

Functional Visual Acuity Assessment of Severe Atopic Keratoconjunctivitis

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Purpose: To evaluate changes in functional visual acuity (FVA) measurements before and after treatment with 0.1% cyclosporine ophthalmic solution for 3 months in patients with severe atopic keratoconjunctivitis (AKC).

Methods: Pairs of eyes were analyzed from 3 boys (mean age 9 ± 3.6 years) who complained of having severe AKC and were recruited for the study. Conventional Landolt visual acuity, FVA, and visual maintenance ratio (VMR) measurements were conducted before and after 3 months of 0.1% cyclosporine eye drop treatment. Tear film lipid layer interferometry, tear film break-up time, fluorescein and rose bengal vital stainings, and the Schirmer test were also performed before and after treatment.

Results: Eye drop treatment was associated not only with improvement of tear function and ocular surface status but also with better quality of visual function. The mean logarithm of the minimum angle of resolution FVA and Landolt visual acuity values improved from 0.45 ± 0.26 and 0.13 ± 0.17 before treatment to 0.16 ± 0.03 and -0.06 ± 0.05 after treatment, respectively. Similarly, the mean VMR values were markedly improved from 0.88 ± 0.06 to 0.95 ± 0.03 after treatment.

Conclusions: FVA and VMR are promising parameters in the assessment of dynamic visual acuity changes in AKC-affected patients and evaluation of treatment outcome.

Key Words: atopic keratoconjunctivitis, visual acuity, eye drop treatment

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Atopic keratoconjunctivitis (AKC) is the chronic manifestation of several ocular surface disorders in the context of atopic dermatitis, which affects many people worldwide. Type 1 hypersensitivity is a proven contributing factor, and type 4 delayed-type hypersensitivity probably contributes to the pathology as well.^{1–3} AKC is always bilateral with symptoms of itching, burning, and tearing. The disease may include lid eczema, chronic blepharitis, and cicatrizing conjunctivitis.^{4,5} Severe AKC is associated with giant tarsal conjunctival papillae, follicles, mucus secretion, and corneal superficial punctate epithelial erosions. It is often refractory to conventional treatment including antihistamines, mast cell stabilizers, and steroids.⁶

Cyclosporine A is a cyclic polypeptide calcineurin inhibitor widely used as an immunosuppressant in organ transplantation and autoimmune diseases.⁷ The therapeutic effects of cyclosporine A in the treatment of severe refractory allergic conjunctivitis diseases have been previously described.^{8–10} An irregular corneal surface resulting from AKC is associated with a poor quality of vision.¹¹ Previous reports showed that functional visual acuity (FVA) testing is a good method to determine impaired visual function that might not be detectable by other methods, and a way to assess visual acuity in detail.^{12–15}

In this study, we investigated visual function changes in patients with severe AKC before and after 3 months of treatment with cyclosporine A using the FVA measurement system.

MATERIALS AND METHODS

Patients

To investigate the applicability of FVA measurement for the assessment of dynamic visual acuity in patients with severe AKC, 6 eyes from 3 boys (aged 6, 8, and 13 years) with AKC were assessed at an allergy subspecialty outpatient clinic in the Ophthalmology Department at the Keio University School of Medicine.

Patients who had severe AKC that did not respond to topical steroids, antihistamines, or mast cell stabilizers were included in this study. The conjunctivitis affected the patients' quality of life and required continuous ophthalmic intervention. A diagnosis of severe AKC was based on medical history and characteristic chronic signs, including photophobia, eyelid swelling, erythema, conjunctival hyperemia, giant tarsal conjunctival papillae, mucus secretion, and corneal superficial punctate epithelial damage.¹⁶ All AKC-affected patients included in this study had active atopic

dermatitis. None of the subjects included in this study had a history of chemical, thermal, or radiation injury, or had undergone any ocular surgery or procedure that would create an ocular surface problem. Patients with other causes of ocular inflammation, such as systemic diseases different from atopy and wearing contact lenses, were excluded. The study was conducted between mid-July and mid-October 2007. There was no relationship between the season and the patient allergic eye disease. This research study followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects, and ethics committee approval was obtained.

Treatment Protocol

The patients were given cyclosporine A eye drops (PapiLock Mini 0.1%; Santen Pharmaceutical Co, Ltd, Osaka, Japan) 4 times a day for 3 months. Patients were examined before and after 3 months of treatment.

FVA Measurement

The changes in visual acuity over time were examined using the FVA measurement system (Nidek, Tokyo, Japan).¹³ The device comprises 3 parts: a monitor, a hard disk, and a joystick. The Landolt optotypes were presented on the monitor, and their sizes changed depending on the correctness of the responses. In brief, the optotypes were displayed starting with the smaller ones first. If the responses were incorrect, larger optotypes were presented automatically. The measurements were begun from a baseline established best-corrected Landolt conventional visual acuity in each subject. The FVA measurement system measures visual acuity from 20/10 to 20/200, depending on the choice of examination distance (5, 2.5, or 1 m). The monitor was placed at a distance of 5 m from the subjects in this study. The outcomes were denoted with a logarithm of the minimum angle of resolution (logMAR) for FVA and visual maintenance ratio (VMR). FVA was defined as the mean value of timewise change of visual acuity during the overall examination. VMR represents the ratio of FVA divided by the value of baseline Landolt visual acuity. In brief, the VMR was calculated as $VMR = (\text{lowest logMAR visual acuity score} - \text{FVA at 60 seconds}) / (\text{lowest logMAR visual acuity score} - \text{baseline visual acuity})$.

FVA was measured during a 60-second normal blink period. Display time of an optotype was set at 2 seconds. Patients delineated the orientation of the automatically presented Landolt rings by handling the joystick.

Tear Film Lipid Layer Interferometry

Tear film lipid layer interferometry (DR-1; Kowa Co, Tokyo, Japan) was also performed to evaluate the status of the tear film in all subjects. DR-1 interferometry observes the specular reflected light from the tear surface.¹⁷ The grading of tear lipid layer patterns was performed as previously described.¹⁷

Tear Stability and Ocular Surface Vital Staining Examinations

The standard tear film break-up time (BUT) measurement was performed after instillation of 2 μ L of 1% fluorescein preservative-free solution in the conjunctival sac with a micropipette. The patients were instructed to blink several times for a few seconds to ensure adequate mixing of the dye. The interval between the last complete blink and appearance of the first corneal black spot in the stained tear film was measured 3 times, and the mean value of the measurements was calculated.

For the assessment of fluorescein staining, the cornea was divided into 3 equal zones: upper, middle, and lower. Each zone had a staining score ranging between 0 and 3 points with the minimum and maximum total staining scores ranging between 0 and 9 points. Likewise, the presence of scarce staining in 1 zone was scored as 1 point, whereas punctate staining covering the entire zone was scored as 3 points.¹⁸ After assessment of BUT and fluorescein staining, 1% rose bengal dye was instilled into the conjunctival sac and scored according to the van Bijsterveld scoring system. Briefly, the ocular surface was divided into 3 zones: nasal conjunctival, corneal, and temporal conjunctival areas. A staining score between 0 and 3 points was used in each zone with the minimum and maximum total staining scores ranging between 0 and 9 points. The presence of scarce punctate staining was marked as 1 point. The presence of denser staining not covering the entire zone was given 2 points, and the presence of rose bengal staining over the entire zone was given 3 points.

Tear Quantity Evaluation

The Schirmer I test without topical anesthesia was performed for further evaluation of tears. Sterilized strips of filter paper (Showa Yakuhin Kako Co Ltd, Tokyo, Japan) were placed in the lateral canthus away from the cornea and left in place for 5 minutes. Readings were recorded in millimeters of wetting for 5 minutes.

Statistical Analyses

The Wilcoxon matched-pairs signed-ranks test was used to investigate changes in the examination values before and after 3 months of treatment. The differences were considered statistically significant if $P < 0.05$. GraphPad InStat 3.0 (GraphPad Software Inc, San Diego, CA) was used for the analyses.

RESULTS

Patients' symptoms and signs showed a marked improvement after treatment. The mean visual acuities, FVA, VMR, tear function, and ocular surface staining scores of both eyes of all patients before and after treatment are summarized in Table 1.

TABLE 1. Visual Acuity, Tear Function, and Ocular Surface Examinations

	Before Treatment	After Treatment
Visual acuity examination		
Landolt VA (LogMAR)	0.13 ± 0.17	−0.06 ± 0.05
FVA (LogMAR)	0.45 ± 0.26	0.16 ± 0.03
VMR	0.88 ± 0.06	0.95 ± 0.03
Tear function and ocular surface examinations		
BUT (s)	1.2 ± 0.4	4.6 ± 2.8
DR-1 grading	3.3 ± 1.0	1.5 ± 0.5
FS (points)	7.8 ± 2.8	2.1 ± 1.4*
RB (points)	7.3 ± 1.9	1.2 ± 1.0*
Schirmer test (mm)	21.2 ± 11.3	27.2 ± 9.6

Wilcoxon matched-pairs signed-ranks test was used for statistical analysis.
 * $P < 0.05$.

DR-1, tear film lipid layer interferometry; FS, fluorescein; RB, rose bengal staining.

Case 1

A 13-year-old boy with allergy and atopic dermatitis first presented at the age of 8 years. His symptoms were controlled over the years by various regimens of topical medication until he developed giant papillae of the tarsal conjunctiva. One year previously, he suffered from uncontrollable symptoms, including itching, discharge, tearing, photophobia, foreign body sensation, and pain. His best-corrected visual acuity was 20/50 in the right eye and 20/25 in the left eye. FVA was 0.70 and 0.40 (logMAR), and VMR was 0.87 and 0.89 in the right and left eyes, respectively. BUT was 1 second, and fluorescein-staining score was 9 points in each eye. Rose bengal staining scores were 9 and 6 points, and Schirmer test values were 8 and 35 mm in the right and left eyes, respectively. Despite receiving topical antihistaminic and steroid treatment, he developed giant papillae in the tarsal conjunctiva, and hyperemia and edema of the bulbar conjunctiva with corneal involvement.

The patient then stopped all treatments and used only topical cyclosporine A (0.1%). After 3 months, his best-corrected visual acuity was 20/20 in the right eye and 20/16 in the left eye. FVA was 0.06 and 0.14 (logMAR), and VMR increased to 1.00 and 0.93 in the right and left eyes, respectively. BUT was 9 seconds, the rose bengal staining score was 1 point, fluorescein staining score was 1 point, and the Schirmer test value was 12 mm in the right eye. In the left eye, BUT was 3 seconds, rose bengal staining score was 2 points, fluorescein staining score decreased to 4 points, and the Schirmer test value was 35 mm. The DR-1 interferometry grades improved from 5 to 2 in the right eye and from 4 to 1 in the left eye after treatment. Visual acuity changes in the right eye of case 1 before and after treatment are shown in Figure 1.

Case 2

An 8-year-old boy with AKC first presented at the age of 2 years. He presented to our clinic with symptoms of AKC and a corneal shield ulcer in the left eye, which did not respond to

topical antihistaminic and steroid treatment. He also developed giant papillae of the tarsal conjunctiva. Eleven months previously, he suffered uncontrollable symptoms, including itching, discharge, tearing, photophobia, foreign body sensation, and pain.

His best-corrected visual acuity was 20/20 and 20/40 in the right and left eyes, respectively. FVA values were 0.48 and 0.80 (logMAR), and VMR scores were 0.93 and 0.79 in the right and left eyes, respectively. BUT was 1 second, and fluorescein staining scores were 9 points in both eyes. Rose bengal staining scores were 6 and 9 points, and the Schirmer test values were 15 and 20 mm in the right and left eyes, respectively. After cyclosporine treatment, the corneal ulcer was almost covered with epithelium. The degree of inflammation and the number of papillae of the upper lid decreased. The patient's best-corrected visual acuity was 20/16 in the right eye and 20/20 in the left eye. FVA was 0.09 and 0.12 (logMAR), and VMR was 1.00 and 0.93 in the right and left eyes, respectively. BUT was 2 and 6 seconds, rose bengal staining scores were 0 and 2 points, and fluorescein staining scores were 1 and 2 points in the right and left eyes, respectively. Schirmer test values were 35 in the right eye and 26 mm in the left eye. The corneal ulcer was almost covered with epithelium after treatment. Grades of DR-1 interferometry improved after treatment from 3 to 1 and from 3 to 2 in the right and left eyes, respectively. Visual acuity changes in the left eye of case 2 before and after treatment are shown in Figure 2.

Case 3

A 6-year-old boy developed house dust allergy, red eye, AKC, and atopic dermatitis 1 year previously. He complained of having increased tearing, eye pain, swollen lids, and photophobia. Despite improvement of the eye condition to a certain extent after treatment with topical antihistamines and steroids, the intraocular pressure started to increase with the appearance of conjunctival hyperemia and giant tarsal conjunctival papillae.

His best-corrected visual acuity was 20/20 in both eyes. FVA was 0.22 and 0.12 (logMAR), and VMR was 0.93 and 0.89 in the right and left eyes, respectively. BUT was 2 and 1 second, rose bengal staining scores were 9 and 5 points, fluorescein staining scores were 9 and 2 points, and Schirmer test values were 35 and 14 mm in the right and left eyes, respectively. The patient stopped steroid treatment and used only topical cyclosporine A (0.1%). After treatment, his best-corrected visual acuity was 20/20 in the right eye and 20/16 in the left eye. FVA was 0.12 and 0.09 (logMAR), and VMR was 0.96 and 0.92 in the right and left eyes, respectively. BUT was 6 and 2 seconds, rose bengal staining scores were 2 and 0 points, fluorescein staining scores were 4 and 1 points, and Schirmer test values were 35 and 20 mm in the right and left eyes, respectively. The DR-1 interferometry grades improved from 3 to 2 and from 2 to 1 in the right and left eyes, respectively, after treatment. Visual acuity changes in the right eye of case 3 before and after treatment are shown in Figure 3.

DISCUSSION

In this study, topical cyclosporine A (0.1%) alleviated the signs and symptoms of severe AKC. The treatment also

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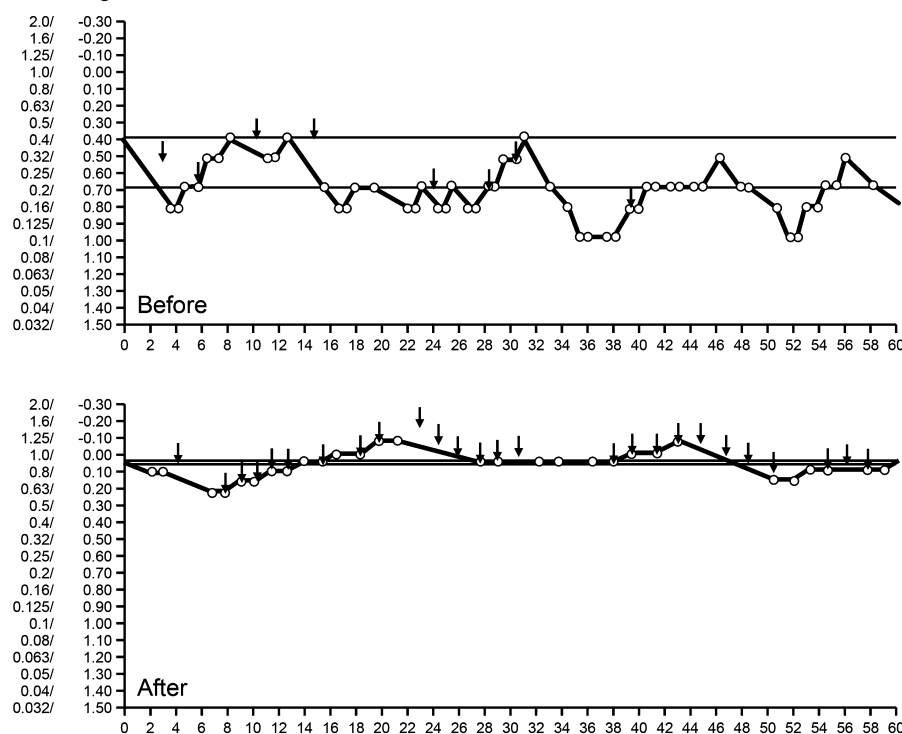


FIGURE 1. Timewise changes of FVA in case 1 before (upper) and after (lower) cyclosporine A treatment. The red line shows the timewise changes of visual acuity during testing. The green line denotes the FVA during 60-second viewing of Landolt rings. The blue line denotes conventional Landolt visual acuity. The yellow dots show the number of correct responses. The blue arrows indicate spontaneous blinks. Functional acuity measurements after treatment were improved and stabilized. Visual acuities before treatment: Landolt visual acuity = 0.40 (logMAR), FVA score = 0.70 (logMAR), and VMR value = 0.87. Visual acuities after treatment: Landolt visual acuity = 0.05 (logMAR), FVA score = 0.06 (logMAR), and VMR value = 1.00.

improved the visual function of patients as shown by Landolt visual acuity, FVA, and VMR.

Severe AKC is a relatively rare but potentially vision-threatening ocular allergic condition.⁶ In our patients,

conventional treatments did not provide satisfactory results. In addition, the patients continued to experience symptoms that affected their vision, ocular tension, and quality of life significantly.

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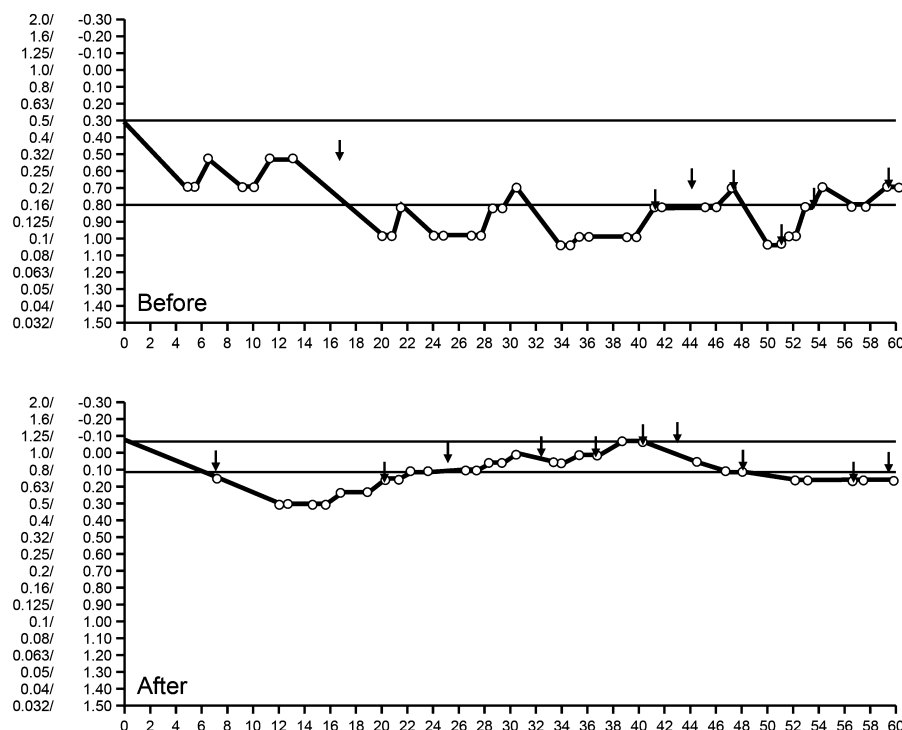
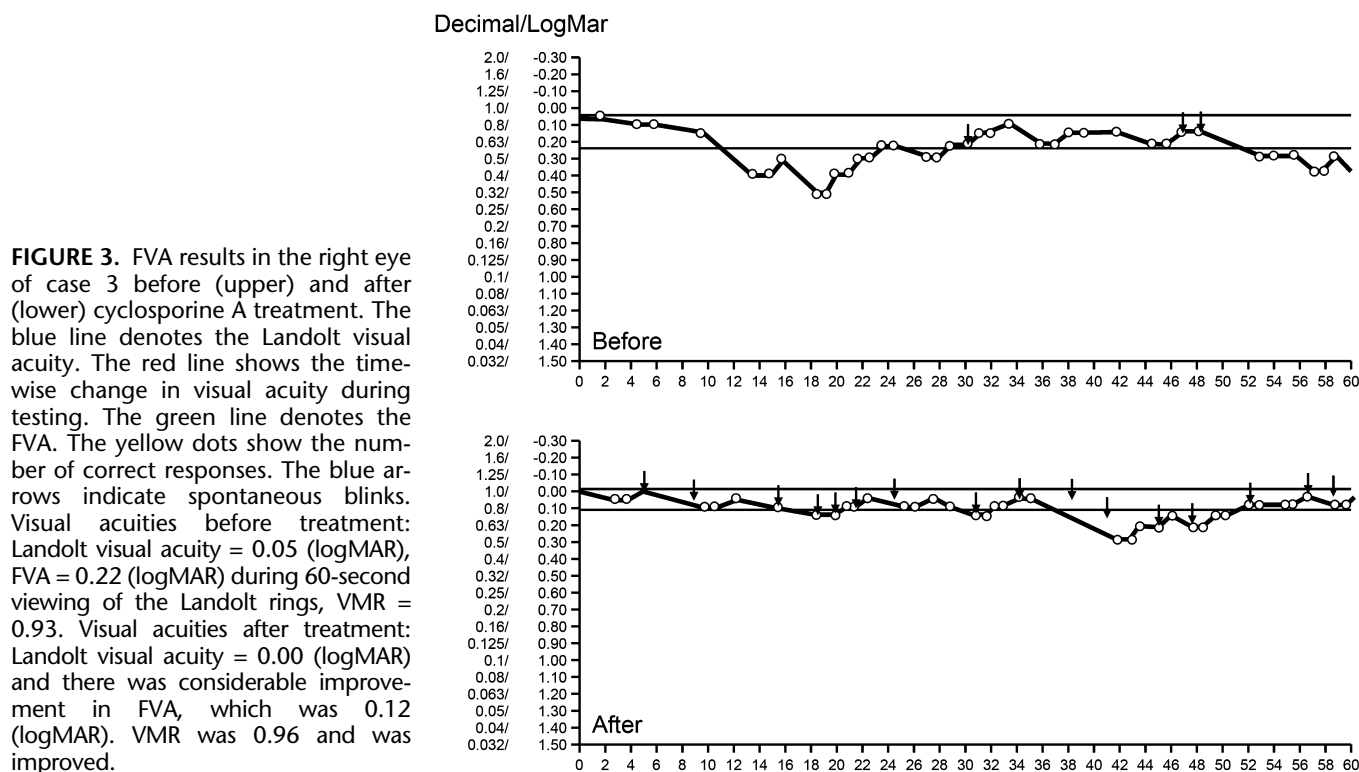


FIGURE 2. Visual acuity changes in the left eye of case 2 before (upper) and after (lower) cyclosporine A treatment. The red line shows the timewise changes of visual acuity during testing. The green line denotes the FVA during 60-second viewing of the Landolt rings. The blue line denotes conventional Landolt visual acuity. The yellow dots show the number of correct responses. The blue arrows indicate spontaneous blinks. Visual acuities before treatment: Landolt visual acuity = 0.3 (logMAR), FVA score = 0.80 (logMAR), and VMR value = 0.78. Visual acuities after treatment: Landolt visual acuity = -0.09 (logMAR), FVA score = 0.12 (logMAR), and VMR value = 0.93.



Several studies have shown that topical cyclosporine A is a beneficial additive treatment in allergic disorders including vernal keratoconjunctivitis and AKC, reducing the need for topical steroids.^{19,20} It causes a reduction in the number and activation of T cells and T-cell cytokine expression, especially interleukin-2 and interferon- γ .⁸ In this study, patients' lid margin thickening, edema, inferior and superior conjunctival hyperemia, upper lid conjunctiva papillae, and ulcers recovered over time after treatment. This was in accordance with the findings of previously published studies, which reported an improvement of the clinical findings of allergic patients, after cyclosporine A treatment.^{6,10}

FVA testing has been proposed as an important indicator of an individual's visual performance of certain daily activities, such as reading, driving, and using visual display terminals.¹³ The usefulness of this methodology has been described in patients with tear instability,^{14,21} mild cataract opacities,²² Stevens-Johnson, and Sjögren syndromes.²³ Another report showed that FVA testing has an acceptable reproducibility²¹ and that the results correlated significantly with tear quantities, tear stability, and ocular surface vital staining scores.²⁴

In this study, FVA measurements revealed impaired visual acuity values compared with the values observed by conventional visual acuity measurement before treatment. Although conventional visual acuity measurement might be good for the assessment of vision at 1 point, FVA can reveal a dynamic and detailed visual acuity over time. After cyclosporine A treatment, fluctuations in visual acuity over a 60-second period stabilized considerably as shown by FVA. Interestingly, FVA measurements improved without complete recovery, unlike Landolt visual acuity, which showed almost

normal values after treatment. These FVA changes occurred in parallel with the alleviation of patients' tear function, ocular surface status, and symptoms, which improved remarkably but did not recover totally. Therefore, FVA could be a more realistic parameter for the evaluation of treatment outcomes that correlate with patients' symptoms and signs. Further, we showed for the first time that FVA measurements could be useful for visual assessment of children.

The formation of clear visual imaging requires a stable tear film layer and a smooth corneal surface.²⁵ Allergic conjunctivitis has been reported to be associated with advanced tear instability, thickening of the tear film lipid layer, and quantitative and qualitative mucin alterations.^{23,26} Likewise, patients in this study had a sufficient quantity of tears before treatment; however, the quality of tears was impaired as shown by DR-1. The lipid layer of the tear film was thickened by its abnormal composition. In addition, ocular surface epithelial damage before treatment could have contributed to the decreased FVA observed. The presence of epithelial damage in the corneal center might interfere with the visual axis, disturb visual imaging, and increase the fluctuations of FVA. Similar changes in FVA have been reported previously in severe dry eye-affected patients with serious ocular surface epithelial damage including Stevens-Johnson syndrome and Sjögren syndrome.²³ The improvement in tear stability and ocular surface epithelial status after cyclosporine A treatment might be attributed to its immunosuppressive and antiinflammatory properties. These improvements consequently led to the recovery of visual acuity. However, one limitation of this study was the lack of a control for cyclosporine A.

Previous reports showed significant recovery of allergy signs and symptoms in patients after the use of 0.1% and 2% cyclosporine eye drops for 6 months.^{6,10} Other studies reported clinical improvement in patient conditions with the use of 0.05% and 2% cyclosporine eye drops for 3 months.^{20,27} As observed in this study, a duration of treatment of >3 months should be recommended for significant improvement. However, this should also be associated with careful monitoring to avoid the side effects reported in these studies, including corneal infection.

Our preliminary findings suggest that AKC-affected patients experience a reduction in FVA associated with complaints of difficulties in reading when patients sustain gazing. However, further studies, including a larger number of patients with placebo controls, might provide statistically significant evidence for the improvement of visual acuity and FVA in AKC-affected patients after cyclosporine A treatment.

In conclusion, the topical cyclosporine A 0.1% solution improved signs and symptoms in children with severe AKC. FVA and VMR are promising parameters for the assessment of dynamic visual acuity changes in AKC-affected patients and for evaluation of treatment outcomes.

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