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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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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

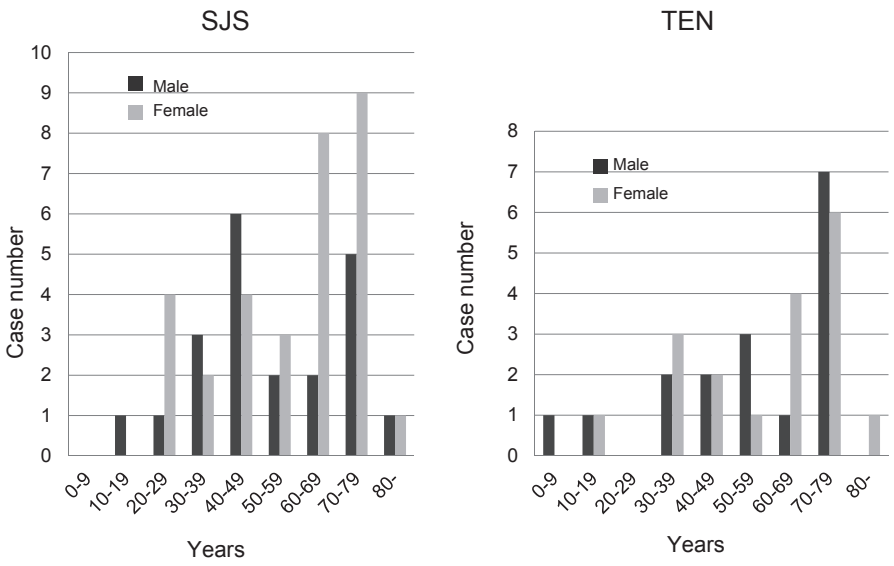

Fig. 1. Ages of patients with SJS and TEN. Fifty-two cases of SJS and 35 cases of TEN were included in this study.

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

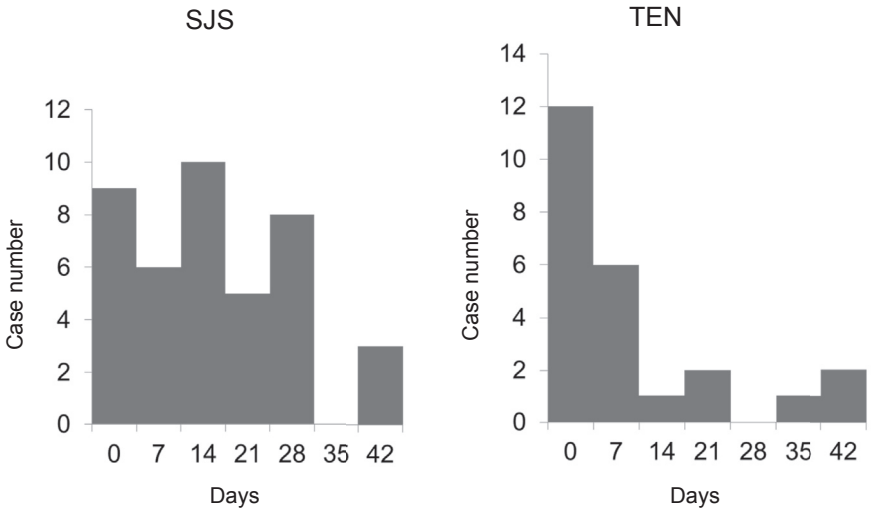

Fig. 2. Time between the first causative drug intake and the onset of symptoms. Forty-one cases of SJS and 24 cases of TEN were examined. The average intervals were 18.0 days in SJS and 11.7 days in TEN.

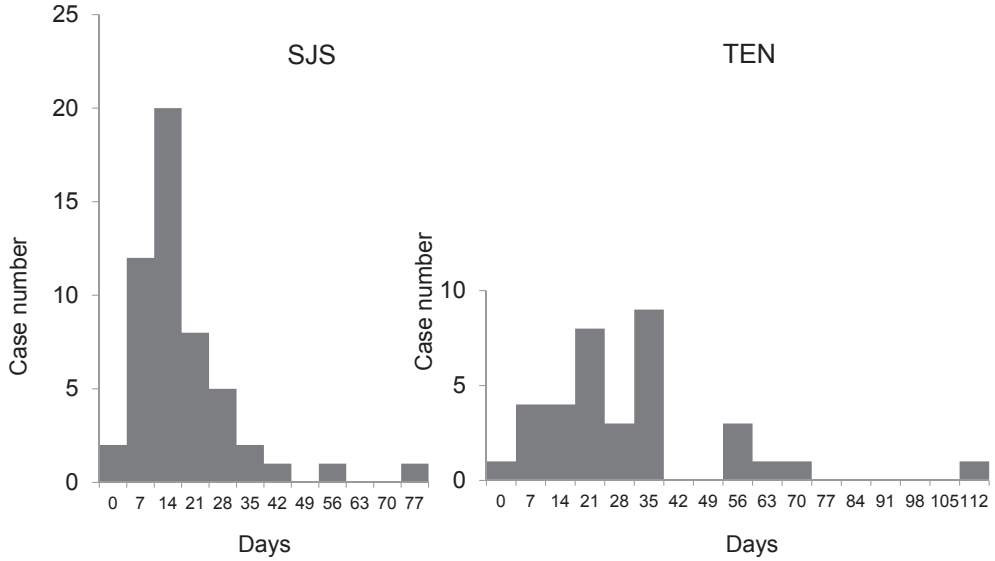

Fig. 3. Total days of the hospital stay. Fifty-two cases of SJS and 35 cases of TEN were examined. The average numbers of days of the hospital stay were 20.8 days in SJS and 34.1 days in TEN.

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	Rheumatoid 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

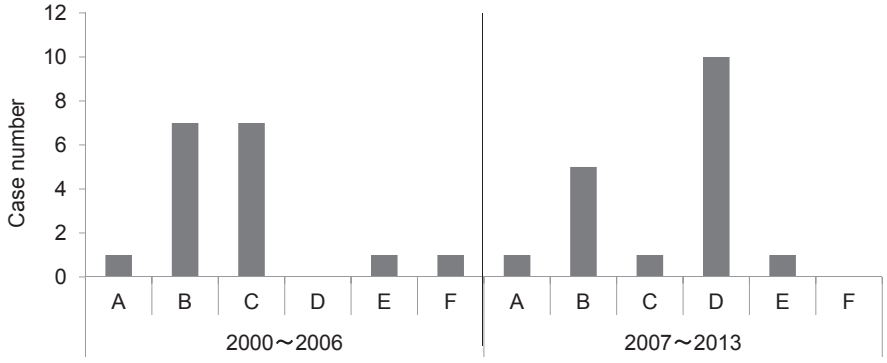

Fig. 4. Changes in the treatments used between 2000–2006 and 2007–2013 in TEN. A, Steroid (without pulse therapy); B, Steroid pulse therapy; C, Steroid and IVIG; D, Steroid and plasmapheresis; E, Steroid, IVIG, and plasmapheresis, F, IVIG (without corticosteroids). IVIG, intravenous immunoglobulin. Seventeen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

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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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