Japanese Journal of Ophthalmology (2019) 63:410–416
https://doi.org/10.1007/s10384-019-00678-3

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Recent trends of ocular complications in patients with atopic dermatitis

Kaori Yamamoto[1] · Yoshihiro Wakabayashi[1] · Setsuko Kawakami[1] · Takafumi Numata[2] · Tomonobu Ito[2] · Yukari Okubo[2] · Ryoji Tsuboi[2] · Hiroshi Goto[1]

Received: 26 September 2018 / Accepted: 16 May 2019 / Published online: 26 June 2019

Abstract

Purpose To elucidate the recent trends in prevalence and characteristics of ocular complications of atopic dermatitis (AD).

Study Design Cross-sectional observational study.

Methods Among AD patients who visited our department between 2012 and 2015, 70 patients (140 eyes; recent AD group) who gave informed consent to participate in the study were analyzed. Following a medical interview, ophthalmological examinations were conducted for ocular complications related to AD. The data were compared to those of 280 AD patients (560 eyes) analyzed in a similar study conducted at our department in 1991–1993 (previous AD group).

Results Blepharitis was found in 58 eyes (41%) in the recent AD group, and the frequency was significantly lower compared to the previous AD group (294 eyes, 53%) ($p < 0.05$). Tears in retina or pars plana ciliaris occurred in 22 eyes (4%) in the previous AD group, compared with none in the recent AD group ($p < 0.01$). Retinal detachment was observed in 12 eyes (2%) in the previous AD group, and none in the recent AD group ($p < 0.01$). Atopic keratoconjunctivitis (AKC) increased significantly in the recent AD group compared to the previous AD group (74.3% vs. 39.5%) ($p < 0.001$). Patients with a habit of slapping around the eye decreased significantly from 32.5% in the previous AD group to 12.1% in the recent AD group ($p < 0.001$).

Conclusions Ocular complications in AD patients show a trend of decrease in recent years, which presumably is attributed to educational activities to increase patient awareness and advances in therapeutic strategy.

Keywords Atopic dermatitis · Atopic keratoconjunctivitis · Retinal detachment · Tacrolimus · Slapping around the eye

Introduction

Atopic dermatitis (AD) is characterized by cycles of exacerbation and remission, and primary lesions of eczema resulting from itching and scratching. According to the definition of AD, many AD patients have a predisposing factor of atopy [1–3]. AD often results in cataracts, retinal detachment, blepharitis, keratoconjunctivitis, and keratoconus [4]. Blepharitis causes intense itching, inducing repeated itch-scratch behavior. The complication rates of atopic cataract is reported to be high in patients with severe skin lesions of the body, especially in the face, and in patients with long duration of facial rash [5]. Our past survey showed that among all patients with atopic cataract including mild cases with minimal lens opacity, 60% had a habit of scratching the eyelids, rubbing or slapping around the eyes, and 90% of the patients with severe skin lesions who underwent surgery had a history of the slapping habit [6]. Persistent self-induced trauma to periocular structures caused by scratching or slapping in response to the itching sensation is reported to be one cause that triggers atopic cataracts [6, 7]. In an earlier study in which detailed ocular examinations were conducted in 280 AD patients (560 eyes) who had visited the Department of Dermatology of Tokyo Medical University Hospital in 1991–1993, ocular complications were found in approximately one-half of the patients, including cataract in 23.8% and retinal detachment or tears in 6% [8]. That study

Corresponding author: Kaori Yamamoto

✉ Kaori Yamamoto
kaorioph@tokyo-med.ac.jp

[1] Department of Ophthalmology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

[2] Department of Dermatology, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

demonstrated the importance of conducting detailed ocular examinations in patients with AD.

On the other hand, many advances in pharmacotherapy for skin lesions of AD have been made in recent years. Ointments of immunosuppressant drugs such as tacrolimus are being used in addition to topical corticosteroids. Treatment strategy has been switched from reactive therapy, in which treatment is given after exacerbation, to proactive therapy [1, 9], in which treatment is given in advance to prevent recurrence. Furthermore, public education has been implemented to increase awareness and raise precautions to avoid mechanical stimulation to the eye to prevent ocular injuries and complications. Accompanying the various changes in environment pertaining to AD, one can presume that the prevalence and severity of ocular complications in AD patients have also evolved since the 1990s. However, no detailed studies on dermatological treatments and frequency of ocular complications in AD patients are reported.

The present study aimed to detect ocular complications in AD patients and to elucidate the recent trends in prevalence and characteristics of ocular complications in AD patients by comparing the results with the findings of a similar study conducted at our hospital in the past [8].

Methods

In this cross-sectional study, subjects were recruited among patients with current or past history of facial AD who visited the Department of Dermatology at Tokyo Medical University Hospital between 2011 and 2015. The diagnosis of AD was based on Japanese guidelines for atopic dermatitis [1–3]. Among these patients, those who were referred by the attending dermatologist to the Department of Ophthalmology and gave consent to undergo ophthalmological examinations for ocular complications of AD were included in the study.

At the Department of Ophthalmology, a medical interview was conducted to verify the presence or absence of the habit of slapping around the eyes or scratching the eyelids, followed by ocular examinations including visual acuity, intraocular pressure (IOP), slit-lamp microscopy and funduscopy to detect ocular complications of AD. Additional examinations were performed as needed. Corneal topography analysis (TMS; Tomey Technology) was performed in patients with astigmatism greater than − 2.0 D, and ultrasound biomicroscopy (UBM) and ultrasonography were performed when the fundus was unobservable. The primary evaluation items were findings of the anterior ocular segment, optic media, and fundus.

Statistical analyses were performed using Microsoft Excel for Windows version 2016 (Microsoft Corp). An unpaired *t* test was used to compare the results of this study (recent AD group) with the results of a past study conducted in the 1990s by Nakano et al. [8] on 280 patients (560 eyes) (previous AD group). Chi squared test was used to analyze the relationship between the habit of slapping around the eye and frequency of ocular complications. A two-tailed p value less than 0.05 was considered to indicate a significant difference.

This study was jointly conducted by the Departments of Ophthalmology and Dermatology, and was approved by Tokyo Medical University Ethics Committee (No. 2033). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

One hundred and seven patients (214 eyes) with AD gave consent to undergo ophthalmological examinations for ocular complications. Of these, 70 patients (65.4%) who underwent ophthalmological examinations (140 eyes) at the Department of Ophthalmology were included in the study (recent AD group).

Patient background

Patients' background is shown in Table 1. The 70 patients (45 men and 25 women) were aged 35.8 ± 11.9 (mean ± standard deviation) years, ranging from 4 to 60 years. The mean estimated disease duration was 26.9 ± 13.8 years, ranging from 2 to 59 years. Sixty-six (94.3%) patients used topical corticosteroids and 55 patients (78.6%) used topical tacrolimus as dermatological treatment. Twenty-two (31.4%) patients used

Table 1 Patient background

Sex	45 males/25 females
Age (years)	35.8 ± 11.9 (mean ± SD)
Estimated disease duration (years)	26.9 ± 13.8 (mean ± SD)
Dermatological treatment (number of patients)	66 (94.3%)
Topical steroids	
Topical tacrolimus	55 (78.6%)
Ophthalmological treatment (number of patients)	22 (31.4%)
Anti-allergic ophthalmic solution	
Corticosteroids ophthalmic solution	3 (4.3%)
Tacrolimus ophthalmic solution	2 (2.9%)
Periocular skin symptom score (points)	4.9 ± 3.5 (mean ± SD)

SD standard deviation

anti-allergic ophthalmic solution, 3 patients (4.3%) used corticosteroids ophthalmic solution and 2 patients (2.9%) used tacrolimus ophthalmic solution as ophthalmological treatment. The severity of periocular skin symptoms was evaluated using the eczema area and severity index (EASI) [10] and was expressed as the periocular score. Erythema, infiltration/papule, abrasion scar, and lichenization was each scored on a scale of 0–3 corresponding to absence (0 point), mild (1 point), moderate (2 points) and severe symptoms (3 points), with a maximum total score of 12. The mean periocular skin symptom score was 4.9 ± 3.5 points.

Age distribution

Age distribution is shown in Fig. 1.

Ophthalmological examinations

The mean best corrected visual acuity (BCVA) of the right eye was 0.125–2.0 in decimal visual acuity, or − 0.09 ± 0.17 converted to logarithm of the minimum angle of resolution (logMAR). Although corrected vision of the left eye could not be measured in one patient due to phthisis bulbi, the mean BCVA of the left eye was 0.001 (hand protection)-2.0 in decimal visual acuity, or − 0.07 ± 0.50 logMAR. The mean spherical equivalent refraction of the right and left eyes was − 2.80 ± 2.80 D (range − 9.125 D to +2.25 D), and − 3.0 ± 2.77 D (range − 10.38 to +0.25 D), respectively. The mean IOP of the right and left eyes were 14.5 ± 3.0 8 (range 8–21) mmHg and 14.5 ± 3.2 (range 9–24) mmHg, respectively. TMS was conducted in 34 eyes and UBM in 2 eyes.

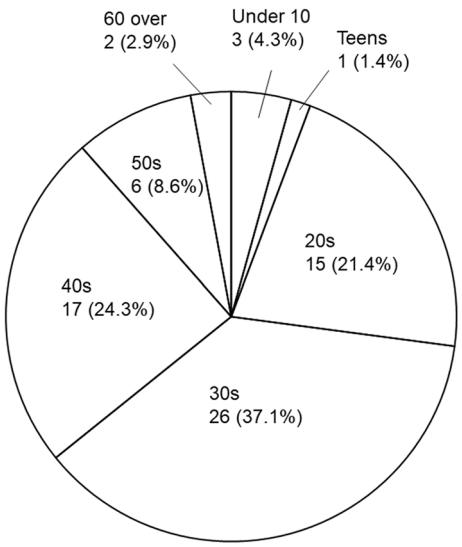

Fig. 1 Age distribution. Number of patients (%)

Ocular complications of AD in 140 eyes of 70 patients in the recent AD group

Ocular complications in the recent AD group are shown in Table 2. Blepharitis was found in 58 eyes (41.1%), atopic keratoconjunctivitis (AKC) [11] in 104 eyes (74.3%), superficial punctate keratitis in 11 eyes (7.9%), and keratoconus in 4 eyes (2.9%). Lens opacity was observed in 24 eyes (17.1%), including anterior subcapsular opacity in 6 eyes (4.3%), which is considered to be caused by AD. Cortical opacity was found in 3 eyes (2.1%), nuclear sclerosis in 22 eyes (15.7%), and posterior subcapsular opacity in 1 eye (0.7%). Nine eyes (6.4%) had undergone cataract surgery. Abnormalities of the vitreous body included vitreous liquefaction in 19 eyes (20.9%), vitreous opacity in 13 eyes (9.3%), and posterior vitreous detachment in 5 eyes (3.6%). Retinal abnormalities with a history of treatment included peripheral degeneration in 15 eyes (10.4%), but there were no eyes with tears in the retina or pars plana ciliaris and no eyes with retinal detachment. A habit of periocular slapping was found in 17 eyes (12.1%) and a habit of scratching in 86 eyes (61.4%).

The relationship between the habit of slapping around the eye and frequency of ocular complications is shown in Table 3. AKC was found in 16 eyes (94.1%) in the group with slapping habit and in 88 eyes (71.5%) in the group without tapping habit. Thus, ocular complications were found significantly more frequently in patients with the habit of slapping around the eye compared with those without ($p < 0.001$). Lens opacity was found in 5 eyes (29.4%) in the group with slapping habit and in 19 eyes (15.4%) in the group without tapping habit, with no significant difference between the two groups. The habit of scratching the eyelids was found in 17 eyes (100%) in the group with slapping habit, compared to 69 eyes (56.1%) in the group without slapping habit, showing a significantly higher frequency in patients with slapping habit. There was no significant difference in periocular skin symptoms score between the groups with and without slapping habit.

The relationship between the mean periocular skin symptom score and blepharitis is shown in Fig. 2. The mean periocular skin symptom score in 58 eyes with blepharitis was 5.9 ± 3.4 points, compared with 4.2 ± 3.4 points in 82 eyes without blepharitis, and was, therefore, significantly higher ($p < 0.01$). The relationship between the mean periocular skin symptom score and AKC is shown in Fig. 3. The mean periocular skin symptom score in 104 eyes with AKC was 5.2 ± 3.6 points, compared with 3.9 ± 3.3 points in 36 eyes with no AKC, and was, therefore, significantly higher ($p = 0.04$). There were no differences in the incidence of ocular complications and age between patients treated with and without topical tacrolimus. Topical corticosteroids were used in almost all cases, but the incidence of ocular

Table 2 Comparison of ocular complications between the recent and previous atopic dermatitis (AD) groups

	Recent AD group (n = 140)		Previous AD group (n = 560)		*p* value
	Number of eyes	(%)	Number of eyes	(%)	
Blepharitis	58	(41.4)	294	(52.5)	0.02*
Atopic keratoconjunctivitis	104	(74.3)	221	(39.5)	0.00*
Superficial punctate keratitis	11	(7.9)	65	(11.6)	0.16
Keratoconus	4	(2.9)	NA	NA	NA
Lens opacity	24	(17.1)	133	(23.8)	0.07
Anterior subcapsular	6	(4.3)	16	(2.9)	0.44
Cortical	3	(2.1)	35	(6.3)	0.01*
Nuclear sclerosis	22	(15.7)	13	(9.8)	0.00*
Posterior subcapsular	1	(0.7)	73	(13.0)	0.00*
Undergone cataract surgery	9	(6.4)	4	(0.7)	0.00*
Vitreous liquefaction	19	(13.6)	24	(4.3)	0.00*
Vitreous opacity	13	(9.3)	26	(4.6)	0.08
Posterior vitreous detachment	5	(3.6)	2	(0.4)	0.04*
Retinal peripheral degeneration	15	(10.4)	77	(13.8)	0.31
Tears in retina or pars plana ciliaris	0	(0)	22	(3.9)	0.00*
Retinal detachment	0	(0)	12	(2.1)	0.00*
History of retinal photocoagulation	5	(3.6)	NA	NA	NA
History of retinal detachment surgery	4	(2.9)	NA	NA	NA
Habit of slapping around the eye	17	(12.1)	182	(32.5)	0.00*
Habit of scratching the eyelids	86	(61.4)	NA	NA	NA

AD atopic dermatitis

*$p < 0.05$, unpaired *t* test

Table 3 The relationship between the habit of slapping around the eye and frequency of ocular complications of atopic dermatitis (AD) in the recent AD group

	Slapping habit (+) (n = 17)		Slapping habit (−) (n = 123)		*p* value
	Number of eyes	(%)	Number of eyes	(%)	
Blepharitis	10	(58.9)	48	(39.0)	0.14
Atopic keratoconjunctivitis	16	(94.1)	88	(71.5)	0.00*
Lens opacity	5	(29.4)	19	(15.4)	0.25
Retinal peripheral degeneration	3	(17.6)	12	(9.8)	0.44
Vitreous opacity	4	(23.5)	3	(2.4)	0.15
Habit of scratching the eyelids	17	(100)	69	(56.1)	0.00*
Periocular skin symptom score (points) (mean ± SD)	5.9 ± 2.8		4.7 ± 3.6		0.12

AD atopic dermatitis, *SD* standard deviation

*$p < 0.05$, Chi squared test

complications between patients treated with and without topical corticosteroids could not be compared.

Comparison between previous and recent AD groups

Table 2 compares the frequencies of ocular complications in the recent AD group (2012–2015) with the previous AD group (1991–1993) studied by Nakano et al. [8]. Blepharitis decreased significantly in the recent AD group compared to the previous AD group (41.4% vs. 52.5%) ($p < 0.05$). AKC increased significantly in the recent AD group compared to the previous AD group (74.3% vs. 39.5%) ($p < 0.001$). The frequency of lens opacity did not change significantly between the recent and previous AD groups (17.1% vs. 23.8%). Cortical opacity decreased significantly in the recent AD group compared to the previous group (1.4% vs. 6.3%) ($p < 0.001$). Posterior subcapsular opacity also decreased significantly in the recent AD group compared to the previous group (0.7% vs. 13.0%) ($p < 0.001$). Nuclear sclerosis

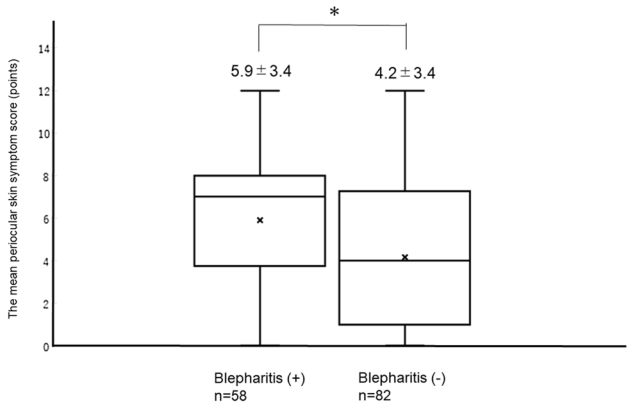

Fig. 2 The relationship between the mean periocular skin symptom score and blepharitis. *$p < 0.05$, Chi squared test

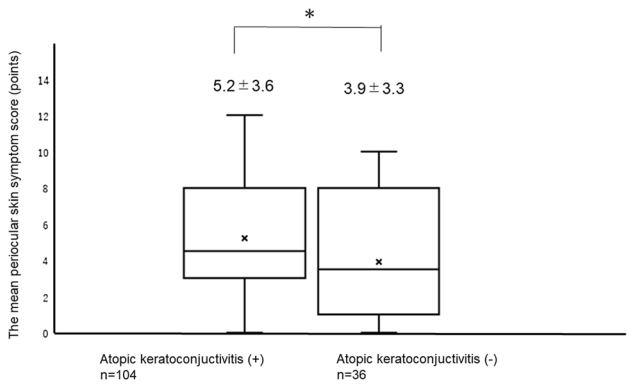

Fig. 3 The relationship between the mean periocular skin symptom score and atopic keratoconjunctivitis. *$p < 0.05$, Chi squared test

increased significantly in the recent AD group compared to the previous group (15.7% vs. 2.3%) ($p < 0.001$). Tears in the retina or pars plana ciliaris were found in 3.9% in the previous AD group but not in the recent AD group ($p < 0.001$). Retinal detachment was observed in 2.1% of the eyes in the previous AD group, but in none of the eyes in the recent AD group ($p < 0.001$). The number of patients with the habit of slapping around the eye decreased significantly from 32.5% in the previous AD group to 12.1% in the recent AD group ($p < 0.001$). The habit of scratching eyelids and periocular skin symptom score were not examined in the previous AD group, and therefore could not be compared.

Discussion

According to a recent report, the proportion of retinal detachment as a complication of AD among all retinal detachments has decreased significantly compared to a decade ago [12], but there are no reports on the changes in prevalence of other ocular complications of AD and the habit of slapping around the eye. In the present study, we found that blepharitis, retinal detachment, retinal tears, and the habit of slapping around the eye have decreased in the recent AD group compared with the previous AD group. This is the first report of a recent trend of decreases in ocular complications other than retinal detachment in AD patients. The slapping habit may be attributed to ocular and periocular itching and scratching but may also involve psychological factors. We observed this relationship also in our previous survey [13]. Recent studies report aging of patients with AD, and increases in allergic diseases as possible underlying reasons [14]. Japanese cedar pollinosis is reported to affect 13.1% of the population [15]. The present study also suggests that AKC is increasing in patients with AD. The increase in allergic diseases may even cancel out the value of decline in slapping habit in decreasing ocular complications in AD patients. Furthermore, in the recent AD group, patients with the slapping habit had a higher frequency of scratching and a higher complication rate by AKC compared to AD patients without the slapping habit. Based on the above findings, chronic AKC may trigger periocular itching or discomfort and induce behavior such as slapping or scratching. Therefore, checking for the habit of slapping around the eye or scratching the eyelids in a medical interview may provide useful information contributing to understanding ocular complications in AD patients. The findings of the present study suggest that AKC should be treated to resolve subjective symptoms of itching and scratching, before the development of severe allergic ocular complications. Early treatment of allergic conjunctivitis would reduce the habits of slapping around the eye and scratching the eyelids, consequently decreasing ocular complications induced by these habits.

The mean periocular skin symptom score was significantly higher in patients with blepharitis and AKC compared to those without, showing that the ocular symptoms diagnosed by the ophthalmologists accord with the periocular skin symptom score assessed by the dermatologists.

A history of cataract surgery and/or anterior subcapsular opacity, presumably associated with AD, was found in 6 eyes (35.3%) in the group with slapping habit and 9 eyes (7.3%) in the group without slapping habit, significantly more common in patients with the slapping habit ($p < 0.05$). This finding suggests that the slapping habit could be involved in the pathogenesis of cataracts. We predicted that lens opacity would have decreased in the recent AD group, but this was not the case. However, the frequency of nuclear sclerosis of the lens increased significantly in the recent AD group, suggesting a difference in age distribution compared to the previous AD group. The mean age of patients in the previous AD group was 22.5 ± 9.2 (range 2–62) years, and more than one-half were in their twenties. In the recent AD group,

however, the mean age was 35.8 ± 11.9 years, and the largest proportion (37.1%) were in their 30 s.

Tacrolimus is an immunosuppressant that suppresses transcription activity through the nuclear factor of activated T cells' (NFAT) pathway. This agent is not readily absorbed through the normal skin because of its large molecular weight. Tacrolimus exhibits therapeutic effects in lesions with lowered barrier functions, such as dermatitis. As the lesion improves, tacrolimus absorption through the skin decreases and transdermal adverse effects are reduced. However, attention should be paid to local inflammation and skin irritation symptoms such as urtication at the time of initiating tacrolimus treatment. Proactive therapy [1, 9, 16–25] is drawing attention in recent years. Proactive therapy comprises anti-inflammatory treatment in the acute phase to improve symptoms, and applying topical steroids [16–19] or tacrolimus ointment [20–24] twice a week to prevent recurrence. However, there is no clear evidence on the safety of long-term use of proactive therapy or the appropriate durations of the successive treatments. In Japan, topical tacrolimus has been approved for AD since 2001. While topical tacrolimus was used by none of the patients in the previous AD group (1991–1993), it was used by 78.6% of the patients in the recent AD group (2012–2015). In the recent AD group, there was no difference in the incidence of ocular complications between the group that used and the group that did not use tacrolimus. In recent years the application of topical tacrolimus as part of proactive therapy has become standard. This therapy may have influenced the frequency of ocular complications in AD patients. The frequency of posterior subcapsular opacity of the lens decreased significantly in the recent AD group compared to the previous AD group. This may reflect the decrease in ocular complications caused by steroids, and also the changes in modes of treatment in recent years. The frequency of blepharitis was the same in patients who used and those who did not use tacrolimus ointment, indicating that skin irritating symptoms such as urtication caused by topical tacrolimus do not increase blepharitis or the habit of slapping around the eye.

This study has several limitations. First, it is a cross-sectional study that observed the ophthalmologic findings at the time of patient consultation at the Department of Ophthalmology, and thus did not study changes over time. Second, the previous and recent AD groups compared in this study had different sample sizes. Further study on a larger sample is warranted to continue monitoring ocular complications in AD patients.

In conclusion, we studied the frequencies of ocular complications associated with AD in our hospital and compared the results with the findings of a similar study conducted previously in our hospital. We found that AKC increased, while retinal detachment, blepharitis and the habit of slapping around the eyes decreased compared to the previous study. These results may be attributed to improved treatment for the primary disease and educational activities to increase awareness of patients.

Conflicts of interest K. Yamamoto, None; Y. Wakabayashi, None; S. Kawakami, None; T. Numata, None; T. Ito, None; Y. Okubo, None; R. Tsuboi, None; H. Goto, None.

References

1. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, et al. The Japanese Society of Allergology. Japanese guidelines for atopic dermatitis 2017. Allergol Int. 2017;66:230–47.
2. Saeki H. Management of atopic dermatitis in Japan. J Nippon Med Sch. 2017;84:2–11.
3. Saeki H, Furue H, Furukawa F, Hide M, Ohtsuki M, Katayama I, et al. Committee for guidelines for the management of atopic dermatitis of Japanese Dermatological Association. Guidelines for management of atopic dermatitis. J Dermatol. 2009;36:563–77.
4. Rich LF, Hanifin JM. Ocular complication of atopic dermatitis and other eczemas. Int Ophthalmol Clin. 1985;25:61–76.
5. Hoshino M, Sekine Y, Takahashi H, Iwata M, Honmura S, Otsuka F. Atopic dermatitis and its ocular complications. Jpn J Dermatol. 1984;104:1361–6 **(in Japanese)**.
6. Goto H, Sanada A, Wakabayashi Y, Yagihashi T, Iwasaki T, Usui M, et al. The role of trauma in the pathogenesis of atopic cataract. Atarashii Ganka (J Eye). 1996;13:1728–32 **(in Japanese)**.
7. Goto H, Yagihashi T, Miyake M, Kusano T, Sanada A, Yamakawa N, et al. Blunt trauma-induced experimental cataract model: the role of trauma in the pathogenesis of atopic cataracts. Atarashii Ganka (J Eye). 1996;13:1733–8 **(in Japanese)**.
8. Nakano E, Iwasaki T, Osanai T, Yamamoto K, Miyauchi M. Ocular complications of atopic dermatitis. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc). 1997;101:64–8 **(in Japanese)**.
9. Wollenberg A, Ehmann LM. Long term treatment concept and proactive therapy for atopic eczema. Ann Dermatol. 2014;24:253–60.
10. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. EASI Evaluator Group. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10:11–8.
11. Takamura E, Uchio E, Ohya Y, Ebihara N, Ohno S, Ohashi Y, et al. The Japanese Society of Allergology. Japanese guidelines for allergic conjunctival diseases 2017. Allergol Int. 2017;66:220–9.
12. Sasoh M, Mizutani H, Matsubara H, Furuta M, Matsui Y, Yamanaka KV, et al. Incidence of retinal detachment associated with atopic dermatitis in Japan: review of cases from 1992 to 2011. Clin Ophthalmol. 2015;9:1129–34.
13. Kawakami S, Goto H, Yagihashi T, Iwasaki T, Usui M. Implication of blunt injury in advanced atopic cataract. Rinsho Ganka (Jpn J Clin Ophthamol). 1999;3:701–4 **(in Japanese)**.
14. Thyssen JP, Toft PB, Halling-Overgaard AS, Gislason GH, Skov L, Egeberg A. Incidence, prevalence, and risk of selected ocular disease in adults with atopic dermatitis. J Am Acad Dermatol. 2017;77:280–6.
15. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. Ann Allergy Asthms Immunol. 2003;91:288–96.
16. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. Br J Dermatol. 2002;147:528–37.
17. Berth-Jones J, Damstra RJ, Golsch S, Livden JK, Van Hooteghem O, Allegrra F, et al. Multinational Study Group. Twice weekly fluticasone propionate added to emollient maintenance treatment

to reduce risk of relapse in atopic dermatitis: randomized, double blind, parallel group study. BMJ. 2003;326:1367–70.
18. Peserico A, Stadtlere G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapse of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicenter, randomized, double-blind, controlled study. Br J Dermatol. 2008;158:801–7.
19. Glazenbulg EJ, Wolkerstorfer A, Gerretsen AL, Mulder PGH, Oranje AP. Efficacy and safety of fluticasone propionate 0.005% ointment in the long-term maintenance treatment of children with atopic dermatitis: differences between boys and girls? Pedriatr Allergy Immunol. 2009;20:59–66.
20. Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, et al. European Tacrolimus Ointment Study Group. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. Allergy. 2008;63:742–50.
21. Breneman D, Fleischer AB, Abramovits W, Zeichner J, Gold MH, Kirsner RS, et al. Tacrolimus Ointment Study Group. Intermittent therapy for flare prevention and long-term disease control in stabilized atopic dermatitis: a randomized comparison of 3-times-weekly applications of tacrolimus ointment versus vehicle. J Am Acad Dermatol. 2008;68:990–9.
22. Wollenberg A, Sidhu MK, Odeyemi I, Porsh B, Koehne-Volland R, Schaffe M, et al. Economic evaluation of maintenance treatment with tacrolimus 0.1% ointment in adults with moderate to severe atopic dermatitis. Br J Dermatol. 2008;159:1322–30.
23. Thaci D, Reitamo S, Gonzalez Ensenat MA, Moss C, Boccaletti V, Cainelli T, et al. European Tacrolimus Ointment Study Group. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicenter, comparative study. Br J Dermatol. 2008;159:1348–56.
24. Chung BY, Kim HO, Kim JH, Chos I, Lee CH, Park CW. The proactive treatment of atopic dermatitis with tacrolimus ointment in Korean patients: a comparative study between once-weekly and thrice-weekly applications. Br J Dermatol. 2013;168:908–10.
25. Schmitt J, von Kobbylezki L, Svensson A, Apfelbacher C. Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: systematic review and metaanalysis of randomized controlled trials. Br J Dermatol. 2011;164:415–28.