Figure 2. Representative photographs showing Stevens-Johnson syndrome/toxic epidermal necrolysis-associated ocular and oral involvement and fingernail loss at the acute stage. A, Conjunctivitis, which was accompanied by extensive loss of bulbar conjunctival epithelium. B, Swollen and crusted lips. C, Fingernail loss and deformation with paronychia.

neously with skin eruptions and that the involvement of oral mucosa was observed in 100% of the cases who could remember the details. Fingernail loss at the acute stage, deformation at the time of the writing of this report, or both also occurred in all of the patients, suggesting that paronychia occurred in all patients at the acute phase.

Visual outcomes were significantly better in the patients who received treatment with topical steroids during the first week from disease onset compared with those of the patients who received no topical steroid treatment. However, those outcomes may be because of the presumed fact that patients who fail to receive treatment with topical steroids are highly likely not going to receive systemic steroids as well. Thus, treatment with topical steroids, systemic steroids, or both at the early stage of the disease helps to decrease the incidence of chronic ocular complications. At the onset of the diseases, both necrotic changes of the skin and the destruction of the ocular surface progress rapidly. Prompt use of topical steroids, and presumably systemic steroids, from disease onset may prove to be important for preventing the loss of corneal epithelial stem cells. Unfortunately, a detailed history concerning the systemic therapy during the acute stage could not be obtained in most instances. Additional studies are needed to confirm the safety and efficacy of those medications.

Of the 94 patients, the mean duration of the illness was 16.1 years, and more than 50% of the eyes manifested visual acuity worse than 20/200. Considering the fact that patients with SJS or TEN experience ocular complications for an extended period, it is vital that strict attention be paid to any ocular involvement. When dermatologists, physicians, and healthcare professionals suspect SJS or TEN, prompt referral to an ophthalmologist is vital for the prevention of permanent loss of vision. Ophthalmologists have to find distinctive appearances such as pseudomembrane formation and corneal or conjunctival epithelial defects, or both.

In the first report by Stevens and Johnson, 2 boys reported eye pain before skin eruptions and manifested a purulent conjunctivitis. Visual prognosis was total blindness in one case and severe corneal scarring in the other case. Both cases had the typical clinical picture clarified in the present study.[1] If their eyes had been treated with topical steroids from disease onset, the visual outcomes might have been different.

To date, the pathophysiologic mechanisms underlying the onset of SJS and TEN have yet to be fully elucidated. The rarity of these diseases has led us to speculate that patients with SJS or TEN genetically are susceptible to specific environmental precipitants. A report from the United States showed an increase of HLA-B12 (HLA-Bw44) antigen in white patients with SJS with ocular involvement.[31] Analyses of TEN patients in France also disclosed an association with HLA-B12 (HLA-Bw44).[32] In Han Chinese, there was a very strong association between carbamazepine-induced SJS and the HLA-B*1502 allele.[33] The authors also reported that in Japanese persons, HLA-A*0206 was strongly associated with SJS and TEN with

AQ: 2

Table 2. Order of Conjunctivitis and Skin Eruptions of the 94 Patients at Disease Onset

Conjunctivitis	Period Preceding Eruption	No. of Patients
Occurred before skin eruption	4 days	1
	3 days	3
	2 days	11
	1 day	12
	Several hours	9
	Unknown	6
		Total = 42
Occurred simultaneously		21
Occurred later		1
Unknown		30
Total		94

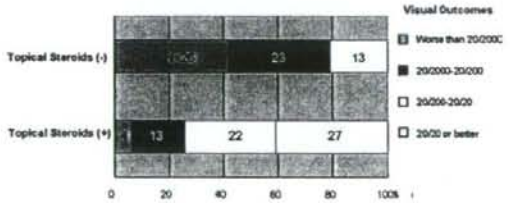

Figure 3. Graph showing the relationship between topical steroid use during the first week from disease onset and visual outcomes. Sixty-six eyes of 33 patients began topical steroid treatment during the first week from disease onset, whereas 62 eyes of 31 patients received no topical steroid treatment or any other treatment. Visual outcomes were significantly better in the group receiving topical steroids at the acute stage compared with those of the no-treatment group ($P<0.00001$).

ocular surface complications.[34,38] These findings suggest that SJS and TEN are associated with a complex genetic inheritance background.

The prodromal symptoms occurred in 82% of the cases in this study. Given the association between the onset of SJS and TEN and infections and the opportunistic infection of ocular surfaces by bacteria such as methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *Staphylococcus epidermidis*,[41] it is highly possible that there is an association between SJS and TEN and a disordered innate immune response. Recently, the association of the polymorphisms in the toll-like receptor 3 gene with SJS and TEN in the Japanese population were reported.[36] Also, an association between SJS and TEN and the IL-4R gene polymorphism and combined IL-13/IL-4R signaling pathway gene polymorphism was reported.[35,39] Thus, both innate immunity and host–defense mechanisms may play a critical role in the development of SJS and TEN.

In conclusion, ocular involvement at disease onset is a helpful symptom for the diagnosis of SJS and TEN. Acute conjunctivitis before or occurring simultaneously with skin eruptions accompanied by very high fever and blisters on the mouth greatly implies the initial signs of SJS and TEN, and prodromal symptoms and genital involvements support that diagnosis. Initiating treatment with topical steroids from the onset seems to be important for the improvement of visual prognosis. A prompt and accurate diagnosis as assisted by the clinical manifestation offers a breakthrough against the historically poor visual outcomes associated with patients with SJS or TEN.

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Footnotes and Financial Disclosures

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[1] Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.

[2] Department of Dermatology, Ehime University School of Medicine, Ehime, Japan.

[3] Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Kanagawa, Japan.

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Correspondence:
Chie Sotozono, MD, PhD, Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-0841, Japan. E-mail: csotozon@koto.kpu-m.ac.jp.

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Successful Treatment of Stevens-Johnson Syndrome with Steroid Pulse Therapy at Disease Onset

YAYOI ARAKI, CHIE SOTOZONO, TSUTOMU INATOMI, MAYUMI UETA, NORIHIKO YOKOI, EIICHIRO UEDA, SABURO KISHIMOTO, AND SHIGERU KINOSHITA

• PURPOSE: To evaluate the visual prognosis of patients with Stevens-Johnson syndrome (SJS) and its severe variant, toxic epidermal necrolysis (TEN), followed by general and topical high-dose corticosteroids administration from disease onset.

• DESIGN: Prospective, observational case series.

AQ: 1 • METHODS: Between May 2003 and June 2005, we enrolled 5 patients with SJS or TEN with ocular complications at the acute stage. Intravenous pulse therapy with methylprednisolone (steroid pulse therapy; 500 or 1000 mg/day for 3 to 4 days) was initiated within 4 days from disease onset. Topically, 0.1% betamethasone was applied over 5 times daily for at least 2 weeks. Visual acuity (VA) and slit-lamp microscopic appearance 1 year from disease onset were evaluated.

• RESULTS: At the first examination, corneal or conjunctival epithelial defects and pseudomembranous conjunctivitis were present in all cases. Skin eruptions dramatically improved after steroid pulse therapy. Although ocular inflammation increased for several days, pseudomembranes disappeared and corneal and conjunctival epithelium regenerated within 6 weeks. At the chronic stage, all eyes had clear corneas with the palisades of Vogt (POV), implying the presence of corneal epithelial stem cells. Best-corrected VA was 20/20 or better in all eyes. Five eyes showed superficial punctate keratopathy. No eye had cicatricial changes except for 1 with slight fornix shortening. No significant adverse effects of steroid occurred during all clinical courses.

• CONCLUSIONS: Steroid pulse therapy at disease onset is of great therapeutic importance in preventing ocular complications. Topical betamethasone also shows great promise for preventing corneal epithelial stem cell loss in the limbal region and cicatricial changes. (Am J Ophthalmol 2009;xx:xxx. © 2009 Published by Elsevier Inc.)

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From the Department of Ophthalmology, Kyoto Prefectural University of Medicine (Y.A., C.S., T.I., M.U., N.Y., S.Kin.); and the Department of Dermatology, Kyoto Prefectural University of Medicine (E.U., S.Kis), Kyoto, Japan.

Inquiries to Chie Sotozono, Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-0841, Japan; e-mail: csotozon@koto.kpu-m.ac.jp

STEVENS-JOHNSON SYNDROME (SJS), FIRST REPORTED in 1922, is an acute inflammatory disease that predominantly affects the skin and mucosal membranes, including the ocular surface.[1] In 1956, Lyell described a clinical condition characterized by extensive epidermal loss, termed *toxic epidermal necrolysis* (TEN).[2] Recent reports suggest that SJS and TEN are the same disorder, but of different severities.[3–5] In the acute stage, these diseases predispose patients to life-threatening complications such as sepsis, respiratory dysfunction, and multiorgan failure. Mucosal sites including the ocular surface and oral membrane commonly are involved at the onset of acute fever and skin eruptions. Although skin usually heals without dysfunction, severe corneal opacity and dry eye often persist during the chronic stage. Patients with SJS or TEN require life-long management for ocular discomfort and morbidity.[6–9] Recently, it was reported that amniotic membrane transplantation (AMT) onto the ocular surface is effective for reducing the destructive inflammation in acute SJS or TEN and for preventing cicatricial change.[10–12] However, safe and effective medical treatment for the prevention of ocular complications has yet to be established.

Although the pathogeneses of SJS and TEN has not been elucidated fully, it has been indicated that soluble FasL-mediated apoptosis plays a crucial role in the pathogeneses of SJS and TEN.[13] Drug-specific cytotoxic CD8+ T lymphocytes were detected in blister fluids of SJS and TEN patients and in cytotoxic lymphocyte cytolytic pathways, including major histocompatibility complex class I.[14] It also has been reported that tumor necrosis factor and interferon-γ also are involved in the mechanisms of epidermal necrosis.[15] Therefore, it is highly possible that medication at the acute stage to downregulate such immunologic reactions is useful for the treatment of SJS and TEN.

The use of systemic corticosteroids for the care of patients with acute SJS and TEN is controversial.[16,17] Although the beneficial effects of corticosteroid therapy during the acute stage has been reported,[18–20] high mortality rates in patients receiving corticosteroids has been shown.[21,22] The timing, dose, formulation, and route of administration of the steroid differ in these reports. At disease onset, skin involvement and ocular involvement progress rapidly, and facial manifestation and general condition became worse from morning to evening. Considering the pathogenesis described above and the rapid progression of SJS and TEN at disease onset, we hypoth-

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esized that the timing and dose of the administered steroid are both key to obtaining beneficial effects.

In patients with SJS- or TEN-induced chronic ocular complications, the total loss of the palisades of Vogt (POV) commonly is observed.[23] POV in the limbal area implies the presence of corneal epithelial stem cells.[24] At the acute stage, corneal epithelial defect or corneal ulceration occur in more than 50% of the patients with SJS or TEN.[25] In cases with limbal stem cell loss, conjunctivalization and neovascularization of the cornea progress, leading to severe visual impairment or blindness.[6–9] Loss of the POV occurs during the acute stage of SJS and TEN and can be accompanied by severe inflammation. The administration of high-dose general and topical corticosteroids from disease onset may downregulate the immunologic reactions described above and may prevent the loss of corneal epithelial stem cells.

The aim of this study was to evaluate the ophthalmic efficacy of high-dose corticosteroid therapy at the acute stage of SJS or TEN. All patients in this study were administered high-dose systemic methylprednisolone (steroid pulse therapy) and topical betamethasone for SJS or TEN with ocular involvement from the onset of the disease. Side effects of the steroids were monitored carefully over the duration of this study, and a great amount of attention was paid to systemic and ophthalmic infections. We then evaluated visual acuity (VA) and the slit-lamp microscopic appearance in these patients at the chronic stage.

METHODS

AQ: 2 BETWEEN MAY 2003 AND JUNE 2005, WE ENROLLED 5 CONsecutive patients (2 males and 3 females, 23 to 49 years of age at disease onset; mean age, 32.8 years) referred to us during the first 4 days from the onset of SJS or TEN accompanied by ocular complications (ocular surface epithelial defects, pseudomembranous formation, or both). The diagnosis of SJS or TEN was confirmed by dermatologists based on clinical and histopathologic classification.[26,27] Prior informed consent to participate in the study was obtained in written form from all patients, their families, or both.

We initiated therapy with intravenous high-dose methylprednisolone and intensive topical betamethasone immediately after the dermatologic and ophthalmologic diagnosis. For initial treatment, the protocol used in this study was as follows: intravenous methylprednisolone at a dosage of 500 to 1000 mg/day was used for 3 to 4 days (steroid pulse therapy) and 0.1% betamethasone was applied topically more than 5 times daily for at least 2 weeks. The topical antimicrobial agent was applied prophylactically.

Signs of systemic and ophthalmic infection were monitored by the culture of blood, conjunctival swab, and the swab of other mucous membranes. The body temperature and the patient's symptoms and biochemical parameters also were monitored carefully.

Patient-related ocular findings and the complications during the acute stage were recorded fully until the remission of the ocular surface inflammation. As for ocular complications, corneal complications (superficial punctate keratopathy [SPK], epithelial defect, loss of the POV, conjunctivalization, neovascularization, opacification, and keratinization), conjunctival complications (hyperemia and symblepharon formation), and eyelid complications (trichiasis, mucocutaneous junction involvement, meibomian gland involvement, and punctal damage) were recorded according to a new grading system for SJS that we previously reported.[23] Tear secretion was assessed by the Schirmer 1 test, and meibomian gland morphologic features were evaluated using meibography.[28,29] VA and ocular findings at the chronic stage were evaluated after 1 year from the onset of the disease.

RESULTS

• OCULAR FINDINGS AND THERAPY DURING THE ACUTE STAGE: Five patients were referred to us within 4 days (0 to 4 days; mean, 1.2 days) from the onset (the initiation of skin eruptions accompanying mucocutaneous illness) of the disease (Table). All patients had rapidly T1
progressing skin eruptions, mucous membrane erosions, and a very high fever (more than 39 C) at presentation. Those symptoms were preceded by common cold-like symptoms (general malaise, fever, sore throat, or a combination thereof) in 4 patients. The causative drugs were cold remedies (Cases 1 and 5), antibiotics (Cases 3 and 5), and nonsteroidal anti-inflammatory drugs (Cases 3, 4, and 5). In 1 patient, high fever and erythematous macules developed after vaccination for measles (Case 2). All 10 eyes had pseudomembranous conjunctivitis. Corneal or conjunctival epithelial defects were present in all cases. Corneal epithelial defects existed in 5 eyes, and severe SPK was present in the other 5 eyes. Conjunctival epithelial defects were observed in 6 eyes (Figures 1 and 2). Skin F1-2
biopsy specimens of the erythematous macules from all patients showed necrotic keratinocytes and liquefaction degeneration that were consistent with the diagnosis of SJS or TEN (Figure 3). F3

In all patients, steroid pulse therapy was initiated immediately after confirming ocular involvement, except 1 case (Case 5) in which steroid pulse therapy already had been initiated previously by a dermatologist. Thereafter, systemic steroids were changed to prednisolone or betamethasone (Table). Topically, 0.1% betamethasone (0.1% betamethasone solution, 0.1% betamethasone eye ointment, or both; 5 to 8 times daily) was used from the day we confirmed ocular involvement. An ophthalmic fluoroquinolone solution (0.3% gatifloxacin or 0.3% ofloxacin; 4 times daily) was used for the prevention of ocular infec-

TABLE. Dosage and Duration of Systemic Corticosteroid Administration during the Acute Stage of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

				Steroid Pulse Therapy (Methylprednisolone)			Steroid Administration after Pulse Therapy (Prednisolone Equivalent)		
Case	Diagnosis	Age (yrs)	Gender	Elapsed Time from Onset to Initiation of Therapy (days)	Steroid Dose (mg/day)	Duration (Days)	Initial Dose (mg/day)	Total Duration (days)	Total Amount (mg)
1	SJS	23	M	1	500	3	40	85	1045
2	SJS	27	F	0	1000	3	40	35	510
3	SJS	31	F	4	500	3	60	20	425
4	SJS	34	F	1	1000	3	40	72	570
5	TEN	49	M	0	500	4	60	9	420
Mean		32.8		1.2				44	594

F = female; M = male; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; yrs = years.

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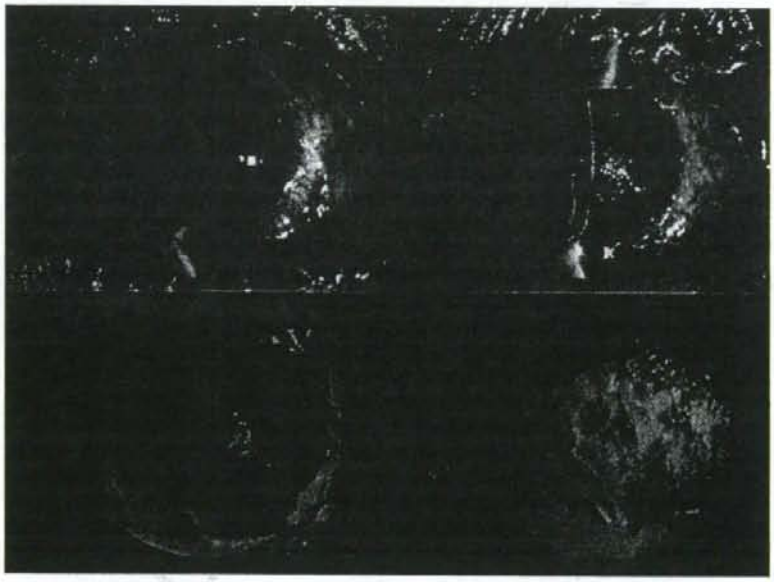

FIGURE 1. Images demonstrated Stevens-Johnson syndrome (SJS) at the acute stage (Case 1). (Top left) Two days after disease onset, pseudomembranous conjunctivitis with conjunctival epithelial defect was present around the limbus. The cornea was clear without defect and superficial punctate keratopathy. (Top right) At the most inflamed phase, 9 days after disease onset and 8 days after the start of steroid pulse therapy, the ocular surface was most inflamed with increased eye discharge, and the pseudomembrane and cilia fell out partially in the lower eyelid. (Bottom left) Corneal epithelial defect. (Bottom right) Conjunctival epithelial defect extending to almost the entire bulbar and palpebral conjunctiva.

tions. Prophylactic systemic antibiotics were not used, because all 5 cases were associated with drug reactions.

Skin eruptions dramatically improved after initiation of the steroid pulse therapy (Figure 4). Despite intensive use of systemic and topical corticosteroids, pseudomembranous formation increased and epithelial defects enlarged during the first several days, peaking at 1 to 9 days (mean, 4.0 days) from their onset. Thereafter, corneal epithelial defects improved day by day and disappeared within 2 to 13 days (mean, 5.2 days). Conjunctival epithelium regenerated completely within 1 to 38 days (mean, 13.0 days).

The administration of systemic steroids was tapered off gradually according to the patient's general and ophthalmic conditions. Whereas cutaneous involvement was quickly eliminated after initiation of steroid pulse therapy, ocular surface inflammation tended to persist longer than cutaneous inflammation. The total amount of steroids was 420 to 1045 mg (changed to prednisolone) during 9 to 85

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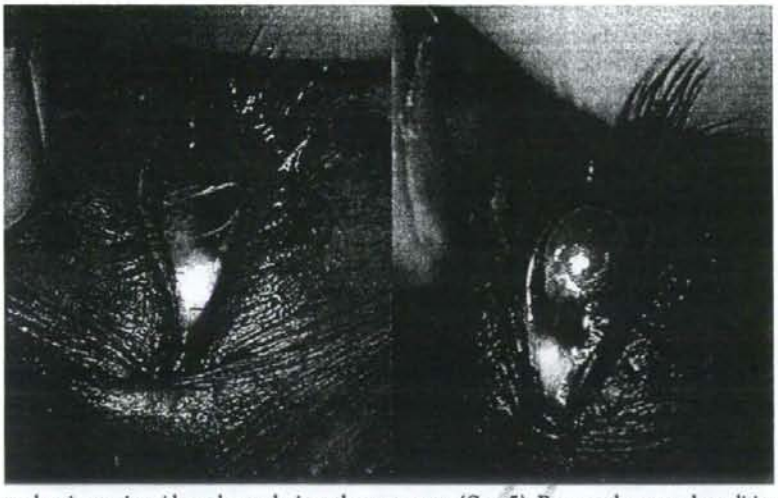

FIGURE 2. Images showing toxic epidermal necrolysis at the acute stage (Case 5). Because the general condition was still critical, the patient was examined on his bed. (Left) Pseudomembrane was present between the upper and lower eyelids. (Right) After removal of the pseudomembrane, corneal epithelial defect was observed.

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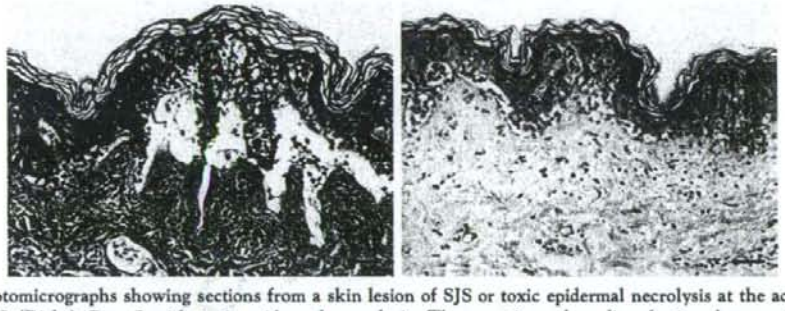

FIGURE 3. Photomicrographs showing sections from a skin lesion of SJS or toxic epidermal necrolysis at the acute stage. (Left) Case 1 with SJS (Right) Case 5 with toxic epidermal necrolysis. These sections show liquefaction degeneration producing a subepidermal cleft. The epidermis contains numerous necrotic keratinocytes with vacuolated cytoplasm or pyknotic nucleus (hematoxylin and eosin, bars = 100 mm).

days from disease onset (Table). One patient with TEN received plasmapheresis[30,31] for 3 days after steroid pulse therapy. Topical 0.1% betamethasone was used for a total of 40 to 165 days (mean, 91.4 days), then switched to 0.1% fluorometholone.

We observed no significant adverse effects from steroid pulse therapy, such as sepsis, pneumonia, or other infections. No cardiac arrhythmia or kidney or liver dysfunction occurred. We continued the culture of the conjunctival swabs during the use of topical or systemic steroids, or both. Methicillin-resistant *Staphylococcus aureus* was detected from the culture of the conjunctival swab in 2 eyes of 1 case at 1.5 months from disease onset, and coagulase-negative *Staphylococci* was observed in 2 eyes of another case at 10 days from disease onset. However, both cases showed no infectious ocular manifestations.

• VISUAL OUTCOMES AND OCULAR FINDINGS AT THE CHRONIC STAGE: In all eyes, best-corrected VA at 1 year from disease onset was 20/20 or better. No eyes had the appearance of an epithelial defect, the loss of the POV, conjunctivalization, neovascularization, opacification, or keratinization. As for corneal complications, only mild SPK was present in 5 eyes. As for conjunctival complications, fornix shortening with mild symblepharon was present only in 1 eye (Case 4). In contrast, all eyes manifested mild lid complications and mild irregularity of AQ: F5
the mucocutaneous junction (Figure 5). All patients ex-

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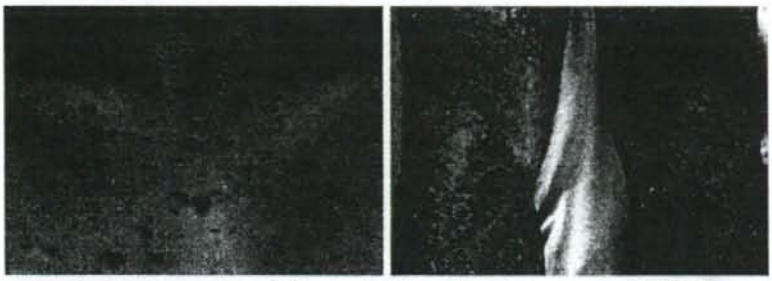

FIGURE 4. Photographs showing skin eruptions of SJS or toxic epidermal necrolysis after steroid pulse therapy. (Left) Case 1 with SJS. (Right) Case 5 with toxic epidermal necrolysis.

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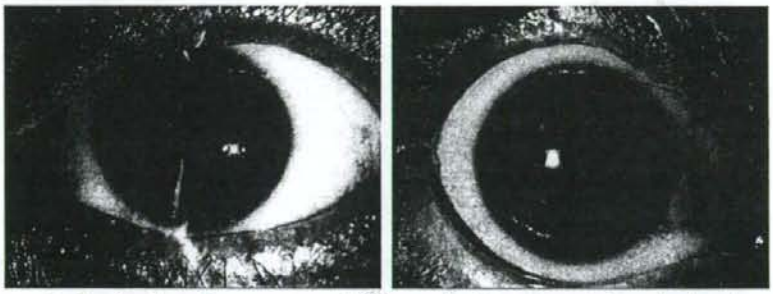

FIGURE 5. Photographs showing the ocular appearances of SJS or toxic epidermal necrolysis at the chronic stage. (Left) Case 1 with SJS. (Right) Case 5 with toxic epidermal necrolysis. The corneas were clear and the ocular surfaces were not inflamed 1 year after disease onset. Mucocutaneous junction involvements were mild.

perienced slight discomfort from irritation to their ocular surface, thus requiring the instillation of artificial tears. The Schirmer 1 test measured less than 5 mm in 4 eyes of 3 cases and 5 mm or more in the other eyes. There was no punctal damage in all eyes. Meibomian gland morphologic features were normal in 8 eyes and mild to moderately dropout in 2 eyes. No increase of intraocular pressure and no infectious keratitis occurred during all clinical courses.

• CASE 1: A healthy 23-year-old man (Case 1) had erythematous skin eruptions on the trunk and extremities after taking cold remedies. The body temperature increased to more than 39 C and the erythematous macules increased rapidly and became blisters. Extensive hemorrhagic erosion on the lips and oral mucosa were also observed when he visited our hospital. He was aware of bilateral red eyes just before the skin eruptions. Eye discharge appeared with skin rashes and markedly increased as the skin and oral site worsened. At first examination, both eyelids were edematous, and pseudomembranous conjunctivitis was noted. The tarsal and bulbar conjunctivae were affected severely, and extensive epithelial defect was observed in both eyes. Lid margins also were ulcerated with the partial loss of cilia (Figure 1). A skin biopsy was performed and histopathologic findings were compatible with the clinical diagnosis of SJS (Figure 3).

Immediately after the diagnosis, steroid pulse therapy (methylprednisolone; 500 mg/day for 3 days) was initiated. Topically, betamethasone was instilled 8 times daily (eye drop and ointment each administered 4 times daily). The improvement was dramatic. First, the development of new lesions stopped after the initiation of steroid pulse therapy. Thereafter, skin eruptions decreased and systemic conditions improved day by day (Figure 4). However, ocular inflammation increased with pseudomembranous formation, bilateral epithelial defects in the center of the cornea, and large conjunctival epithelial defects extending to nearly the entire bulbar and palpebral conjunctiva. After the peak of ocular surface inflammation at 9 days from disease onset, corneal and conjunctival epithelium began to regenerate.

Steroid pulse therapy was switched to intravenous betamethasone at a dosage of 4 mg/day for 5 days and then gradually tapered off. The total amount of systemic steroid was 1045 mg of a prednisolone equivalent, administered for a total of 85 days. Topically, betamethasone was initially administered for 31 days, with a total duration of 165 days. The pseudomembrane was removed daily and symblepharon was separated with a glass rod for 15 days. Although skin eruptions diminished without recurrence, pseudomembranous conjunctivitis recurred after the reduc-

tion of systemic or topical steroids at 2 to 4 weeks from disease onset. Both systemic and topical steroids were tapered off carefully according to the ocular surface appearance. Corneal epithelial defects healed within 3 days from their appearance. Large conjunctival epithelial defects needed 21 and 38 days for epithelization, respectfully. Ocular inflammation gradually subsided over a 5-month period.

At the chronic stage, 1 year from disease onset, VA was AQ: 4 better than 20/20 in both eyes. Both corneas were clear with POV and there existed no symblepharon, trichiasis, conjunctivalization, or neovascularization. Only the mucocutaneous junction showed slight cicatricial changes with mild irregularity (Figure 5). The Schirmer 1 test showed 1 mm in the right eye and 2 mm in the left eye. Meibomian gland morphologic features were normal in both eyes. The patient used topical artificial tears, and mild SPKs existed. He reported either no or slight discomfort on the ocular surface.

DISCUSSION

AT THE BEGINNING OF THIS STUDY, WE HYPOTHESIZED that it is important to start steroid pulse therapy at the acute stage as soon as possible. Because the destruction of the ocular surface epithelium, especially corneal epithelial stem cells, at the acute stage progresses rapidly, the initiation time of corticosteroid therapy may be the key to obtaining a good prognosis. Based on this hypothesis, we prospectively used high-dose methylprednisolone and intensive topical betamethasone immediately after the dermatologic and ophthalmologic diagnosis in cases with ocular involvement.

Five cases of SJS, including 1 case of TEN, were enrolled in this study. We initiated steroid pulse therapy with methylprednisolone 0 to 4 days (mean, 1.2 days) from disease onset. Simultaneously, topical betamethasone treatment was initiated immediately. One year after disease onset, VA was 20/20 or better in all 10 eyes.

It is noteworthy that the POV were maintained completely in all eyes in this study, suggesting the survival of corneal epithelial stem cells. Although it is uncertain whether stem cell loss is the primary or secondary damage of SJS and TEN, it is probable that steroid pulse therapy at the onset of the disease protected corneal epithelial stem cells from depletion. Intriguingly, antioxidative agents reportedly restore the reconstitutive capacity of hematopoietic stem cells.[32] Corneal epithelial stem cells may be protected via the reduction of oxidative stress by high-dose corticosteroid instillation.

Previously, we reported that the most severely affected ocular components in SJS and TEN at the chronic phase were loss of the POV (82.6%) and meibomian gland involvement (73.9%).[23] In the cases reported in this study, there existed no cicatricial changes on the cornea, and only 1 eye showed fornix shortening. It is highly possible that intensive steroid therapy also prevented the destruction of the meibomian gland, thus resulting in much fewer lid-related complications. In 1 case (Case 1), pseudomembranous conjunctivitis recurred after the reduction of systemic or topical steroids. A careful reduction of general and topical steroids is necessary to prevent cicatricial changes of the ocular surface. Both the systemic and topical application of steroids is needed to suppress the ocular surface inflammation effectively, which sometimes persists for a longer period than the cutaneous inflammation.

Although this study was not a randomized trial, we also compared the patients with SJS and TEN at the chronic stage during the period of this research. Six patients (3 males and 3 females; 6 to 67 years of age at disease onset; mean age, 32.7 years) without systemic and topical steroids at the acute stage showed severe cicatricial changes of the ocular surface. Their VA was between hand movements and 40/200. Additional studies are needed to compare the systemic and ophthalmologic prognosis of SJS and TEN patients with or without the early administration of steroids.

Several reports have suggested the advantage of using cryopreserved AMT for the treatment of acute SJS and TEN.[10–12] The similarity between these reports and ours is the intervention of the treatment at the acute stage. It is noted that both treatments demonstrated the beneficial effects of reducing ocular surface inflammation at the acute stage, as well as positive results in preventing cicatricial changes at the chronic stage. It seems probable that early intervention limited the cicatricial changes later. Although the intensive steroid therapy in this study was started within 4 days from disease onset, the timing of AMT in the previous reports was later than the initiation of treatment shown in our study.[12] In addition, the use of systemic and topical steroids was not described in the previous reports. For these reasons, we are unable to compare the effect of AMT and steroid pulse therapy on the ocular complications in SJS and TEN. Further studies are needed to compare and elucidate the effects, indication, and complications associated with treatment by surgery vs medical intervention.

It should be emphasized that in this study, steroid pulse therapy was initiated within 4 days from disease onset. If extensive mucocutaneous damage already has progressed, the risks of general and local infections increase. Although all 5 cases in this study were associated with drug reactions, not all cases of SJS and TEN are caused by drugs. A fraction of cases are caused by viral (such as herpes simplex virus) or mycoplasma infection. It is important to confirm that there are no signs of infectious activity before the administration of steroid pulse therapy by monitoring vital signs and by detecting potential pathogens by serum antibody titer, blood culture, and the polymerase chain reaction method. Intensive management by a medical

team consisting of at least 1 dermatologist, 1 ophthalmologist, 1 physician, and 1 infection control doctor is needed to obtain the best results.

Our recent reports, and those of others, have indicated the participation of genetic endowment in SJS and TEN.[33–41] For instance, there are statistically significant differences in SNPs of TLR3, interleukin 4R/interleukin 13, and FasL in SJS and TEN; thus, genetic screening may help to deliver a more rapid diagnosis or prevention of SJS and TEN in the future. At present, however, prompt diagnosis and early treatment with high-dose steroids is a vital aspect of preventing general and ophthalmic complications.

In conclusion, steroid pulse therapy at the disease onset is of great therapeutic importance in preventing ocular complications. Although both SJS and TEN are self-limiting diseases, appropriate intervention during the acute stage holds great promise for the prevention of corneal epithelial stem-cell loss and corneal and conjunctival cicatricial changes. An appropriate and prompt diagnosis followed by the administration of high-dose corticosteroids may improve the visual prognosis of these 2 devastating diseases.

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Biosketch

Dr. Yayoi Araki graduated and received her medical degree from Kyoto Prefectural University of Medicine in 2003, and completed her residency training at the Department of Ophthalmology at Kyoto Prefectural University Hospital, Kyoto, Japan. Dr. Araki currently specializes in clinical research and cornea-related diseases.

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Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. *Yayoi Araki, Chie Sotozono, Tsutomu Inatomi, Mayumi Ueta, Norihiko Yokoi, Eiichiro Ueda, Saburo Kishimoto, and Shigeru Kinoshita*

This article highlights the usefulness of steroid pulse therapy at the onset of Stevens-Johnson syndrome. Patients who received steroid pulse therapy combined with topical betamethasone within 4 days from disease onset showed clear corneas at 1 year from the onset. No eye had cicatricial changes except 1 with slight fornix shortening, and best-corrected visual acuity was 20/20 or better in all eyes.