, 113, 140, 141, 169, 197, 225, 253, 281, and 309. On infusion days, samples were collected after lirentelimab dosing.

Patients completed the ACS Questionnaire daily during screening and treatment periods and weekly until day 309 (or end of study) during the follow-up period. On the ACS Questionnaire, patients evaluated severity of symptoms of itching, light sensitivity, eye pain, feeling of foreign body in eye, and watering eyes on a scale from 0 to 10 for each symptom, with 0 being no symptom and 10 being the worst possible experience of the symptom during that time. If the patient had a history of atopic dermatitis, allergic asthma, or allergic rhinitis, the patient also rated disease severity of each comorbidity on a 0 to 10 scale for each comorbidity. The comorbidity score was completed daily during the treatment period, weekly during follow-up, and was part of the electronic ACS Questionnaire. The comorbidity score was based on a general disease severity self-assessment and not based on a visual analog scale.

Investigators assessed signs and symptoms using the OSS tool at baseline, day 15, before each monthly infusion, and monthly during the follow-up period. The OSS assessment graded severity of itching (0-4 scale), redness (0-3 scale), tearing (0-3 scale), and chemosis (0-3).

Response rates were defined as complete response (≥90% reduction from baseline in the total score), partial response (≥50% to <90% reduction), minimal response (≥30 to <50% reduction), and nonresponse (<30% reduction) for ACS and OSS assessments. Patients with greater than or equal to 30% reduction in total score were defined as responders. Change from baseline end points was assessed at weeks 21 to 22 (2 weeks after the final dose) and day 140 for the ACS Questionnaire and the OSS tool, respectively.

The self-administered patient QOL measurement (NEI VFQ 25)[22] included assessment of the following subdomains: general health, general vision, ocular pain, near activities, distance activities, vision specific, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. Both the patient-administered NEI VFQ 25 and the investigator-assessed ocular signs and symptoms (OSS) were conducted on days −1, 15, 28, 44, and 56 and every 28 days until day 309 or end of study.

Tear collection and cytokine analysis

The collection of tear fluid samples was optional and was performed on 7 patients at baseline, day 84, day 169, and day 309. Basal tear fluid samples were collected with uncoated 10-μL and 40-μL glass capillaries from the lateral part of the lower conjunctival fornix without stimulation. Tear fluid was expelled from the capillaries into prefrozen (or precooled) Eppendorf microcentrifuge tubes and stored at −80°C. Tear cytokines and chemokines were thawed and measured using a multiplex magnetic bead assay according to the manufacturer's instructions (Luminex, Millipore, Burlington, Mass). Concentration of the following mediators was determined using a custom kit: CCL24, CCL11, CCL5, IL-10, CCL26, PDGF, IL-13, IL-17A, IL-33, CXCL9, IL-4, IL-23, IL-6, IL-8, IP-10, CCL2, CCL3, CCL4, and CCL17. For the analysis of cytokine/chemokine concentrations in patient tears, a value of "0" was assigned if the concentration was below the limit of detection of the assay kit. The concentration of the analyte in patient tears was calculated by factoring in the dilution factor needed to reach the total assay volume of 50 μL.

Safety

Safety and tolerability were assessed throughout the study by monitoring adverse events (AEs) in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines from the time of first study drug infusion and ending at day 309 or the end of trial visit. Additional safety end points included physical examination, vital signs, complete blood cell

counts with differential, blood chemistries, urinalysis, and antidrug antibody testing.

Statistical analysis

All patients who received at least 1 dose of the study drug were included in the primary safety and tolerability analysis. All patients with at least 1 dose of the study drug and at least 1 postbaseline assessment of PD or efficacy were included in the PD/efficacy subset. Descriptive statistics and shift tables were used unless otherwise indicated, including demographic and baseline values, safety end points, and PD/efficacy data. Sample size was determined by common practice in early-phase, proof-of-concept studies.

ACS Questionnaire daily symptom and total scores were averaged to derive the weekly mean symptom and total scores for each patient. When the daily scores were missing for the entire week during the treatment period, imputation was made for missing data whereby the missing weekly scores were imputed using the last observation carried forward method.

RESULTS

Demographic and patient characteristics

Thirty patients were enrolled (n = 33 patients screened) into 3 cohorts according to their diagnosis of AKC (n = 13), VKC (n = 1), or PAC (n = 16), all of whom received at least 1 dose of the study drug, and 29 of whom were evaluable for PD and efficacy end points; 1 patient with PAC was excluded because of lack of any postbaseline PD or efficacy assessment. Baseline demographic and patient characteristics are presented in Table I. The median age of the patients was 52 years (range, 23-79 years) with median body mass index of 27 kg/m^2 (range, 19-43 kg/m^2), and the population was evenly split between males and females. The median age of onset of AC was 43 years (range, 7-72 years), and patients had a median 6 years (range, 0-38 years) of history of an AC diagnosis. There was a high proportion of patients with atopic comorbidities, with 87% having a history of at least 1 comorbidity (atopic dermatitis, asthma, or rhinitis) and 60% had at least 2 comorbidities. Differences between subgroups included a higher proportion of patients with AKC with comorbid atopic dermatitis and asthma, whereas more patients in the PAC group had allergic rhinitis. Furthermore, the baseline blood eosinophil level was higher among patients with AKC.

Drug exposure, safety, and tolerability

The study period was from February 2018 to August 2019. In all patients who received at least 1 dose of lirentelimab, the mean duration of exposure was 133 ± 28 days. All 30 patients received a first dose of 0.3 mg/kg lirentelimab. Ninety percent of patients (27 of 30) received all 6 monthly doses of lirentelimab during the treatment period. Five patients (2 with AKC and 3 with PAC) discontinued, 2 because of withdrawal of consent (1 elected to discontinue participation, 1 chose to initiate a drug prohibited by the protocol), 1 because of physician decision (for best interest of patient due to cardiac history), and 2 because of sponsor decision (both for noncompliance). Patient flow is summarized in Fig E1 in this article's Online Repository at www.jacionline.org.

The most common AEs were mild to moderate IRRs, which consisted of flushing, feeling of warmth, headache, nausea, or dizziness (Table II). The only treatment-related AEs were IRRs, which occurred mainly as a result of the first infusion. The IRR rate on first infusion was 16.7%, which declined to 0.7% on subsequent infusions. There was no drug-related serious AE and no deaths or study withdrawals due to AEs. There was 1 treatment-emergent serious AE, a patient with AKC with a worsening of osteoarthritis that was assessed as moderate in severity, and the event was not deemed related to lirentelimab. Two patients developed lirentelimab antidrug antibodies; the presence of antidrug antibodies had no effect on safety or efficacy. Transient lymphopenia was detected in 23 patients (77%); none had any clinical consequence.

Efficacy

Improvement in patient-reported ocular symptoms (total ACS Questionnaire score) was observed at posttreatment time points (Fig 1, *A*). Improvement in ACS Questionnaire score was maintained during follow-up time points until approximately week 40 (20 weeks after the final dose). At weeks 21 to 22, corresponding to the 2-week period following the final lirentelimab dose, mean change from baseline was −61% (95% CI, −75% to −48%; n = 29; Fig 1, *B*; see Table E3 in this article's Online Repository at www.jacionline.org). This improvement in AC symptoms was consistent across all 3 forms of AC, with −63% (95% CI, −83% to −42%), −87%, and −59% (95% CI, −80% to −37%) change in total ACS Questionnaire scores relative to baseline for patients diagnosed with AKC, VKC, and PAC , respectively (Fig 1, *B*, and Table E3). Furthermore, ACS Questionnaire scores of individual symptoms decreased from baseline across all measured symptoms (Fig 1, *C*; see Table E4 and Fig E2 in this article's Online Repository at www.jacionline.org) at weeks 21 to 22. The responder analysis based on week 21 to 22 ACS Questionnaire scores demonstrated that 79% of patients were responders, including complete response in 28% of patients. Sixty-nine percent of patients reported at least a 50% improvement in total ACS Questionnaire scores (see Table E5 in this article's Online Repository at www.jacionline.org).

Investigator-assessed ocular signs and symptoms (total OSS) were improved at posttreatment time points (Fig 2, *A*). Improvement in OSS was maintained during follow-up time points until approximately week 32 (12 weeks after the final dose). At the final dose time point (day 140), there was a −53% (95% CI, −76% to −31%) mean change in total OSS compared with baseline (Fig 2, *B*; see Table E6 in this article's Online Repository at www.jacionline.org). Improvements in total OSS were also consistent for each individual sign and symptom measured (Fig 2, *C*; see Table E7 and Fig E3 in this article's Online Repository at www.jacionline.org). Responder analysis based on total OSS demonstrated response in 83% of patients, including 17% as complete responders and 55% as partial responders (see Table E8 in this article's Online Repository at www.jacionline.org). Conjunctival abnormalities on day 140 assessed by slit lamp color photography revealed reduced incidence of conjunctival discharge and chemosis compared with baseline (see Table E9 in this article's Online Repository at www.jacionline.org).

Patients with preexisting atopic comorbidities (comorbid atopic dermatitis n = 11, asthma n = 9, and rhinitis n = 11) were evaluated for changes in daily symptom severity of their concomitant atopic condition as part of the ACS Questionnaire. Patient-reported symptom scores for atopic dermatitis, allergic asthma, and allergic rhinitis reflected a decrease in perceived severity at all postbaseline treatment time points (Fig 3, *A*). At weeks 21 to 22, there was a mean −55% (95% CI, −78% to −31%), −50% (95% CI, −82% to −19%), and −63% (95%

TABLE II. Treatment-emergent AEs (safety population)

Adverse event, no. of patients (%)	AKC (n = 13)	VKC (n = 1)	PAC (n = 16)	Overall (n = 30)
Any serious event	1 (8)*	0	0	1 (3)
Any event that occurred in ≥5% of patients				
IRR†	2 (15)	1	2 (13)	5 (17)
Blood creatinine phosphokinase increased	2 (15)	0	1 (6)	3 (10)
Hypersensitivity‡	2 (15)	0	0	2 (7)
Sinusitis	1 (8)	0	1 (6)	2 (7)
Urinary tract infection	0	0	2 (13)	2 (7)

*The serious adverse event that occurred in the AKC group was worsening of osteoarthritis and was not deemed related to lirentelimab.
†IRRs included flushing, a feeling of warmth, headache, nausea, or dizziness. IRRs predominantly occurred on the first infusion.
‡Hypersensitivity, worsening of underlying allergic rhinitis and asthma.

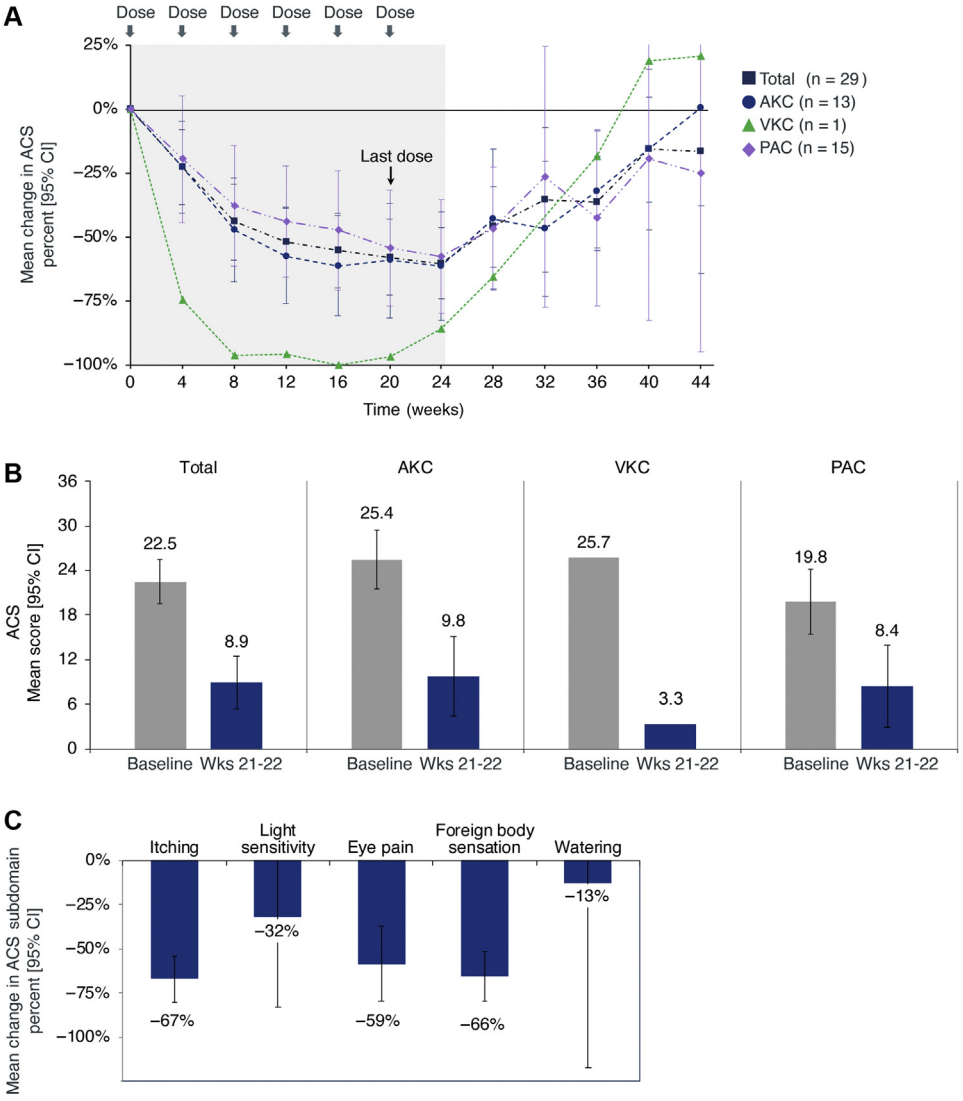

FIG 1. ACS Questionnaire score. **A,** Mean percent change in total ACS Questionnaire score ± 95% CI over time. **B,** Mean total ACS Questionnaire score ± 95% CI at baseline and weeks 21 to 22 for all patients (n = 29) and patients with AKC (n = 13), VKC (n = 1), and PAC (n = 15). **C,** Mean percent change from baseline to weeks 21 to 22 ± 95% CI in ACS Questionnaire score by individual symptoms.

CI, −87% to −38%) change compared with baseline symptom severity of atopic dermatitis, allergic asthma, and allergic rhinitis, respectively (Fig 3, *B*; see Table E10 in this article's Online Repository at www.jacionline.org).

QOL as measured by the NEI VFQ 25 demonstrated that at day 140, patients reported improved or stable QOL subdomains compared with baseline values (see Fig E4 in this article's Online Repository at www.jacionline.org). Visual depictions of 2

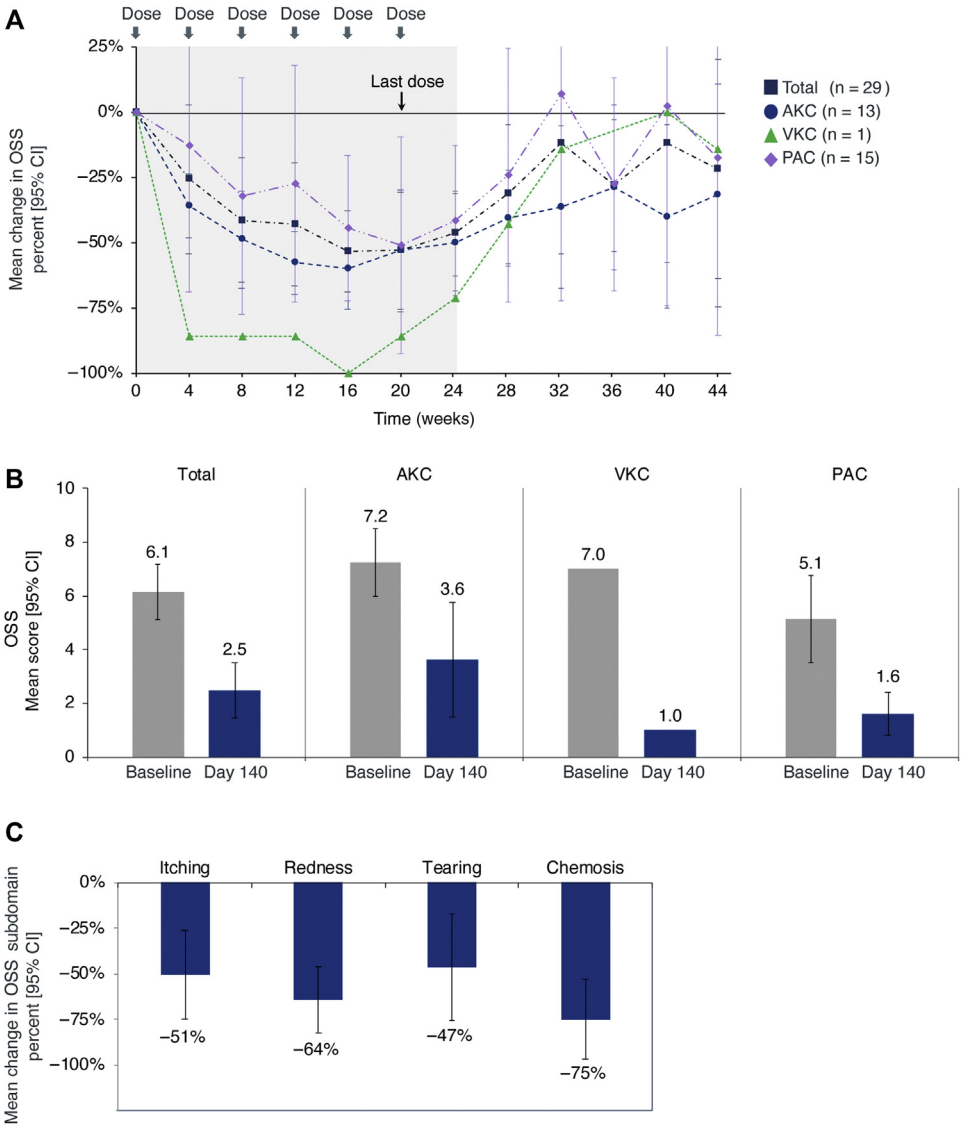

FIG 2. Investigator-assessed OSS. Score criterion is listed in Table E2. **A,** Mean percent change in total OSS ± 95% CI over time. **B,** Mean total OSS ± 95% CI at baseline and day 140 for all patients (n = 29) and patients with AKC (n = 13), VKC (n = 1), and PAC (n = 15). **C,** Mean percent change from baseline to day 140 ± 95% CI in OSS by individual symptoms. Chemosis was evaluated via slit lamp examination.

representative cases (patients with AKC) demonstrated that before treatment, some subjects had giant tarsal papillae at baseline and it resolved after lirentelimab treatment (see Figs E5 and E6 in this article's Online Repository at www.jacionline.org). Changes in signs and symptom scores of individuals representative of patients with severe AKC with at least 2 atopic comorbidities demonstrated that lirentelimab treatment resulted in improvement in AKC, and reduced perceived severity of atopic dermatitis, allergic rhinitis, and allergic asthma signs and symptoms (see Figs E5-E7 in this article's Online Repository at www.jacionline.org).

PD evaluation

Eosinophil counts in peripheral blood decreased from baseline at all posttreatment time points, including 1 week after the first dose of lirentelimab (see Fig E8 in this article's Online Repository at www.jacionline.org). Eosinophil depletion was maintained during follow-up time points until week 40.

Measurement of tear cytokines and chemokines

Cytokines and chemokines associated with ocular inflammation were quantitatively assessed in 7 patients (n = 2 with AKC; n = 5 with PAC) by measuring the concentration in patient tears at baseline, day 84, day 169, and day 309 (24 weeks after the final dose). Decreased levels of key type-1 (CCL3, CCL5), type-2 (IL-4, IL-10, IL-13, CCL11, CCL26), and type-17 (IL-17A, IL-23) cytokines and chemokines were observed at posttreatment time points compared with baseline levels (Fig 4). Many of the mediators returned to baseline levels at day 309, suggesting that the observed decrease in cytokines and chemokines was treatment dependent.

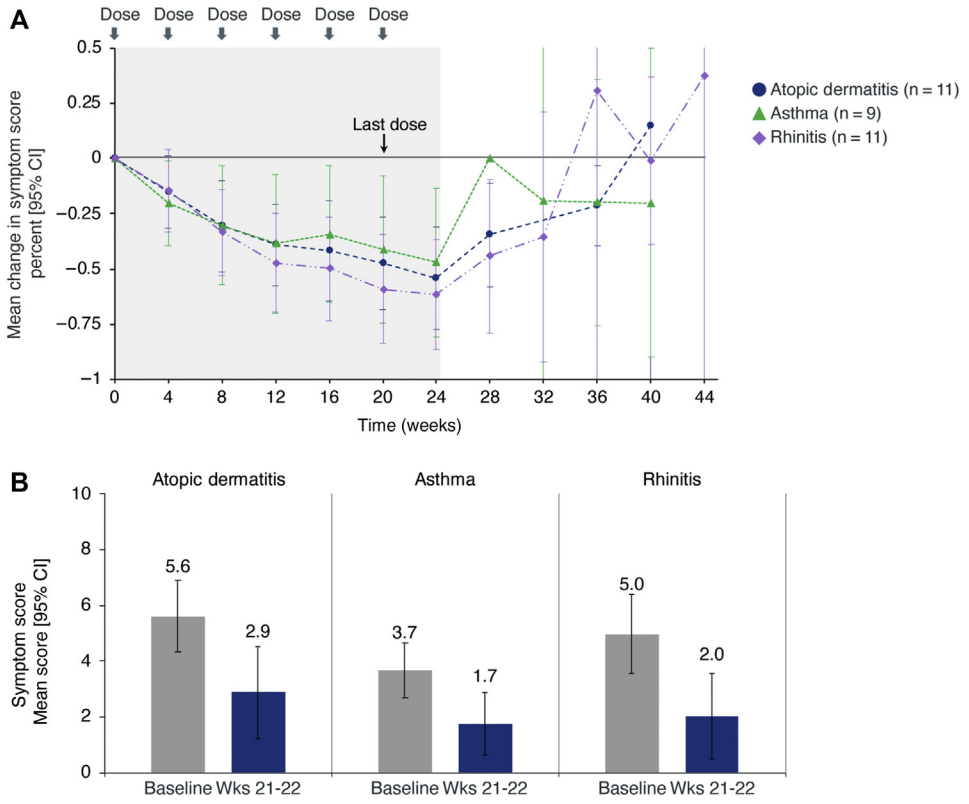

FIG 3. Symptom scores of atopic comorbidities. **A,** Mean percent change in atopic comorbidity symptom scores ± 95% CI over time for patients with comorbid atopic dermatitis (n = 11), asthma (n = 9), and rhinitis (n = 11). **B,** Mean atopic comorbidity symptom score ± 95% CI at baseline and week 21 to 22 for patients with comorbid atopic dermatitis (n = 11), asthma (n = 9), and rhinitis (n = 11).

DISCUSSION

In this trial, up to 6 monthly infusions of lirentelimab were well tolerated and demonstrated clinical activity in relieving the signs and symptoms of AKC, VKC, and PAC disease. Both patient- and investigator-assessed symptoms and clinical signs (ACS Questionnaire and OSS tool) demonstrated improvements across all measured domains, with similar effect to mean ACS Questionnaire, OSS, and QOL across the 3 types of conjunctivitis. In addition, across the treatment period, lirentelimab reduced nonocular symptoms of concomitant atopic dermatitis, asthma, and rhinitis, suggesting that lirentelimab may also have clinical activity in these allergic comorbidities. Furthermore, clinical activity of lirentelimab is also evidenced by the return of ocular and concomitant atopic disease severity to baseline levels in the 6-month off-treatment follow-up period. Consistent with the improvements in ocular signs and symptoms, lirentelimab reduced levels of inflammation associated with cytokines and chemokines in patient tears. Lirentelimab treatment was well tolerated; the only treatment-related AEs reported were IRRs, which were transient and almost exclusively occurred on first infusion. IRRs have been reported in studies of other infused mAbs that deplete cells through a mechanism involving antibody-dependent cellular cytotoxicity.[23,24]

Notably, our study also assessed inflammation associated with tear cytokines and chemokines at multiple time points in a subset of patients with AKC and PAC. Consistent with active disease, all patients evaluated at baseline had detectable levels of inflammatory mediators in their tears, such as IL-4, IL-13, IL-17A, IL-23, CCL5, and CCL11. Many studies have shown upregulation of these mediators in tears of patients with AC.[25,26] In addition to IL-4 and IL-13, treatment with lirentelimab reduced levels of cytokines associated with type-1 and type-17 inflammation, possibly due to suppression of eosinophil and mast cell activity.[27,28] Although limited in sample size, these data provide additional mechanistic insight into the pathogenesis of AC and suggest that lirentelimab may be effective in reducing local ocular inflammation.

There is a substantial unmet need for a targeted and steroid-sparing therapy for the treatment of AC, particularly in patients who experience chronic and severe symptoms. There have been no curative treatments identified for severe AC, and symptomatic treatments are often associated with significant side effects.[29] Current frontline options are limited to topical decongestants, oral antihistamines, and antiallergic eye drops (mast cell stabilizers), which can cause rebound hyperemia, mydriasis, and conjunctivitis medicamentosa when used long-term.[29,30] Progression to corticosteroid use when symptoms persist or worsen is common, but two-thirds of patients with AKC managed with this regimen eventually develop significant keratopathy and vision loss. Topical ophthalmic and nasal corticosteroid use for more than a few weeks also has potential to induce elevated intraocular pressure, glaucoma, cataracts, and corneal infections.[31] Despite the scarcity of treatment options and high prevalence of disease,[32] there have been no innovations in therapy to relieve the burden of the disease. Our study is the first ever clinical trial conducted of a biologic targeting

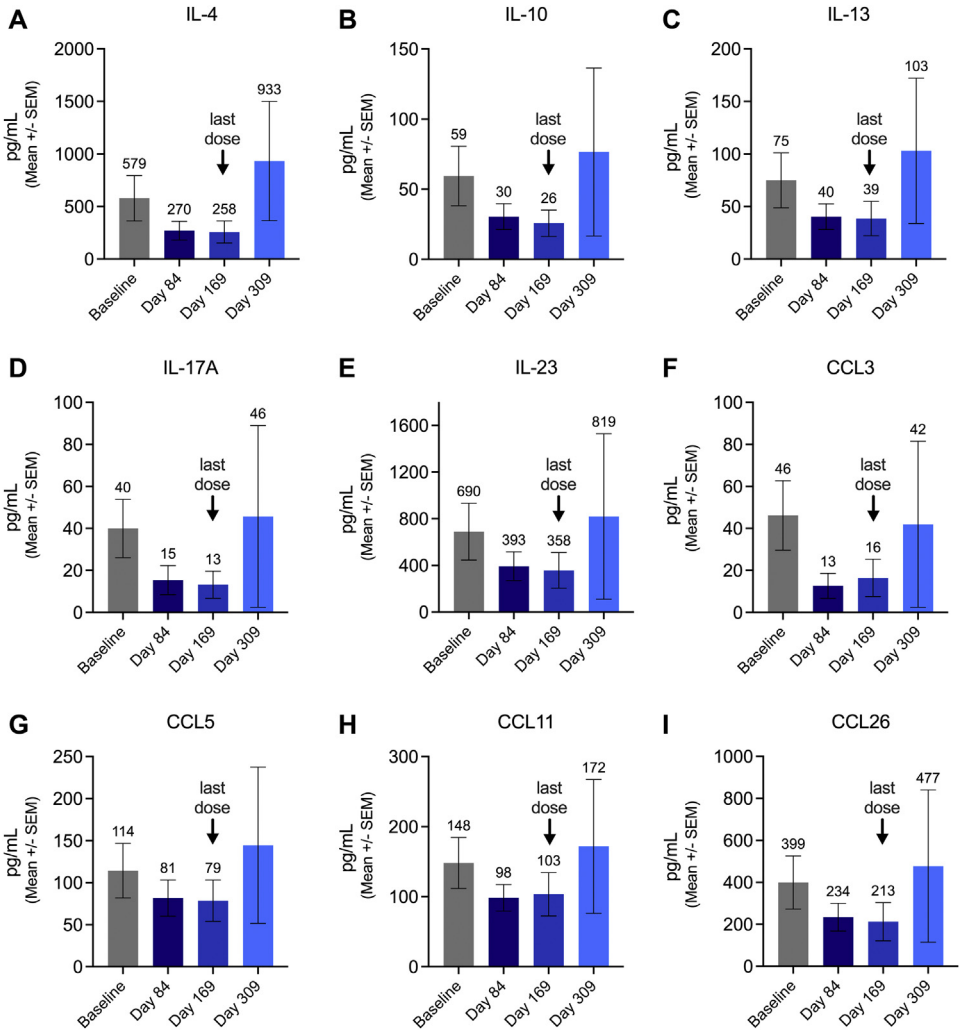

FIG 4. Concentration of tear cytokines and chemokines. **A-I,** Mean concentration (pg/mL) ± SEM at baseline (AKC n = 2; PAC n = 5), day 84 (AKC n = 2; PAC n = 5), day 169 (AKC n = 2; PAC n = 4), and day 309, 24 weeks after the final dose (AKC n = 1; PAC n = 4).

AC, and we demonstrated preliminary efficacy in reducing the symptoms of patients with moderate to severe AKC, VKC, and PAC.

Lirentelimab has been studied in multiple disease areas and has now shown clinical activity in eosinophilic gastritis and/or eosinophilic duodenitis, indolent systemic mastocytosis, multiple forms of chronic urticaria, and 3 forms of AC. With the exception of the eosinophilic gastritis and/or eosinophilic duodenitis study, all these studies were open-labeled, and randomized, double-masked, placebo-controlled studies are required to further demonstrate any potential effect. Because the index trial was a small, open-label study, substantial inherent limitations apply. Although patients were diagnosed by an ophthalmologist using classic diagnostic criteria for these diseases, confirmatory serologic testing and skin testing were not required for study entry. However, the lack of treatment-related AEs beyond IRRs combined with the clinical activity observed in treating multiple allergic conditions and the return of signs and symptoms off treatment make lirentelimab a potentially promising candidate for severe AC and multiple eosinophil- and mast cell–driven inflammatory diseases.

Allakos was the sponsor and funder of the study. We thank the patients who participated in the trial; Robert P. Schleimer, PhD, and Bruce S. Bochner, MD, for reviewing and editing the manuscript for scientific content; University of Texas Health Sciences Center for analyzing the tear cytokine data, contracted by Allakos; Cory Mekelburg, BS, an employee of Allakos at the time the work was conducted, for data analytical assistance; staff members of Etera Solutions for statistical assistance, funded by Allakos; and Jocelyn Hybiske, PhD, a professional medical writer funded by Allakos, for preparing and editing the manuscript draft on the basis of direction from the named authors.

Clinical implications: Lirentelimab treatment has potential to elicit a broad clinical response in patients with allergic conditions such as severe AC as well as atopic dermatitis, asthma, and rhinitis.

REFERENCES

1. Leonardi A, Bogacka E, Fauquert JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, et al. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. Allergy 2012;67:1327-37.
2. Takamura E, Uchio E, Ebihara N, Ohno S, Ohashi Y, Okamoto S, et al. Japanese guidelines for allergic conjunctival diseases 2017. Allergol Int 2017;66:220-9.
3. Singh K, Axelrod S, Bielory L. The epidemiology of ocular and nasal allergy in the United States, 1988-1994. J Allergy Clin Immunol 2010;126:778-83.e6.

4. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Fujii T, et al. Changing prevalence and severity of childhood allergic diseases in Kyoto, Japan, from 1996 to 2006. Allergol Int 2009;58:543-8.
5. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. Allergy 1983;38:25-9.
6. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997;99:S773-80.
7. Bielory L, Delgado L, Katelaris CH, Leonardi A, Rosario N, Vichyanoud P. ICON: diagnosis and management of allergic conjunctivitis. Ann Allergy Asthma Immunol 2020;124:118-34.
8. Wang HY, Pizzichini MM, Becker AB, Duncan JM, Ferguson AC, Greene JM, et al. Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. Pediatr Allergy Immunol 2010;21:867-77.
9. Foster CS, Calonge M. Atopic keratoconjunctivitis. Ophthalmology 1990;97: 992-1000.
10. Power WJ, Tugal-Tutkun I, Foster CS. Long-term follow-up of patients with atopic keratoconjunctivitis. Ophthalmology 1998;105:637-42.
11. Leonardi A, De Dominicis C, Motterle L. Immunopathogenesis of ocular allergy: a schematic approach to different clinical entities. Curr Opin Allergy Clin Immunol 2007;7:429-35.
12. Tsubota K, Takamura E, Hasegawa T, Kobayashi T. Detection by brush cytology of mast cells and eosinophils in allergic and vernal conjunctivitis. Cornea 1991;10:525-31.
13. Bruschi G, Ghiglioni DG, Osnaghi S, Rosazza C, Pires Marafon D, Landi M, et al. Role of ocular cytology in vernal keratoconjunctivitis. Immun Inflamm Dis 2020;8: 3-7.
14. Leonardi A, Curnow SJ, Zhan H, Calder VL. Multiple cytokines in human tear specimens in seasonal and chronic allergic eye disease and in conjunctival fibroblast cultures. Clin Exp Allergy 2006;36:777-84.
15. Kiwamoto T, Kawasaki N, Paulson JC, Bochner BS. Siglec-8 as a drugable target to treat eosinophil and mast cell-associated conditions. Pharmacol Ther 2012;135:327-36.
16. O'Sullivan JA, Chang AT, Youngblood BA, Bochner BS. Eosinophil and mast cell Siglecs: from biology to drug target. J Leukoc Biol 2020;108:73-81.
17. Youngblood BA, Leung J, Falahati R, Williams J, Schanin J, Brock EC, et al. Discovery, function, and therapeutic targeting of Siglec-8. Cells 2020;10:19.
18. Youngblood BA, Brock EC, Leung J, Falahati R, Bochner BS, Rasmussen HS, et al. Siglec-8 antibody reduces eosinophils and mast cells in a transgenic mouse model of eosinophilic gastroenteritis. JCI Insight 2019;4:e126219.
19. Youngblood BA, Brock EC, Leung J, Falahati R, Bryce PJ, Bright J, et al. AK002, a humanized sialic acid-binding immunoglobulin-like lectin-8 antibody that induces antibody-dependent cell-mediated cytotoxicity against human eosinophils and inhibits mast cell-mediated anaphylaxis in mice. Int Arch Allergy Immunol 2019;180:91-102.
20. Dellon ES, Peterson KA, Murray JA, Falk GW, Gonsalves N, Chehade M, et al. Anti-siglec-8 antibody for eosinophilic gastritis and duodenitis. N Engl J Med 2020;383:1624-34.
21. Hogan MJ. Atopic keratoconjunctivitis. Am J Ophthalmol 1953;36:937-47.
22. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119:1050-8.
23. Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck R, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. J Allergy Clin Immunol 2010;125:1237-44.e2.
24. Levin AS, Otani IM, Lax T, Hochberg E, Banerji A. Reactions to rituximab in an outpatient infusion center: a 5-year review. J Allergy Clin Immunol Pract 2017;5: 107-13.e1.
25. Roy N, Levanon S, Asbell PA. Potential biomarkers for allergic conjunctival diseases. Eye Contact Lens 2020;46:S109-21.
26. Shoji J. Ocular allergy test and biomarkers on the ocular surface: clinical test for evaluating the ocular surface condition in allergic conjunctival diseases. Allergol Int 2020;69:496-504.
27. Asada Y. Roles of type 2 immune response-initiating cytokines and detection of type 2 innate lymphoid cells in mouse models of allergic conjunctivitis. Cornea 2020;39:S47-50.
28. Iwasaki N, Terawaki S, Shimizu K, Oikawa D, Sakamoto H, Sunami K, et al. Th2 cells and macrophages cooperatively induce allergic inflammation through histamine signaling. PLoS One 2021;16:e0248158.
29. 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.
30. Spector SL, Raizman MB. Conjunctivitis medicamentosa. J Allergy Clin Immunol 1994;94:134-6.
31. Ilyas H, Slonim CB, Braswell GR, Favetta JR, Schulman M. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. Eye Contact Lens 2004;30:10-3.
32. Bielory L, Skoner DP, Blaiss MS, Leatherman B, Dykewicz MS, Smith N, et al. Ocular and nasal allergy symptom burden in America: the Allergies, Immunotherapy, and RhinoconjunctivitiS (AIRS) surveys. Allergy Asthma Proc 2014;35: 211-8.