Table 2. Severity-of-illness score

	Score 0	Score 1	Score 2	Score 3	Score 4	Score 5	Score 6
Ophthalmic lesions							
Pseudomembrane formation	None	Slight pseudomembrane formation	Pseudomembrane is formed but the patient is able to open the eyelids	Difficulty in opening the eyelids	–	–	–
Conjunctival hyperemia	None	Mild conjunctival vascular hyperemia	Moderate conjunctival vascular hyperemia	Severe conjunctival vascular hyperemia	–	–	–
Lip/oral lesions							
Blood crust or hemorrhage or oral erosion	None	Erosion without blood crust or hemorrhage	Erosion with blood crust or hemorrhage on the lip	Erosion with extensive blood crust or hemorrhage on the lip and in oral cavity	–	–	–
Cutaneous lesions							
Effusion in the erosion/ulcer area	Stopped/ none	Slight	Mild	Severe	–	–	–
Hemorrhage in the erosion/ulcer area	Stopped/ none	Mild	Moderate	Severe	–	–	–
Extent of epidermal detachment[†]	0%	<5%	≥5%, <10%	≥10%, <15%	≥15%, <20%	≥20%, <30%	≥30%
Extent of erythema[‡]	0%	<10%	≥10%, <20%	≥20%, <30%	≥30%, <40%	≥40%, <50%	≥50%
Cutaneous/mucosal pain	None	Slight pain	Considerable pain	Intolerable pain, requiring sedation	–	–	–
General condition							
Oral intake	Normal	The patient eats more than half	The patient eats less than half.	The patient does not eat meals (including nil p.o. status)	–	–	–
Malaise	None	Mild	Moderate	Severe	–	–	–
Fever	<37.0°C	≥37.0°C, <37.5°C	≥37.5°C, <38.5°C	≥38.5°C	–	–	–

–, not scored.
[†]The extent of epidermal detachment was measured on the assumption that the patient's palm (including fingers) was equivalent to 1% of the body surface area. The epithelialized areas were excluded. [‡]The extent of erythema was measured on the assumption that the patient's palm (including fingers) was equivalent to 1% of the body surface area. The pigmented areas were excluded.

Table 3. Severity-of-Illness Score for Toxic Epidermal Necrolysis

Risk factor		Weight
Age	≥40 years	1
Associated malignancy	Yes	1
Heart rate (b.p.m.)	≥120	1
Detached or compromised body surface	≥10%	1
Serum BUN (mg/dL)	>27	1
Serum bicarbonate (mEq/L)†	<20	1
Serum glucose (mg/dL)	>250	1

†Serum bicarbonate was not determined because of concerns about an increased burden on patients.

and 51.4% (SJS, 25–75%; TEN, 30–75%), respectively, on day 1, and 0.3% (SJS, 0% in all patients; TEN, 1% in all patients) and 17.1% (SJS, 0–15%; TEN, 1–80%), respectively, on day 7, representing mean reductions of the two indicators of 9.2% and 34.3%, respectively, from the values on day 1. The non-responder with TEN (case 5) had an increase of 10% (50%→60%) in the extent of epidermal detachment on day 7 compared with day 1, but achieved a reduction of 20% (90%→70%) in the extent of erythema on day 7.

Ophthalmic lesions were observed in seven patients at baseline. Ophthalmic lesions were improved in six of seven patients during the study period. Little symptomatic improvement was observed in a patient with TEN who failed to respond to IVIG (Case 5).

Lip/oral lesions were also observed in all patients at baseline. Symptoms resolved on day 7 of IVIG in four of the eight patients. On day 20 of IVIG (at the end of the study), six of the eight patients were free of symptoms. Of the two patients in whom lip/oral lesions persisted at the end of the study, one showed an improvement (score 3→1) (TEN, case 6), but symptoms remained unchanged in the other patient (TEN, case 5).

Finally all of the eight patients receiving IVIG survived.

One TEN patient (case 5) who was decided to be a non-responder on day 7 was treated with plasma exchange 4 days after IVIG and recovered, although with visual sequela. None of the responders had sequelae.

Presentation of representative cases. Cases 2 and 3 are briefly described below as representative cases of SJS and TEN, respectively.

Case 2, a 41-year-old man with SJS (Fig. 3), developed macular lesions 9 days before IVIG (day −9). The patient was started on prednisolone at 15 mg/day p.o. on day −4, which was increased to 20 mg/day on day −3. However, the affected areas appeared to be worsening with many new blisters (skin detachment, 9% of BSA) and a fever of 39°C or more. Painful erosions also developed on lips and in the oral cavity with erythema on the periorbital lesion. These findings suggested that the patient failed to respond well to prednisolone at 20 mg/day p.o., requiring more intensive add-on therapy. Laboratory data were normal apart from mildly elevated

Table 4. Diagnosis and symptoms of patients

No.	Age (years)	Sex	Type of disease	Suspected drug	Severity-of-illness score (points)†	Extent of epidermal detachment (%)†	Extent of erythema (%)†	Lip/oral lesions†	Ophthalmic lesions†	Fever (°C)†	SCORTEN†
Case 1	51	Male	SJS	Anticonvulsants	14	0	45	Yes	Yes	35.4	1
Case 2	41	Male	SJS	None‡	17	9	60	Yes	No	35.8	1
Case 3	53	Male	TEN	Cold medicine	22	30	75	Yes	Yes	37.0	3
Case 4	78	Male	SJS	Supplements	15	0	75	Yes	Yes	36.4	1
Case 5	65	Female	TEN	Allopurinol	31	50	90	Yes	Yes	36.8	3
Case 6	52	Male	TEN	Fenofibrate, allopurinol	23	18	30	Yes	Yes	36.6	2
Case 7	67	Female	SJS	Antibiotics, cold medicine	14	0.1	50	Yes	Yes	36.0	1
Case 8	57	Male	SJS	Carbamazepine	15	9	25	Yes	Yes	37.2	1

†Each parameter was assessed at baseline. ‡No drug administration. SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis..

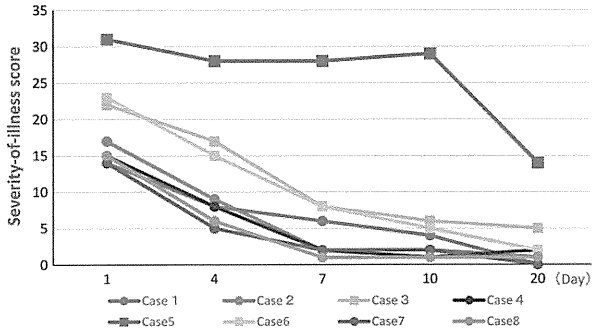

Figure 1. Changes over time in severity-of-illness score for all patients.

lactate dehydrogenase (346 U/L) and C-reactive protein (CRP; 1.58 mg/dL). Because the cause of SJS was suspected to be an undetermined infection because he had not taken any medication, IVIG was initiated. The lesions started to improve on day 2 and blisters were re-epithelized immediately. On day 11 of IVIG, steroid therapy was reduced to 15 mg/day. On day 13, the patient was discharged and steroid was tapered in an outpatient clinic.[30]

Case 3, a 53-year-old man with TEN (Fig. 4), developed macules with blisters after intake of cold medicines for 9 days (9 days before start of IVIG: day −9) followed by ocular, oral and genital lesions. The patient was started on prednisolone at 50 mg/day p.o. on day −8, steroid pulse therapy (1000 mg/day of methylprednisolone for 3 days) on day −6, and Ig (5 g/day for 3 days) and betamethasone at 6 mg/day p.o. (equivalent to 60 mg/day of prednisolone) on day −3. However, new erythematous lesions and blisters appeared to be spreading (skin detachment, 30% of BSA) accompanied by progressing liver dysfunction: alanine transaminase (ALT; 316 U/L), γ-glutamyltransferase (207 U/L) and alkaline phosphatase (501 U/L) on day −1. Because the symptoms were progressing with corneal erosion, IVIG was initiated. Soon after IVIG initiation, the progression stopped and his general condition improved. Erosions on the skin dried up on day 2 and started to re-epithelize on day 3. Erosions on the lips and in the oral cavity began to re-epithelize on day 2 and the corneal erosion and liver dysfunction recovered gradually. On day 12 of IVIG, the dose of betamethasone was reduced to 4 mg/day p.o. (equivalent to 40 mg/day of prednisolone) and the steroid dose was reduced continuously to 20 mg of prednisolone. However, the eye injection and skin erythematous lesions persisted and were observed on day 34. Therefore, semi-pulse therapy (500 mg of methylprednisolone for 3 days) was performed, followed by steroid tapering along with improvement of symptoms. The patient was free of sequelae and discharged on day 46.

Safety results. Mild and moderate side-effects occurred in 87.5% (7/8) of the patients. Three patients experienced hepatic dysfunction, two patients experienced anemia, and each of the patients experienced renal impairment, CRP increase and brain natriuretic peptide increase. No serious side-effects were observed.

The hepatic dysfunction was considered moderate in one patient (case 3), who had an aspartate aminotransferase (AST) level of 190 U/L and ALT level of 316 U/L at baseline, which increased to 209 and 417 U/L, respectively, on day 2 and 449 and 930 U/L, respectively, on day 6. One of the two patients with mild hepatic dysfunction (case 1) had an AST level of 30 U/L and an ALT level of 70 U/L at baseline, which increased to 50 and 85 U/L, respectively, on day 7. In the other patient (case 2), AST and ALT levels increased from 29 to 44 U/L at baseline to 42 and 53 U/L, respectively, on day 3.

These events, except mild anemia, were resolved. Although the anemia did not improve during the study period, it was not followed up because it was mild.

These side-effects were found in the "Adverse Reactions" section of the prescribing information for IVIG preparation available on the website of the US Food and Drug Administration or the electronic version of Physicians' Desk Reference (http://www.pdr.net/).

DISCUSSION

Stevens–Johnson syndrome/TEN are life-threatening conditions. Although corticosteroids and IVIG therapy are used in the treatment of SJS/TEN, the usefulness of these treatments is still controversial, and there is no established systemic therapy.

In the treatment of allergic and autoimmune diseases, IVIG works through a number of mechanisms, such as inhibition of autoantibody by anti-idiotypic antibody in IVIG, inhibition of inflammatory cells and modulation of immune function.[31] In 1998, Viard *et al.*[10] reported that apoptosis due to interactions between Fas and FasL expressed in keratinocytes played a central role in the development of SJS/TEN lesions and that anti-Fas antibodies present in IVIG blocked the interactions. However, a recent report has indicated that granulysin produced by cytotoxic T cells, natural killer (NK) cells and NKT cells is a key mediator for apoptosis in SJS/TEN.[11] Moreover, it has been demonstrated that the necroptosis pathway, which is induced by interaction between monocyte-derived annexin A1 and formyl peptide receptor 1 expressed on keratinocytes, may mediate SJS/TEN.[32] Taken together, inhibition of a variety of inflammatory cells and products from these activated cells is likely to be a major mechanism of efficacy of IVIG in SJS/TEN.

Regulatory T (Treg) cells are also likely to be implicated in the mechanism of SJS/TEN. Takahashi *et al.*[33] have suggested that defective Treg cells in patients with SJS/TEN may cause excessive activation of effector T cells, and an *in vitro* experiment by Kessel *et al.*[34] has shown that IVIG may enhance the function of Treg cells. Therefore IVIG may provide some clinical benefits by restoring the impairment of Treg cells in SJS/TEN.

Kirchhof *et al.*[12] reported that in their single-center retrospective chart review of 64 patients with SJS/TEN, patients treated with IVIG (average dose, 3 g/kg) had a higher mortality than that predicted by SCORTEN, whereas those treated with cyclosporin had a lower mortality. In this report, however, more TEN patients were included in the IVIG group compared with

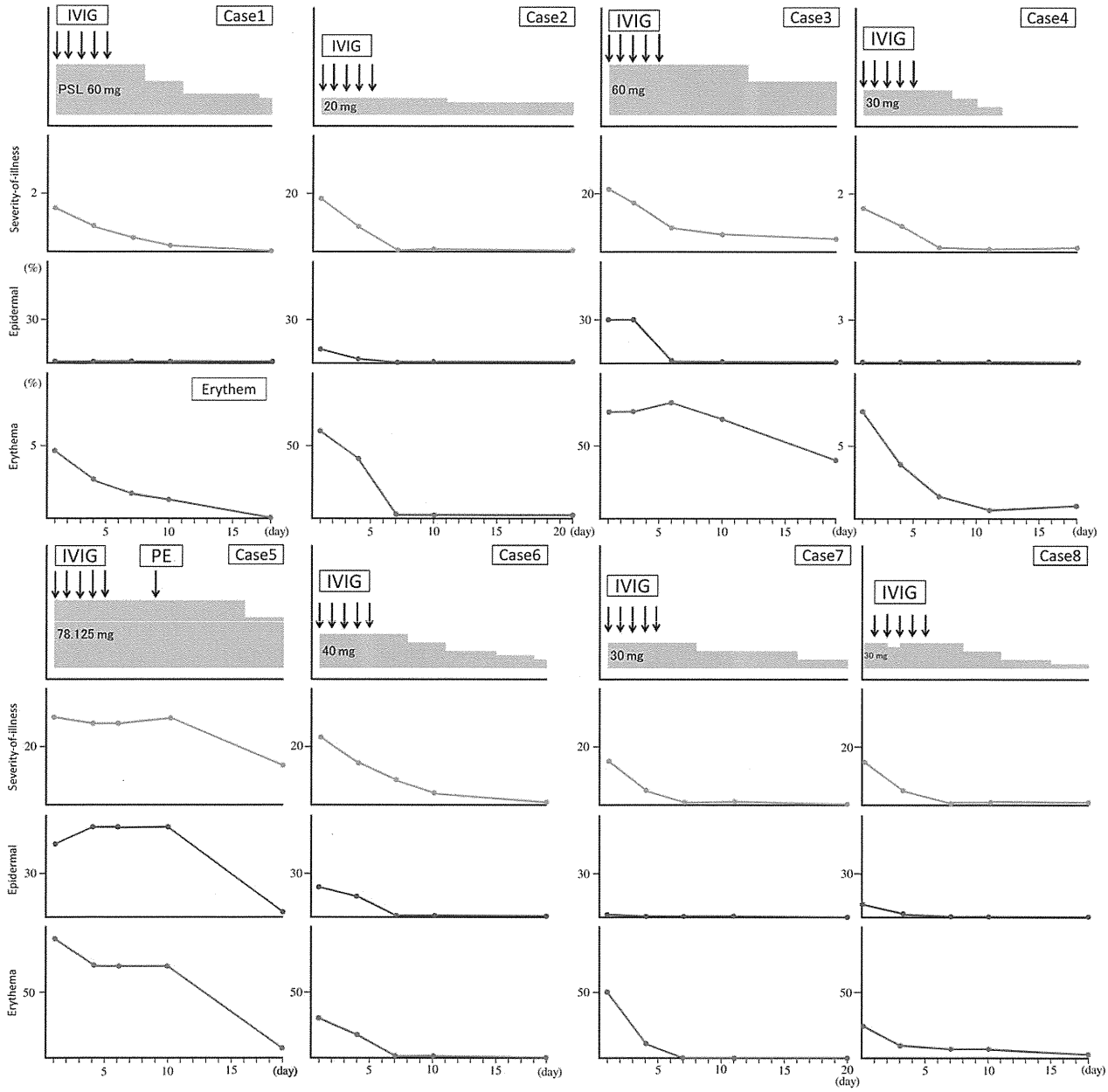

Figure 2. Treatment history and changes over time in severity-of-illness score, extent of epidermal detachment and extent of erythema in individual patients. IVIG, i.v. immunoglobulin G; PE, plasma exchange.

those in the cyclosporin group (21.6% vs 11.8%) and greater maximal epidermal detachment was seen in TEN patients treated with IVIG. Also, the average time from admission to initiation of systemic treatment was longer in the IVIG group than in the cyclosporin group. These differences may affect the results and conclusion of the report. In addition, the number of patients with pre-existing renal dysfunction was greater in the IVIG group than in the cyclosporin group (14% vs 6%). In SCORTEN, renal dysfunction is not included despite its importance in prognosis of SJS/TEN. This point should be considered when mortality of SJS/TEN is discussed.

Huang *et al.*[19] conducted a systematic review and meta-analysis of work published before July 2011 in order to evaluate the efficacy of IVIG in the treatment of TEN. They compared the effects of high-dose IVIG (≥2 g/kg) with those of low-dose IVIG (<2 g/kg): a multivariate logistic regression model adjustment did not show an IVIG dose effect in mortality, although high-dose IVIG exhibited a trend towards improved mortality (high dose, 18.9%; low dose, 50%). Pediatric patients treated with IVIG had a good prognosis no matter the dose. However, concomitant steroid administration and pretreatment with steroids in each group were not considered

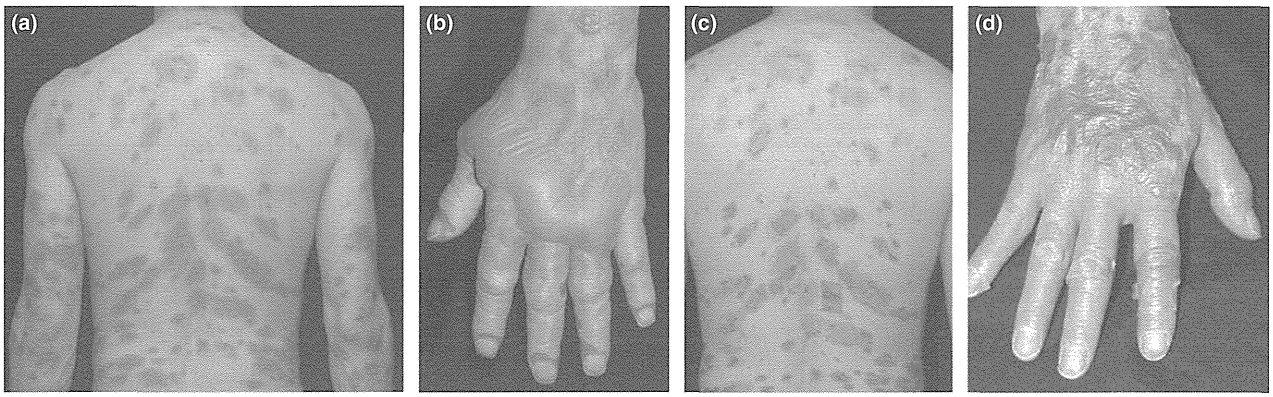

Figure 3. Pictures of lesions on right hand and trunk in case 2 (Stevens–Johnson syndrome) at baseline (a,b) and on day 10 (c,d) after initiation of therapy. Blisters were re-epithelized on day 10.

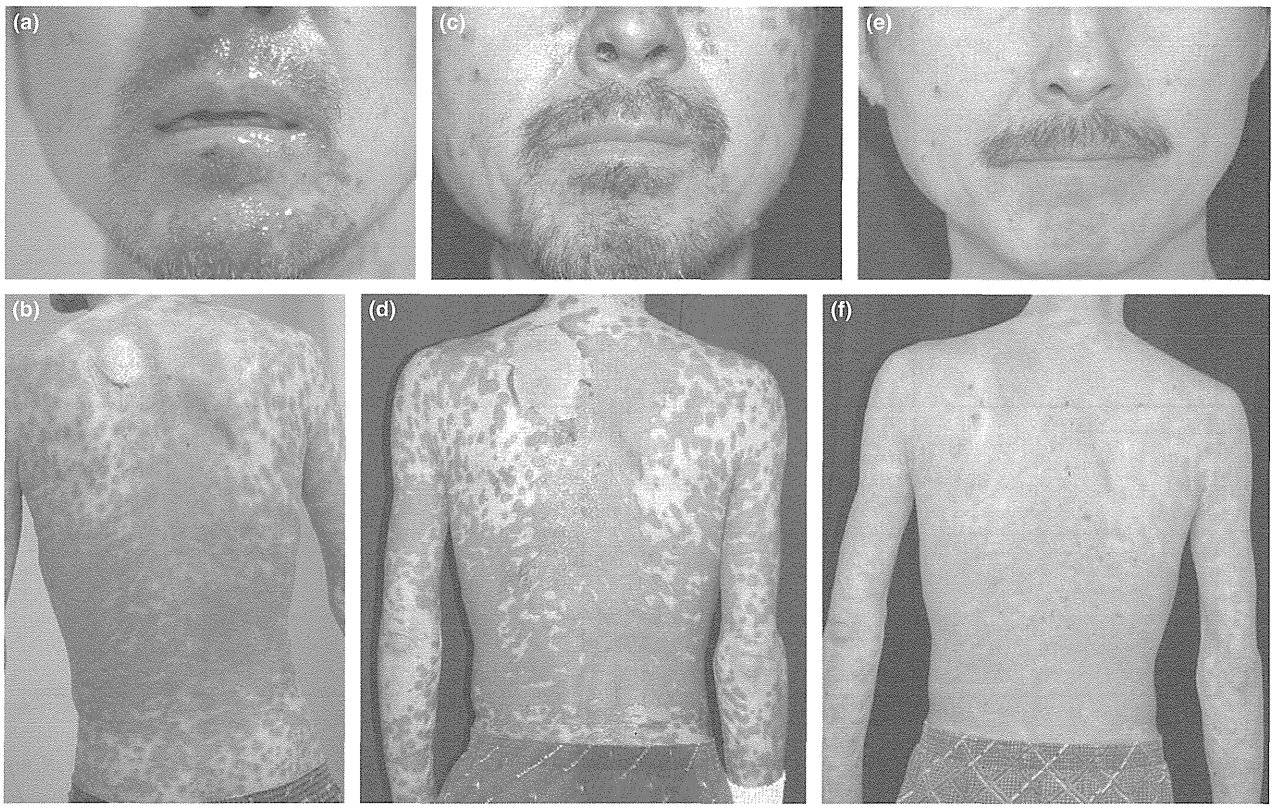

Figure 4. Pictures of major lesions in case 3 (toxic epidermal necrolysis) at baseline (a,b) and on days 7 (c,d) and 20 (e,f) after initiation of therapy. Erosions on the lips and trunk were resolved on day 7 and erythema was improved on day 20.

in their study. They concluded that a prospective RCT is needed to arrive at any conclusion.

IVIG has been used with or without systemic steroids in the treatment of SJS/TEN.[16,17,21] Chen *et al.*[16] reported that early application of steroids provided beneficial effects in SJS/TEN, and that combination therapy with steroids and IVIG showed better therapeutic effects than did steroids alone. They recommended total doses of more than 2 g/kg of IVIG.

In the present study, we evaluated the efficacy of IVIG in combination with steroids in patients who showed progressing or were unchanged symptoms after systemic steroid therapy. In this study, IVIG was administrated at 400 mg/kg per day for 5 days consecutively (total 2 g/kg), which is the dose approved for the treatment of autoimmune diseases (e.g. chronic inflammatory demyelinating polyneuropathy [CIDP], pemphigus) in Japan, and the results provided evidence of efficacy in SJS/

TEN.[16,21] Some guidelines or consensus statements on IVIG therapy recommend doses of 2 g/kg or higher, too.[35–37]

For this study, a severity-of-illness rating scale that scores ophthalmic lesions, lip/oral lesions, cutaneous lesions and general condition was newly set up as an efficacy parameter to assess clinical outcomes in early stages after IVIG. The results showed that IVIG was effective in seven (five SJS and two TEN) of the eight (five SJS and three TEN) patients (87.5%) on day 7 (2 days after 5 days of IVIG), and all of the eight patients survived. Mild and moderate side-effects occurred in seven patients but no serious side-effects were observed. In the responders, clinical improvement observed early on day 4 (first scoring day after IVIG initiation) (Figs 1,2) indicated that the efficacy is apparent in the early stage of IVIG. Actually, this means that progression of the mucocutaneous lesions stopped and the general condition started to recover before day 4. However, there is controversy as to whether IVIG is really effective in these patients because we could not deny completely that IVIG was performed at the beginning of recovery in some cases. Recently, Hirahara *et al.*[38] reported the efficacy of the methylprednisolone pulse therapy in eight patients including three SJS, two overlap and three TEN. All but one patient with TEN responded well. The seven responders started to recover within 3 days after initiating steroid pulse.[38] In our study, two responders were pretreated with steroid pulse from day −6 to day −4 in case 3 and from day −11 to day −9 in case 7. This means that the effect of steroid pulse was not observed for 6 days or 11 days after initiation of steroid pulse in the two patients and the recovery of these patients does not seem to be due to steroid pulse.

No sequela was observed in seven responders. However, in one TEN responder, an eye lesion had not recovered sufficiently 20 days after initiating IVIG despite satisfactory recovery of skin lesions (Case 3); the eye lesion disappeared soon after additional methylprednisolone administration of 500 mg for 3 days. This may show that additional high-dose steroid is useful to facilitate recovery after IVIG.

In the seven responders, IVIG was started from 3 days to 13 days after the onset of cutaneous symptoms and 23 days after the onset in the non-responder with TEN. This time difference suggests that it is important to add IVIG promptly if a patient does not respond well to steroid therapy.

In this study, the maximum steroid doses were remarkably different between the patients. Therefore, it is difficult to assess if steroids were insufficiently effective in the patients not treated with pulse therapy. However, we suggest that the combination therapy with IVIG and steroids, even at relatively low or moderate doses of steroids, is effective in progressing SJS/TEN.

There are several limitations to our study. Only eight SJS/TEN patients participated, because these diseases are rare and many patients started to recover with steroid therapy within several days. With a small number of patients, we could not show significant difference between the predictive number of deaths (one patient) and our study (all survived). Moreover, patient and treatment heterogeneity, such as pretreatment with steroids, severity of diseases and timing of IVIG administration, is a major criticism. In addition, it is difficult to evaluate efficacy of pretreatment accurately, because some time lag between treatments and appearance of the effect is sometimes observed in SJS/TEN. Double-blind and controlled RCT are necessary to reach any conclusion regarding clinical benefit of IVIG, but it is not realistic to plan such studies because these diseases are life-threatening and progress rapidly.

In summary, this study evaluated the efficacy of IVIG at a dose of 2 g/kg (400 mg/kg per day for 5 days consecutively) in Japanese SJS/TEN patients who showed progressing or unchanged symptoms with systemic corticosteroid treatment. Analysis of the clinical course showed a possibility that IVIG provided beneficial effects soon after its initiation in SJS/TEN patients, when administrated at an early stage of SJS/TEN in combination with corticosteroids. Therefore, we suggest that early treatment with IVIG together with corticosteroids is effective in SJS/TEN patients. In addition, when it is difficult to treat SJS/TEN patients with sufficient steroid due to possible risks associated with the underlying disease and infection, IVIG may be a potential treatment modality. A larger trial is required to define the therapeutic efficacy of IVIG with concomitant use of systemic steroids in SJS/TEN.

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APPENDIX 1

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Main researchers: Masafumi Iijima, Shin-Yurigaoka General Hospital; Yoshiro Ikezawa, Yokohama City University; Chie Sotozono, University Hospital, Kyoto Prefectural University of Medicine; Tomoko Ohkawa, Shuichi Ishida and Kenzen Kou, Yokohama City University Hospital; Kazuko Nakamura, Yokohama City University Medical Center; and Toshifumi Yamaoka, Osaka University.

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Original article

Retrospective analysis of Stevens–Johnson syndrome and toxic epidermal necrolysis in 87 Japanese patients – Treatment and outcome

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Treatment

Abbreviations:
SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; IVIG, intravenous immunoglobulin; J-SCAR, Japanese Research Committee on Severe Cutaneous Adverse Reaction; BSA, total body surface area; SCORTEN, a severity-of-illness scoring system for TEN prognosis; NSAIDs, nonsteroidal anti-inflammatory drugs; DIC, disseminated intravenous coagulation; MRSA, Methicillin-resistance *Staphylococcus aureus*; DFPP, double filtration plasmapheresis; DDS, diaphenylsulfone; PE, plasma exchange; CTLs, cytotoxic T cells; sFasL, soluble Fas ligand; PBMCs, peripheral blood mononuclear cells; RCT, randomized controlled trial

ABSTRACT

Background: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe adverse drug reactions with high mortality.
Methods: To present the clinical characteristics of SJS and TEN in Japan and evaluate the efficacy of treatments, we retrospectively analyzed cases of SJS and TEN treated in 2 university hospitals during 2000–2013.
Results: Fifty-two cases of SJS (21 males and 31 females; average age, 55.1 years) and 35 cases of TEN (17 males and 18 females; average age, 56.6 years) were included in this study. Twenty-eight cases of SJS (53.8%) and all cases of TEN were caused by drugs. Hepatitis was the most common organ involvement in both SJS and TEN. Renal dysfunction, intestinal disorder, and respiratory disorder were also involved in some cases. The major complication was pneumonia and sepsis. All cases except for 3 cases were treated systemically with corticosteroids. Steroid pulse therapy was performed in 88.6% of TEN. Plasmapheresis and/or immunoglobulin therapy was combined with steroid therapy mainly in TEN after 2007. The mortality rate was 6.9% and the rates for SJS and TEN were 1.9% and 14.3%, respectively. These were much lower than predicted mortality according to a severity-of-illness scoring system for TEN prognosis (SCORTEN) score. When comparing the mortality rate between 2000–2006 and 2007–2013, it was decreased from 4.5% to 0.0% in SJS and from 22.2% to 5.3% in TEN.
Conclusions: Treatment with steroid pulse therapy in combination with plasmapheresis and/or immunoglobulin therapy seems to have contributed to prognostic improvement in SJS/TEN.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are potentially fatal disorders, characterized by high fever, wide-spread blistering exanthema of macules, and atypical target-like lesions, accompanied by mucosal involvement.[1–3] Both of these disorders are often accompanied by complications in numerous

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organs, such as liver, kidney, and lung, which make treatment difficult and sometimes determine the length of convalescence. They are considered to be diseases on the same spectrum but with different severities.[4,5] In SJS, the less severe of the 2 conditions, detachment of the epidermis occurs on less than 10% of the body surface area. The area of epidermal detachment is wider in TEN, and this disorder is often accompanied by more complications in more organs than are found in SJS.

The treatment for these diseases is not well established. In addition to supportive care, systemic corticosteroids,[6,7] high-dose intravenous immunoglobulin (IVIG),[8–11] and plasmapheresis[12–14] have been used and considered effective in many reports. However, the effects of these therapies are still controversial.[15] In Japan, treatment with systemic corticosteroid has increasingly been used, since guidelines for the management of SJS and TEN were established in 2007 and revised in 2009 by the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) supported by the Ministry of Health, Labour, and Welfare of Japan.[16] Under these guidelines, systemic corticosteroids are regarded as the first line of treatment and, in severe cases, steroid pulse therapy is recommended. IVIG and plasmapheresis are considered as additional modalities for use with systemic corticosteroids. After plasmapheresis for SJS/TEN became eligible for coverage by health insurance in Japan in 2006, use of plasmapheresis in the treatment of SJS/TEN has been increasing, especially in intractable TEN.

The aim of this study is to present the clinical characteristics of SJS/TEN and to evaluate the current treatments. We retrospectively analyzed cases of SJS/TEN treated in our 2 university hospitals from 2000 to 2013. The data showed low mortality with intensive treatments, particularly in patients treated after 2007.

Methods

We collected the cases of SJS and TEN, which were treated in Yokohama City University Hospital and Yokohama City University Medical Center between January 2000 and December 2013. The diagnosis of SJS/TEN was based on Bastuji-Garin criteria.[3] For SJS, symptoms should include acute conditions characterized by mucous membrane erosions and skin lesions (described as macules, atypical target-like lesions, bulla, or erosions) with a maximum epidermal detachment of less than 10% of the total body surface area (BSA); and for TEN the symptoms should include a maximum epidermal detachment of more than 10% of the BSA in addition to the symptoms above. Cases that were classified as overlap of SJS/TEN according to the Bastuji-Garin criteria with a maximum epidermal detachment of 10–30% of the BSA were included as TEN in this study.

The following data were collected: Demographic information (age and sex), relevant past medical history and coexisting conditions, antecedent use of medications, time between the first causative drug intake and the onset of symptoms, maximum epidermal detachment as a percentage of BSA, presence and extent of mucous membrane involvement, laboratory data, results of patch testing and lymphocyte stimulation tests using suspected drugs, organ involvement and complications, treatments including corticosteroid therapy, intravenous immunoglobulin therapy (IVIG), and plasmapheresis, and mortality. Causative drugs were determined by considering the history of drug administration and the results of patch testing and lymphocyte stimulation tests if performed.

To evaluate the efficacy of treatments, SCORTEN, a severity-of-illness scoring system for TEN prognosis was used. SCORTEN, which consists of 7 clinical values, was advocated by Bastuji-Garin S *et al.* in 2000 and is now widely accepted as the standard prognostic tool for the prediction of mortality in patients with TEN and SJS.[17] The SCORTEN criteria are: serum blood urea nitrogen >10 mmol/L, serum bicarbonate <20 mmol/L, serum glucose >14 mmol/L, age ≥40 years, malignancy present, heart rate ≥120 bpm, and percentage of BSA with epidermal detachment ≥10%. The mortality rate was predicted according to the SCORTEN total score as follows: 0–1 points, 3.2%; 2 points, 12.1%; 3 points, 35.3%; 4 points, 58.3%; and 5 or more points, 90%.

Results

Age and sex (Fig. 1)

Eighty-seven cases including 52 of SJS and 35 of TEN were treated during the 14 years of the study period and all of them were analyzed in this study. Patients with SJS, comprising 21 males and 31 females, were aged between 17 and 87 years (average, 55.1 years). Patients with TEN, comprising 17 males and 18 females, were aged between 2 and 80 years (average, 56.6 years). Average ages were not different between SJS and TEN, but peaks were noted of patients aged in their 40s and 70s in SJS and of patients in their 70s in TEN.

Interval between the first drug intake and onset of symptoms (Fig. 2)

The intervals between the first drug intake and the onset of symptoms of 41 cases of SJS and 24 cases of TEN are shown in Fig. 2. The average intervals were 18.0 days in SJS and 11.7 days in TEN. In TEN, symptoms usually developed within 7 days of first drug intake; TEN thus seemed to develop earlier after drug intake than did SJS.

Total number of days of the hospital stay (Fig. 3)

The total number of days of the hospital stay was counted to evaluate the period in which care was required for SJS/TEN. All patients, except 2 patients with SJS whose symptoms were mild, were hospitalized for treatments. In cases that developed SJS/TEN during treatment of coexisting disorders in hospital, the total number of days of the hospital stay was counted from the day of the first consult with dermatologists to the day of nearly recovered condition.

The average numbers of days of the hospital stay were 20.8 days in SJS and 34.1 days in TEN. One patient with SJS was hospitalized for 77 days with *Cytomegalovirus* infection, *Aspergillus* pneumonia, and acute hepatitis due to antifungal drugs. TEN patients who were discharged within 14 days included 2 deceased cases. Except for those cases, 1 case was transferred to another hospital because of a coexisting psychological disorder and another case was enrolled to the cardiovascular medicine department because of severe mitral stenosis. Only a 35-year-old man with overlap of SJS/TEN left the hospital in 13 days. He had no complications except mild hepatitis and was treated with corticosteroids alone. He recovered immediately without developing any complications after he was admitted to the hospital.

Causes of SJS and TEN

In SJS, 28 cases (53.8%) were considered to be caused by an adverse reaction to drugs, and 8 cases (15.4%) were suspected to be caused by infection, including 3 cases of *Mycoplasma pneumonia*. The causes of the other cases were not determined. In contrast, all TEN cases were suspected to be caused by an adverse reaction to drugs. Causative drugs of SJS and TEN are listed in Table 1. In agreement with past reports, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), cold medicines, and anticonvulsants

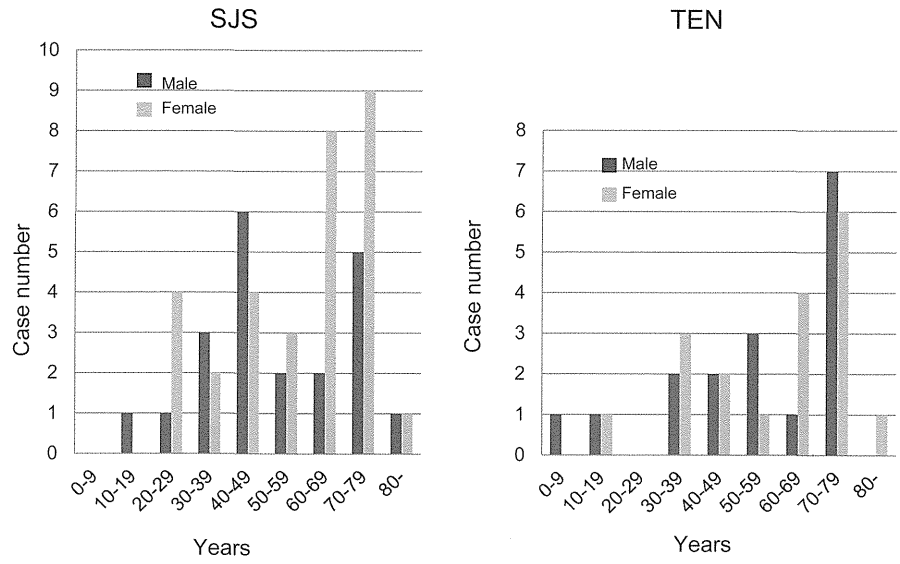

Fig. 1. Ages of patients with SJS and TEN. Fifty-two cases of SJS and 35 cases of TEN were included in this study.

were the major causative drugs. However, it is noteworthy that anticonvulsants were remarkably frequent as causative drugs in SJS.

Skin and mucocutaneous lesions

The degree of maximum epidermal detachment in TEN varied widely. The range was 10%–100% of BSA and the average was 44.7% of BSA. One-third of TEN patients showed a maximum epidermal detachment of more than 50% of BSA and 5 cases (14.3%) showed a maximum epidermal detachment of more than 90% of BSA.

As for the mucocutaneous lesions, keratoconjunctivitis was observed in 39 cases (75.0%) of SJS and 17 cases (48.6%) of TEN. Keratoconjunctivitis included clinical features such as conjunctival injection and erosion of the keratoconjunctiva, pseudomembrane of the conjunctiva, and eye mucus. Painful labial and oral erosions were observed in 50 cases (96.2%) of SJS and 19 cases (54.3%) of TEN. Genital problems, found mainly by pain during urination, were observed in 19 cases (36.5%) of SJS and 17 cases (48.6%) of TEN.

Organ involvement and complications

Organ involvement and other complications commonly accompanied both SJS and TEN (Table 2), and were found more frequently in TEN. Hepatitis was the most common complication in SJS (26 cases, 50%) and TEN (15 cases, 42.9%). Renal dysfunction (5 cases, 9.6%) and gastro-intestinal disorder (5 cases, 9.6%) followed liver dysfunction in SJS. As for TEN, renal dysfunction and gastro-intestinal disorder were observed in 8 cases (22.9%) and 4 cases (11.4%), respectively. One TEN case with severe renal dysfunction received hemodialysis. Encephalopathy was sometimes associated with SJS and TEN. It was observed at a higher frequency (5 cases, 14.3%) in TEN than in SJS (2 cases, 3.8%). One case developed convulsion and the others manifested decreased levels of consciousness without accompaniment by cerebrovascular disorder.

Infections such as pneumonia and sepsis were the main complications both in SJS and TEN. Especially in TEN, sepsis was a serious problem and 3 of 6 cases that developed sepsis went on to

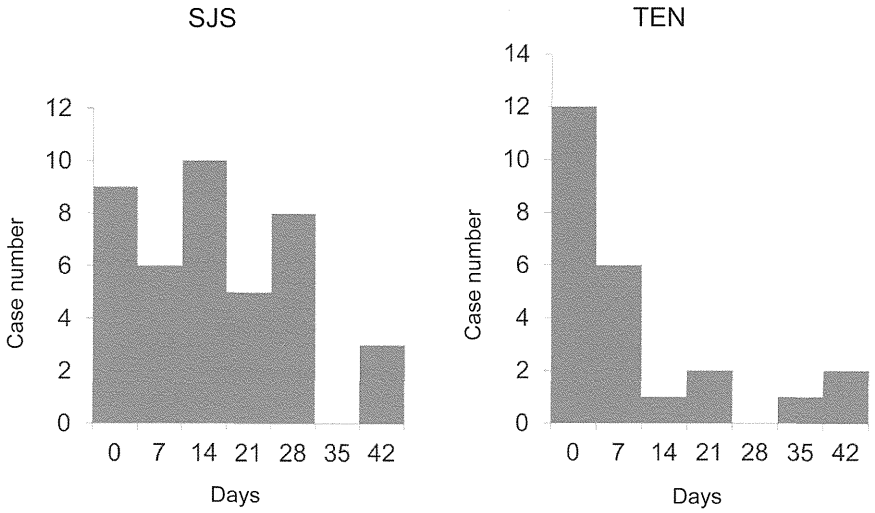

Fig. 2. Time between the first causative drug intake and the onset of symptoms. Forty-one cases of SJS and 24 cases of TEN were examined. The average intervals were 18.0 days in SJS and 11.7 days in TEN.

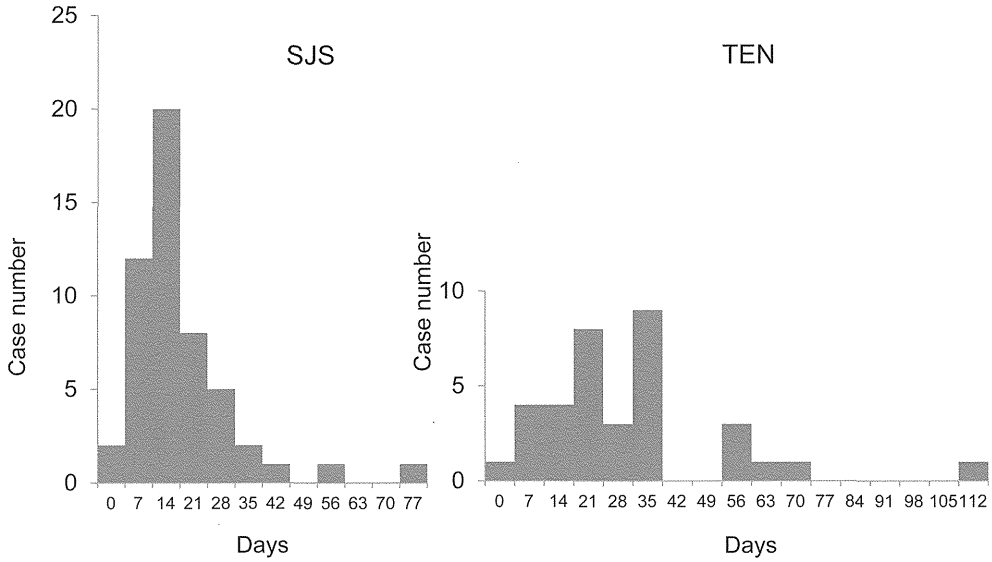

Fig. 3. Total days of the hospital stay. Fifty-two cases of SJS and 35 cases of TEN were examined. The average numbers of days of the hospital stay were 20.8 days in SJS and 34.1 days in TEN.

Table 1
Causative drugs of SJS and TEN.

Number of cases	SJS	TEN
Antibiotics	2	7
Penicillins	0	2
Carbapenems	1	4
Polypeptides (vancomycin)	1	1
NSAIDs and cold medicine	5	6
NSAIDs	3	5
Cold medicine	2	1
Anticonvulsants	13	4
Carmabazepine	4	1
Zonisamide	3	0
Phenobarbital	2	1
Lamotrigine	2	0
Alebiatin	1	0
Varpric acid	1	1
Gabapentin	0	1
Others	19	8[†]
Not determined	16	17
Total	53	42

[†] Including 3 cases of Omeprazole and 2 cases of Allopurinol.

Table 2
Organ involvements and complications in patients with SJS and TEN.

Number of cases (%)	SJS	TEN	Total
Hepatitis	26 (50.0%)	15 (42.9%)	41 (47.1%)
Renal dysfunction	5 (9.6%)	8 (22.9%)	13 (14.9%)
Hemodialysis	0	1	1
Gastro-intestinal disorder[†]	5 (9.6%)	4 (11.4%)	9 (10.3%)
Respiratory disorder[‡]	2 (3.8%)	3 (8.6%)	5 (5.7%)
Encephalopathy	2 (3.8%)	5 (14.3%)	7 (8.0%)
Myocarditis	1 (1.9%)	1 (2.9%)	2 (2.3%)
Pneumonia[§]	4 (7.7%)	4 (11.4%)	8 (9.2%)
Sepsis	1 (1.9%)	6 (17.1%)	7 (8.0%)
Rhabdomyolysis	0 (0%)	1 (2.9%)	1 (1.1%)
DIC[¶]	0 (0%)	3 (8.6%)	3 (3.4%)

[†] Gastro-intestinal disorder includes: diarrhea, intestinal bleeding, severe appetite loss, perforation of intestine.
[‡] Respiratory disorder includes: edema of trachea/larynx, respiratory failure.
[§] Pneumonia includes: Methicillin-resistance *Staphylococcus aureus, Cytomegalovirus, Aspergillus, Candida.*
[¶] Disseminated intravenous coagulation.

develop disseminated intravenous coagulation (DIC). Within the 3 cases, 2 cases died (described in deceased cases) and only 1 case was survived. Alived case was 72-year-old man and he also had hepatitis and severe renal dysfunction needed to receive hemodialysis. A case of sepsis in SJS was 87-year-old woman who already had pneumonia when she developed SJS and the treatment was started 9 days after the development of SJS.

Treatments

The major systemic treatments that were adopted in addition to supportive care were corticosteroids, IVIG, and plasmapheresis. The treatments performed are shown in Table 3. All cases, except 2 cases of SJS and 1 case of TEN, were treated with corticosteroids with or without other therapies. Prompt tapering of the steroid dose was performed along with amelioration of symptoms. In SJS, most cases (45 cases, 86.5%) were treated with corticosteroids alone. Of the cases, 18 (34.6% of all SJS) were performed pulse therapy (500–1000 mg/day of methylprednisolone for 3 days). On the other hand, in TEN, steroid pulse therapy was performed in 31 cases (88.6%) of all cases. Less than half cases (14 cases, 40%) were

Table 3
Treatments in patients with SJS and TEN.

Treatments		Number of cases	
		SJS	TEN
Supportive care only		2 (3.8%)	0
Steroid therapy		45 (86.5%)	14 (40.0%)
Steroid pulse therapy		18 (34.6%)	12 (34.3%)
IVIG	<2 g/kg	0	1 (2.9%)
Steroid therapy and IVIG		3 (5.8%)	8 (22.9%)
	>2 g/kg	0	1
	<2 g/kg	3	7
Steroid therapy and plasmapheresis		1 (1.9%)	10 (28.6%)
Steroid therapy, IVIG, and plasmapheresis		1 (1.9%)	2 (5.7%)
	>2 g/kg	0	1
	<2 g/kg	1	1
Total		52 cases	35 cases

IVIG, intravenous immunoglobulin.

treated with corticosteroids alone and among them 12 cases were performed pulse therapy (500–1000 mg/day of methylprednisolone for 3 days). The case treated without steroid was a 62-year-old woman who was treated with IVIG (20 g/day for 2 days) alone, because she had acquired Methicillin-resistance *Staphylococcus aureus* (MRSA) pneumonia after the operation of acute aorta dissection when she developed TEN. IVIG was highly effective in this case and resulted in remarkable recovery from the TEN eruption.

A combination treatment with IVIG and corticosteroids was performed only in 3 cases of SJS. All 3 cases received less than 2 g/kg (more than 1 g/kg) of immunoglobulin in total. Two of the 3 cases were performed pulse therapy (500–1000 mg/day of methylprednisolone for 3 days). One case of SJS was already being treated with 60 mg/day of prednisolone for systemic lupus erythematosus when she developed SJS and she received the additional treatment of double filtration plasmapheresis (DFPP). Another SJS case was treated with corticosteroids, IVIG, and plasmapheresis sequentially. This case had developed SJS as a reaction to diaphenylsulfone (DDS) taken for pemphigus foliaceus. To treat pemphigus foliaceus together with SJS, DFPP was performed.

On the other hand, combination therapies were positively chosen in TEN. Before starting IVIG or plasmapheresis, all cases were performed steroid pulse therapy. Eight cases (22.9%) were treated with the combination of IVIG (more than 1 g/kg) and corticosteroids, and 10 cases (28.6%) with the combination of plasmapheresis and corticosteroids. Two cases (5.7%) were treated with steroid pulse, IVIG, and plasmapheresis because of the progression of symptoms. In contrast to SJS, 2 cases of TEN treated with IVIG after 2008 were administered with a total amount of more than 2 g/kg immunoglobulin. All plasmapheresis treatments performed in TEN were plasma exchange (PE) except for 1 case treated with steroid pulse, IVIG (1 g/kg), and DFPP before 2006.

Mortality, deceased cases, and sequelae

Total mortality was 6.9%. One case of SJS (mortality rate, 1.9%) and 5 cases of TEN (mortality rate, 14.3%) died. The average SCORTEN score was 2.34, thus the predicted mortality rate was 25.3% (8.9 cases) in TEN.

A summary of the deceased cases is shown in Table 4. The deceased SJS case was a 47-year-old man. He developed an acute respiratory disorder after the eruption had begun to show signs of recovery. The death was doubted to have been caused by the malignant lymphoma that was the primary disease. As for TEN, the ages of the deceased cases varied from 39 to 79 years, with an average age of 63.4 years. All cases were treated with corticosteroids and 3 of them were treated with combination therapy of IVIG (<2 g/kg) or PE. Sepsis and DIC accompanied TEN in 3 cases. A 79-year-old woman caused sepsis and DIC after developing severe renal dysfunction. In this case, the dose of the administered corticosteroids was increased gradually from prednisolone 30 mg/day to 100 mg/day and finally changed to betamethasone 20 mg/day. A 54-year-old man case already had showed very severe general condition at the start of the treatment of TEN, which made it difficult to administer the corticosteroids at the high-dose, and ended to septic shock. A 71-year-old woman had developed TEN during the treatment of fever of unknown origin, which could be suspicious of some kind of systemic infection hidden and led to septic shock and DIC.

No cases showed severe sequelae in either SJS or TEN. Only 1 case of TEN, a 17-year-old man, showed a loss of fingernails. Although many reports indicate that eye complications often result in severe eye sequelae, no cases in this study showed eye sequelae.

Table 4
Deceased cases of SJS and TEN.

Case No. /age/sex	Underlying disease	Causative drugs	Indication for drug therapy	Maximum skin detachment (%)	Clinical course of the skin lesion	Severe complications and cause of death	Maximum doses of corticosteroids and other therapies	SCORTEN	Time to death[†]
SJS									
1/47/M	Not particular	Not determined (imipenem/cilastatin sodium? Amphotericin B?)	Malignant lymphoma	10%>	Recovering gradually	Respiratory failure	PSL 60 mg/day	2	24 days
TEN									
2/39/F	Caesarotomy	Not determined (Cefditren pivoxil? NSAIDs?)	Cold	48%	No change	Edema of trachea/larynx Rhabdomyolysis	mPSL1000 mg/day × 3 days,	4	8 days
3/79/F	Rhematoid arthritis, Hepatitis C virus (HCV) positivechronic hepatitis	Herbal medicine	Cold	>30%	Recovering gradually	Renal dysfunction Sepsis, DIC	Bethamethazone 20 mg/day	1	28 days
4/74/M	Diabetes mellitus, Renal failure, Asthma, Hypertension, Angina petoris	meropenem?	Acute aorta dissociation	40%	Recovered completely	Perforation of intestine, Pneumonia, DIC	mPSL 1500 mg/day × 3 days, I mmunoglobulin 20 g/day × 3 days	4	31 days
5/54/M	Chronic nephritis	Not determined	Multiple myeloma	95%	Recovered slightly	Septic shock	PSL 40 mg/day CyA 35 mg/day Immunoglobulin 20 g/day × 3 days	6	66 days
6/71/F	Diabetes mellitus, Renal failure (under hemodialysis), Bullous pemphgoid	Not determined (Piperacillin Sodium? Ceftriaxone Sodium Hydrate?)	fever of unknown origin	10%	No change	Convulsion, DIC, Septic shock Intestinal bleeding	mPSL1000 mg/day × 3 days Plasma exchange 2 days	3	12 days

mPSL, Methylprednisolone; DIC, Disseminated Intravenous Coagulation; PSL, Prednisolone; CyA, Cyclosporin A; NSAIDs, Nonsteroidal anti-inflammatory drugs.
[†] Time between the onset of eruption and death.

Comparison of treatment modalities used and mortality rates between 2000–2006 and 2007–2013 in TEN

After plasmapheresis for SJS/TEN became eligible for coverage by health insurance in 2006, the available options of treatment modalities have been changing in TEN. Therefore, we separated the cases by the date of each 7 years before and after this change (2000–2006 and 2007–2013) and compared the treatment modalities used and the mortality rates in these 2 periods. From 2000 to 2006, 22 cases of SJS and 17 cases of TEN were evaluated. From 2007 to 2013, 30 cases of SJS and 18 cases of TEN were evaluated. Although steroid pulse therapy and the combination of IVIG therapy (<2 g/kg) with corticosteroid therapy were the mainstream until 2006, the frequency of cases treated with the combination of plasmapheresis and corticosteroid therapy increased remarkably after 2007 (shown in Fig. 4).

The mortality rates showed a remarkable decrease after 2007, compared with 2000–2006, from 4.5% to 0.0% in SJS and from 23.5% to 5.6% in TEN, although the average SCORTEN scores were somewhat elevated after 2007 (2.18 in 2000–2006 and 2.50 in 2007–2013). We compared the predicted mortality rate of TEN cases with the actual rate. Only a little difference was shown in 2000–2006; the predicted rate was 23.9% (4.1 cases) and the actual rate was 23.5% (4 cases). However, it showed a relatively large gap in 2007–2013; the predicted rate was 26.5% (4.8 cases) and the actual rate was 5.6% (1 case). Furthermore, when comparing the average SCORTEN score of the non-deceased cases between the 2 periods, it showed a relatively large increase from 1.69 to 2.47.

Discussion

SJS and TEN are rare but life-threatening disorders. The mortality rates for these conditions were recently reported to be 34% at 1 year for SJS/TEN in Europe[18] and 3% and 19% for SJS and TEN, respectively, in Japan.[19] Recent studies have revealed new details about the apoptotic pathways of keratinocytes and immunological changes that are related to adverse drug reactions in these diseases.[8,20–23] In addition to the direct cytotoxicity by the cytotoxic T cells (CTLs), several soluble factors such as tumor necrosis factor-α, nitric oxide, soluble Fas ligand (sFasL), granulysin, annexin A1 are now considered to mediate keratinocyte apoptosis. Abe *et al.* reported that peripheral blood mononuclear cells (PBMCs) from SJS/TEN patients secrete sFasL on stimulation with the causal drug. In addition, they demonstrated that patients sera induce apoptosis in cultured keratinocytes, indicating that sFasL produced by PMBCs may contribute to the pathogenesis of SJS/TEN.[21] Chung *et al.* clarified that granulysin produced by CTLs or natural killer cells concentrations in the blister fluids of SJS/TEN skin lesions were two to four orders of magnitude higher than perforin, granzyme B or sFasL concentrations, and depleting granulysin reduced the cytotoxicity of the keratinocytes. Furthermore, they showed that injection of granulysin into mouse skin resulted in features mimicking SJS-TEN.[22] Recently Saito *et al.* revealed the contribution of annexin A1 in keratinocyte necroptosis of SJS/TEN. Depletion of annexin A1 by a specific antibody diminished supernatant cytotoxicity. SJS/TEN keratinocytes expressed abundant formyl peptide receptor 1, the receptor for annexin A1, whereas control keratinocytes did not. They also showed that inhibition of necroptosis completely prevented SJS/TEN-like responses in a mouse model of SJS/TEN.[23]

There is no established therapy for SJS/TEN, although many treatment modalities including corticosteroid, plasmapheresis, and IVIG have been used. The challenge remains that it is difficult to assess the efficacies of treatments for such serious and rare disorders in a large clinical randomized controlled trial (RCT).

In this study, we presented the current clinical characteristics and treatments of SJS and TEN in 87 patients treated in our 2 hospitals to evaluate the usefulness of these treatments retrospectively.

The ages of patients with SJS and TEN were widely distributed from young to older. The major causative drugs were antibiotics, anticonvulsants, NSAIDs, and cold medicines. The predominance of these drugs in causing the diseases seems to have been unchanged since Aihara *et al.* analyzed 269 cases of SJS and 287 cases of TEN that were reported from 1981 to 1997 in Japan.[24] However, in our study, anticonvulsants were more frequently the causative drugs than has been previously reported in SJS. This might be related to the fact that in recent years, anticonvulsants have been used not only for convulsions but also for other diseases, such as neurogenic pain and bipolar disorder.

In addition to the severe skin symptoms, many organ involvements were observed. The organs most commonly involved were liver and kidneys. However, while less common than hepatitis and renal dysfunction, respiratory and gastro-intestinal disorders were severe conditions often resulting in fatality. In addition to multi-organ involvement, another major problem in the clinical course was secondary infections, especially sepsis.

As for treatments, systemic corticosteroid therapy was mainly used both in SJS and TEN in Japan.[25] The use of corticosteroids is based on the idea that corticosteroids effectively suppress an excessive immune response. While their use is still controversial,[18,26] recent studies have suggested them to be a valid treatment

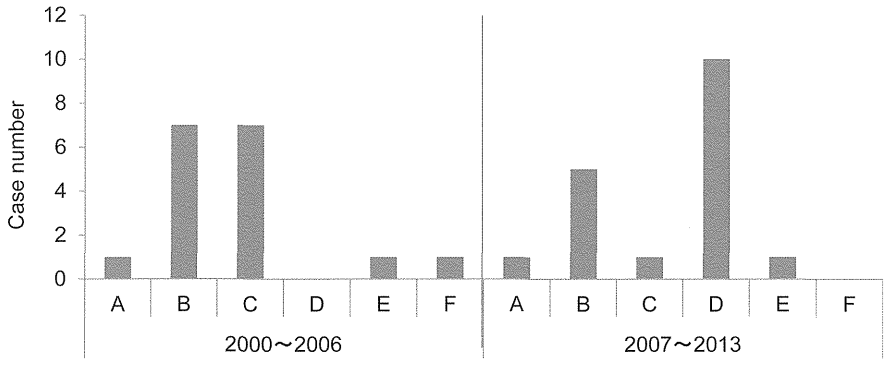

Fig. 4. Changes in the treatments used between 2000–2006 and 2007–2013 in TEN. A, Steroid (without pulse therapy); B, Steroid pulse therapy; C, Steroid and IVIG; D, Steroid and plasmapheresis; E, Steroid, IVIG, and plasmapheresis, F, IVIG (without corticosteroids). IVIG, intravenous immunoglobulin. Seventeen cases of TEN (2000–2006) and 18 cases of TEN (2007–2013) were evaluated.

modality for SJS/TENS.[6,7,27] Tripathi *et al.* reviewed 67 patients, and only 1 patient died of causes not related to steroid therapy.[6] They recommended the prompt use of high-dose systemic corticosteroids for a relatively brief period for the treatment of SJS. Hirahara *et al.* evaluated 8 patients treated with methylprednisolone pulse. They reported no deaths among these patients, whereas the predicted mortality was 1.6 deaths according to the SCORTEN scoring system (the mean SCORTEN score was 2.1).[27]

In the present study, corticosteroids were used to treat all patients except 3, and many of them were treated with steroid pulse therapy. The mortality was 6 deaths (6.9%) and all deceased cases were treated with steroids. However, this mortality was much lower than the predicted mortality (8.9 deaths, 25.3% in TEN) according to the SCORTEN scoring system. As we mentioned in detail about the 3 deceased TEN cases with sepsis, 2 cases received administration of corticosteroids in inadequate dose. Another 1 case with fever of unknown origin was suspected to have had underlying systemic infection. Although it is undeniable that corticosteroids may facilitate secondary infection, prompt tapering of the dose after amelioration of SJS/TENS symptoms was considered to reduce the risk of fatal adverse effects of the systemic corticosteroids.

In addition to the steroid therapy, plasmapheresis (mostly PE) and IVIG were performed in severe TEN cases. Plasmapheresis has been reported to be effective in several studies of TEN after the middle of the 1980s.[13,14,28,29] The mechanism of its effectiveness remains speculative, but most likely involves the removal of drugs and drug metabolites, soluble Fas ligand, and chemical mediators from the blood circulation. In our study, 14 patients including 12 TEN with average SCORTEN score 2.58 (predicted mortality 3.68 deaths, 30.6%) were treated with plasmapheresis and only one TEN patient died (mortality rate 7.4%). This data might show the possibility that plasmapheresis is useful modality in the treatment of refractory TEN after starting steroid therapy.

IVIG therapy with an acute TEN patient was first reported by Viard *et al.* in 1998.[8] After that report, many studies have revealed the effectiveness of IVIG therapy. The mechanisms are suspected to involve the inhibition of Fas-mediated keratinocyte death by naturally occurring Fas-blocking antibodies in the administered immunoglobulins and the inhibition of inflammatory cytokines. In addition, it has been thought that IVIG works through mechanisms of inhibition of inflammatory cells and modulation of immune function in inflammatory diseases.[30] However, the effect of IVIG is still controversial.[31,32] In 2006, French *et al.* summarized the clinical studies reported and suggested that the use of more than 2 g/kg of body weight of intravenous immunoglobulin is beneficial on the mortality associated with TEN.[9] Barron *et al.*[33] conducted a meta-analysis with meta-regression of 13 observational studies conducted during the period of 1966–2011 to assess IVIG in the treatment of SJS/TEN based on the SCORTEN scoring system. They showed that IVIG at doses of 2 g or more/kg appears to significantly decrease mortality. Chen *et al.*[34] also recommended the use of IVIG with total doses of more than 2 g/kg for the treatment of SJS/TEN. They reported that early application of steroids provided beneficial effects, and that combination therapy with steroids and IVIG showed better therapeutic effects than did steroids alone. In our study, 15 patients including 11 TEN with average SCORTEN score 2.09 (predicted mortality 2.59 deaths, 23.6%) were treated with IVIG and the mortality rate was 13.3% (2 deaths). The total amount administered was less than 2 g/kg in 13 cases, including 2 deceased cases administered with a total of 60 g each of IVIG (SCORTEN scores 4 and 6, respectively). IVIG was administered in combination with corticosteroids except in 1 case of TEN with underlying infection. In 2 of these cases with TEN, plasmapheresis was additionally performed after IVIG administration because it had not been effective enough. In addition, since only 2 patients were treated with IVIG at a dose of more than 2 g/kg in the study period, we are not able to discuss the efficacy of IVIG in terms of dose-dependence. Taken together, it is difficult to evaluate the additional effects of IVIG accurately from these data.

In the comparison of the data between 2000–2006 and 2007–2013, it was shown that the average SCORTEN score of the non-deceased cases rose from 1.69 to 2.47 after 2007 and the mortality rate fell from 23.5% to 5.6% in TEN. These changes seem to owe to the alterations in the treatments predominantly used for TEN between these 2 time periods. More cases were treated with the combination of corticosteroid therapy and PE at the early stage of each disease after 2007, because plasmapheresis as a treatment for SJS and TEN became eligible for coverage by health insurance in April 2006 in Japan. In addition, IVIG therapy at a dose of more than 2 g/kg was started in these latter years. In these patients, each treatment was started immediately one after another, when the initial treatment was thought not to be effective enough. From these facts, it is likely that treatments based on steroid therapy in combination with plasmapheresis and possibly IVIG are effective in SJS and TEN. The major factors influencing the efficacy of combination therapy seem to be the dose of steroids and timing of start of each treatment.

In conclusion, improvement of mortality of SJS/TEN was observed in 2007–2013, compared with 2000–2006. Treatment with steroids in combination with plasmapheresis and/or IVIG more than 2 g/kg seems to have contributed to this improvement. To inform the development of guidance as to the optimum treatment regimen, RCT studies are required. However, it is difficult to perform RCT for these diseases because of ethical problems.

Acknowledgment

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

YY and MA designed the study and wrote the manuscript. All other authors contributed to data collection. All authors read and approved the final manuscript.

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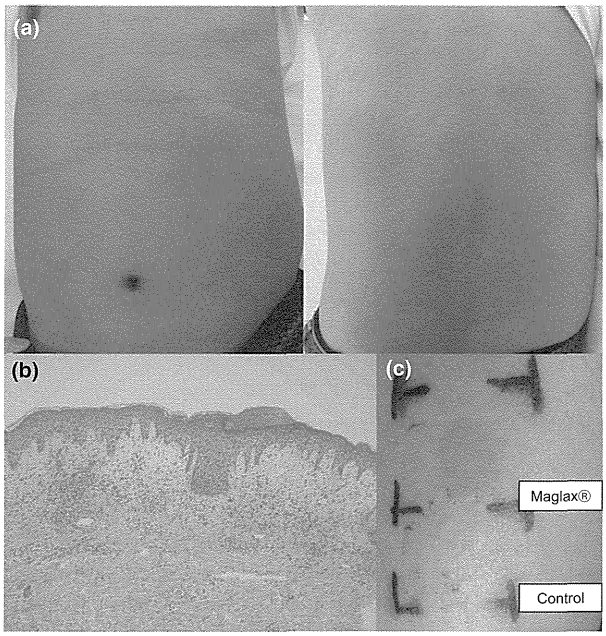

Figure 1. (a) Skin rash around the patient's abdomen and back. (b) Superficial and deep perivascular dermatitis with epidermal changes (hematoxylin–eosin, original magnification ×25). (c) Positive patch test reactions to Maglax® 1 month after improvement of his skin.

his skin rash. Our provisional diagnosis was skin rash elicited by Maglax.

We treated him with i.v. hydrocortisone sodium succinate, 300 mg daily for 2 days, followed by oral prednisolone, 35 mg daily for 4 days. His skin lesions improved gradually and prednisolone was tapered off in 1 month. There was no relapse.

A Maglax patch test (20%) was positive 1 month after the improvement of his skin rash (Fig. 1c). A drug-induced lymphocyte stimulation test (DLST) for Maglax revealed a ^{3}H-thymidine uptake of 586 c.p.m.; the control uptake is 109 c.p.m. The stimulation index was 537 (normal, <180). These findings confirmed the diagnosis of drug eruption due to Maglax. DLST of all six components – namely, magnesium oxide, carmellose calcium, crospovidone, calcium stearate, light anhydrous silicic acid and crystalline cellulose – were all positive. However, the patch tests were all negative. There is a possibility of conformational change of these components in the process of mixing.

Skin eruptions due to drugs containing magnesium are rare. Our review of the published work uncovered only five such cases.[1–4] Fixed eruptions observed in three patients were induced by magnesium hydroxide[1,2] and magnesium trisilicate.[3] The other two patients went into preterm labor and received magnesium sulfate i.v.; their urticarial rash appeared 30 min later.[4] In four of the five patients, the diagnosis was based on their clinical course. In the other patient with magnesium trisilicate-induced fixed eruption, oral challenge test reproduced the eruption.[3] In our patient, positive patch test and DLST identified Maglax as the causative factor. To our knowledge, this is the first case of Maglax-induced drug eruption confirmed by these tests.

CONFLICT OF INTEREST: None declared.

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Case of food-dependent exercise-induced anaphylaxis due to peach with Pru p 7 sensitization

Dear Editor,

A 54-year-old woman was referred to our dermatology department because she experienced several allergic reactions, including eyelid edema, tightness of larynx and nasal congestion after ingestion of peaches and cherries over 1 year. She developed the most severe reaction during a walk 1 h after ingestion a piece of peach for lunch. She also developed nasal congestion 1 h after drinking *ume* (Japanese apricot) juice. Her

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(a)

Challenges with			Results
Peach*	Exercise**	Aspirin intake	
130 g	−	−	No symptoms
260 g	−	−	No symptoms
130 g	+	−	No symptoms
130 g	−	+	Redness and swelling of face, especially eyelids, wheals on the neck, laryngeal tightness, and running nose.

*The weight of a whole peach is approximately 260 g.

** The exercise stress test was performed according to the Bruce protocol (up to stage 4) using a treadmill.

(b)

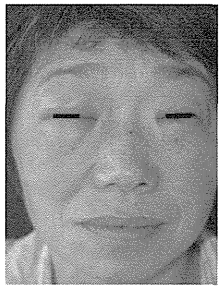

Figure 1. (a) Results of oral challenge tests of peaches with exercise or intake of aspirin as a cofactor. Oral challenge of 130 g peach pulp after intake of 500 mg aspirin induced swelling of her face, wheals on her neck, oropharyngeal tightness and running nose. (b) Prominent edema of face, especially eyelids, induced by oral challenge of 130 g peach pulp after intake of 500 mg aspirin.

other medical history was pollinosis. We suspected anaphylactic reactions due to peaches, cherry and Japanese apricots, and the involvement of exercise as a cofactor, which exacerbates allergic reactions.

In ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden), the levels of serum-specific immunoglobulin (Ig)E to peach, apple, kiwi, alder pollens and birch pollens were normal. In skin prick test (SPT) using the prick-prick method, with raw peach pulp and skin, canned peach, raw *ume* and *ume* juice were positive.

We performed oral challenge test of peaches with intake of aspirin as a cofactor (Fig. 1).[1] Oral challenge of 130 g peach pulp after intake of 500 mg aspirin induced swelling of her face, especially eyelids, wheals on her neck, oropharyngeal tightness and running nose in a few minutes, although oral challenge of approximately 260 g peach pulp was negative. To identify the causative allergen, we measured specific IgE (sIgE) against four peach components: rPru p 1 (Bet v 1-homolog), rPru p 3 (lipid transfer protein, LTP), rPru p 4 (LTP) and nPru p 7. ImmunoCAP for rPru p 1, rPru p 3 and rPru p 4 was negative, whereas sIgE against purified nPru p 7 was positive using enzyme-linked immunoassay (absorbance at 450 nm, 0.548). These results indicated that the present case was peach allergy enhanced by cofactors, such as exercise and aspirin intake, so-called food-dependent exercise-induced anaphylaxis (FDEIA), due to Pru p 7 sensitization. Although the challenge test with aspirin was not performed, the patient had never experienced adverse reactions after recent intake of aspirin.

Food-dependent exercise-induced anaphylaxis due to peaches was rarely reported, but the causative allergen has not been well clarified. In Mediterranean countries, like Spain and Italy, LTP has been identified as the causative allergen candidate of FDEIA due to plant foods. Pascal *et al.*[2] indicated that 32.4% of FDEIA due to plant-derived LTP could be cofactor dependent, such as non-steroidal anti-inflammatory drugs and exercise. On the other hand, Bianchi *et al.*[3] indicated the case with discrepancy of results between SPT with commercial crude extract and ImmunoCAP for Pru p 3. We reported the first case of FDEIA to peaches due to Pru p 7 sensitization. Pru p 7 is an antimicrobial peptide, Peamaclein. Pru p 7 shows heat stability and digestion resistance due to a high cystein content, with the result that it could induce severe reactions after ingestion of peaches.[4,5] As the Japanese population generally eat peach pulp alone after peeling, they may be rarely sensitized to Pru p 3 as a consequence, which is located exclusively in peach peel.[5] Therefore, in Japan, Pru p 7 could be a marker related to systemic reactions due to peaches, that is including not only food-induced anaphylaxis but also FDEIA.

CONFLICT OF INTEREST: None declared.

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sion, there was marked improvement, and no relapse was seen during the subsequent 14 months (Fig. 1c).

Plasmacytoid dendritic cell precursors (PDC) are pivotal in the pathogenesis of psoriasis. PDC-derived type 1 interferon induces naive T cells to T helper 1 cells via the activation of TNF-α and inducible nitric oxide synthase-producing dendritic cells, which are then stimulated by TNF-α produced by macrophages.[4] Because TNF-α inhibits the production of interferon-α by PDC and the conversion of immature dendritic cells to PDC, the neutralization or blockade of TNF-α results in increased interferon-α secretion and the activation of the PDC pathway, leading to the development of psoriatic lesions.[5] The paradoxical reaction is due to the imbalance in the TNF/TNF-receptor system.

Elsewhere, we reported the clinical effectiveness of GMA for intractable skin diseases attributable to activated neutrophils and macrophages. GMA removes pathogenic granulocytes and macrophages that express macrophage-1 antigen. As anticipated in this case, our patient's lesions responded well to GMA, demonstrating for the first time the beneficial effect of GMA for a paradoxical reaction to infliximab.

CONFLICT OF INTEREST: The GMA columns used in this study were provided by JIMRO (Takasaki, Japan).

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Non-drug-induced Stevens–Johnson syndrome successfully treated with high-dose i.v. immunoglobulin

Dear Editor,

Stevens–Johnson syndrome (SJS) is a severe skin and mucosal disorder usually caused by a hypersensitive reaction to drug(s); rarely, it can be parainfectious. It is characterized by high fever, widespread blistering exanthema and mucous membrane erosions on less than 10% of the body surface area (BSA). Although there is no standard treatment, corticosteroids have been widely used. More recently, high-dose i.v. immunoglobulin (IVIG) has been used to treat SJS and toxic epidermal necrolysis (TEN), a more severe reaction with wider skin detachment,[1–3] although its effectiveness remains controversial.[4] We describe here a patient with non-drug-induced SJS successfully treated with high-dose IVIG.

A 41-year-old man presented to our hospital with an 8-day history of high fever and painful mucocutaneous lesions. The skin rash had expanded from the hands and feet to the whole body in the previous 3 days despite treatment with 15 mg prednisolone (PSL) for 1 day and 20 mg PSL for 2 days. He had no medical history of note and took no medications or supplements.

On examination, his lips were swollen, erythematous and crusted, and painful ulcers were present on the palate. Macular lesions with bullae and erosions were scattered on the whole body and frequently confluent (skin detachment, <10% BSA) (Fig. 1a–c). Mild erythema on the periorbital area was observed with slightly injected conjunctiva (Fig. 1d), but no genital lesions were observed. Laboratory data were normal apart from mildly elevated lactase dehydrogenase (346 IU/L) and C-reactive protein (1.58 mg/dL). Chest X-ray and electrocardiogram were normal. Antibodies against *Mycoplasma* were not detected.

Skin biopsy from a macular lesion on the back showed keratinocyte apoptosis and substantial epidermal necrosis with a moderate mononuclear cell infiltrate and a subepidermal split (Fig. 1e,f). SJS was diagnosed.

Because an infectious cause was suspected, IVIG was additionally administrated at a dose of 400 mg/kg per day for 5 days. The lesions started to improve 2 days after the initiation of IVIG, and the patient was discharged 13 days after admission. The cause of his SJS was unknown, but his antibody titer against *Mycoplasma pneumoniae*, a major cause of SJS in young adults, increased 1 month after admission (particle agglutination method, ×80); however, this mild increase after IVIG is not strong evidence. Antibodies against Herpes simplex, Epstein–Barr virus, and Coxsackie virus A4, A7 and A16 showed no significant increases during the course.

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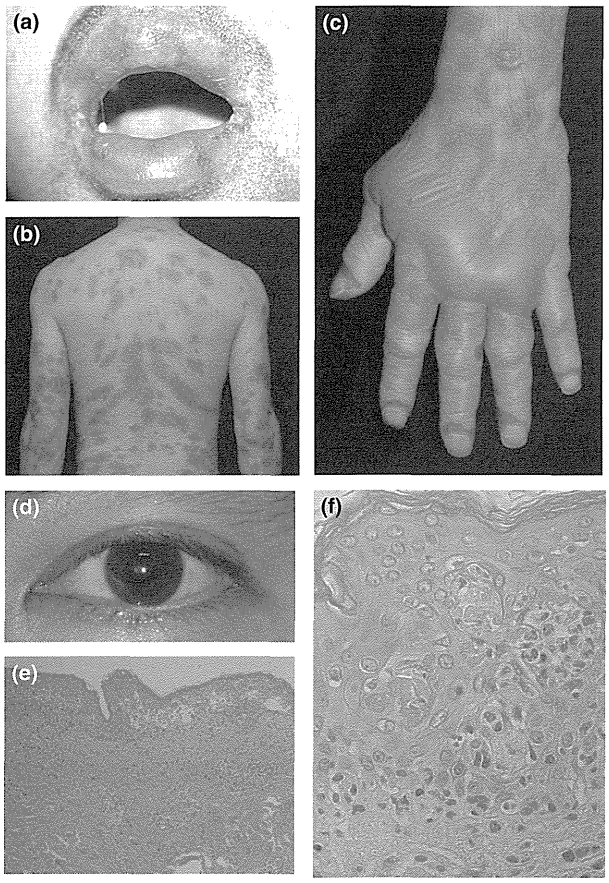

Figure 1. Clinical and histological findings. (a–d) Clinical findings on admission. (a) Swollen lips with erythema, crust and erosion. (b) Multiple macular lesions on the trunk and limbs. (c) Numerous tense bullae on the hands and feet. (d) Mild erythema on the periorbital area with slight injection. (e,f) Histological examination showing keratinocyte apoptosis and necrotic epidermis with inflammatory cell infiltration and a subepidermal blister (hematoxylin–eosin, original magnifications: [e] ×100; [f] ×400).

Treatment of SJS includes symptomatic care and, in severe cases, systemic corticosteroids. Corticosteroids have adverse effects, such as immunosuppression and retardation of re-epithelialization, and consequently there are concerns over their use.[5] High-dose corticosteroids should be used with caution in patients suspected of infection-induced SJS, such as our patient. Many studies of IVIG for SJS and TEN have reported an arrest of disease progression and a reduction in the time to skin healing particularly with doses totaling more than 2 g/kg. Although the mechanisms by which IVIG counteracts SJS and TEN are not fully understood, immunomodulating effects are suspected. Therefore, high-dose IVIG would be considered as one of therapeutic options for SJS and TEN, and especially for infection-induced SJS.

CONFLICT OF INTEREST: None.

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Proposal of the new name "eruptive papular collagenoelastopathy" to unify the two indistinguishable entities, eruptive collagenoma and papular elastorrhexis

Dear Editor,

Eruptive collagenoma (EC) is a rare, acquired, connective tissue nevus that appears during youth.[1,2] Connective tissue nevi are histopathologically characterized by the abnormal accumulation of extracellular matrix components, such as collagen, elastic fibers and glycosaminoglycans. Clinicopathologically, papular elastorrhexis (PE) is a similar disease.[3] Since it was first reported, there has been nosological controversy regarding EC

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CONCISE COMMUNICATION

Reduction of interleukin-10 production by B cells in intractable toxic epidermal necrolysis

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ABSTRACT

Several interleukin (IL)-10 producing B-cell subsets have been identified recently. However, few studies have examined the role of them in toxic epidermal necrolysis (TEN). We describe a 41-year-old woman with TEN who had B-cell lymphoma and a history of treatments including B-cell depletion therapy. Her re-epithelization was still ongoing after 7 months, despite treatments. To investigate her immune system, we compared cytokine and chemokine production from B cells and non-B cells isolated from the patient and another non-lymphoma TEN patient. IL-10 production from B cells decreased in the patient compared with the control TEN-only patient. Cytokine and chemokine levels from non-B cells involved in inflammation were elevated in the patient compared with the control patient. In conclusion, this study demonstrates that IL-10 from B cells as well as regulatory T cells is critical in the pathogenesis of TEN, and that B-cell dysfunction based on B-cell lymphoma and B-cell depletion therapy may be involved in the intractability of TEN.

Key words: **anti-CD20 antibody, B-cell depletion therapy, interleukin-10, regulatory B cell, toxic epidermal necrolysis.**

INTRODUCTION

Toxic epidermal necrolysis (TEN) is characterized clinically by widespread detachment of skin and mucosal involvement, and histologically by epidermal necrosis in denuded areas.[1,2] After discontinuation of the causative drug and proper treatment, re-epithelization usually occurs within some weeks in recovering patients. Cytotoxic T lymphocytes play a pivotal role in TEN pathogenesis.[2] In addition to keratinocyte apoptosis,[2,3] it was recently reported that necroptosis is involved in the keratinocyte death in TEN.[4]

The balance between pro-inflammatory and anti-inflammatory cytokines also contributes to TEN pathogenesis.[5–7] Takahashi *et al.*[8] demonstrated a role for regulatory T cells (Treg), widely known as a primary source of interleukin (IL)-10, in cutaneous adverse drug reactions (cADR) pathogenesis and suggested that expanded Treg would limit the severity of T-cell-mediated immune-inflammatory drug responses. Recently, besides Treg, several IL-10 producing B-cell subsets have been identified. However, few studies have examined the role of them in cADR.

Here, we describe a Japanese woman with TEN who had B-cell lymphoma and a history of treatments including B-cell depletion therapy. Surprisingly, her re-epithelization was still ongoing after 7 months. We further investigated her immune system and compared the results with those of other TEN patient.

CASE REPORT

A 41-year-old woman was transferred to our hospital because of prolonged fever and systemic skin erosions. She was diagnosed as having follicular lymphoma (B-cell lymphoma) 7 years prior and had been treated with chemotherapy. She was treated with four courses of cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (CHOP) combined with rituximab (anti-CD20 antibody). Eight courses of bortezomib, two courses of CHOP, and four courses of fludarabine with rituximab were consequently administrated. Finally, she received six courses of ofatumumab, another anti-CD20 antibody. During the last treatment with ofatumumab, oral mucosal erosion appeared. Ocular hyperemia and erythema developed on her upper arms despite withdrawal of ofatumumab and administration of 30 mg oral prednisolone (PSL). She was suspected of cADR and all suspect medications, such as sulfamethoxazole and acyclovir, were discontinued. However, her symptoms progressed and a skin biopsy showed many apoptotic keratinocytes and widespread liquefaction at the epidermal–dermal

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