ORIGINAL ARTICLE

Analysis of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan from 2000 to 2006

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ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse drug reactions with high mortality.
Methods: To present the current clinical characteristics and treatment of SJS and TEN in Japan, we retrospectively analyzed reports of SJS and TEN published in medical journals from 2000 to 2006.
Results: Fifty-two cases of SJS (19 males and 33 females; mean age, 45.2 years) and 65 cases of TEN (31 males and 34 females; mean age, 45.7 years) were reported. Thirty-six cases of SJS (69.2%) and all cases of TEN were caused by drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and anticonvulsant drugs. Hepatitis was the most common organ involvement in both SJS and TEN. Renal dysfunction and respiratory disorders were also involved in some cases. The major complication was sepsis, but in only 1.9% of SJS and 10.8% of TEN. Most cases were treated systemically with corticosteroids, and 42 cases (80.8%) of SJS and 39 cases (60.0%) of TEN were treated with corticosteroids alone. Plasmapheresis and/or immunoglobulin therapy was combined with corticosteroid therapy in some cases. The mortality rates for patients with SJS and TEN were 1.9% and 6.2%, respectively. The mortality in TEN decreased remarkably from 21.6% (58/269) during the previous 17 years (1981 to 1997).
Conclusions: Improvement of treatment may be one of the reasons for the decrease in mortalities of both SJS and 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] In SJS, detachment of the epidermis is less than 10% of the body surface area; the detachment is wider in TEN.[3] In addition to the severe skin symptoms, both diseases are often accompanied by complications in numerous organs, such as the liver, kidney, and lung. Although many factors have been proposed as causes of these diseases, including adverse drug reactions, malignant disorders, graft-versus-host disease and infections by microorganisms such as viruses and *Mycoplasma*

pneumoniae, hypersensitivity to medications accounts for most of the cases.[4] Some investigators have proposed that SJS and TEN are variations of the same disease expressed with different severity,[5] but there is still strong disagreement regarding this concept. However, the clinical manifestations and the pathologic tests support the concept and show that SJS and TEN differ from erythema multiforme, which shows acrally distributed typical target or raised edematous papules with or without mucosal involvement, caused mainly by herpes simplex virus.[6] The pathogenesis of SJS and TEN remains to be elucidated but apoptotic mechanisms, including involvement of cytotoxic T cells, tumor necrosis factor (TNF)-α, and Fas, Fas ligand (FasL) interaction, are considered to be relevant to these diseases.[7-10]

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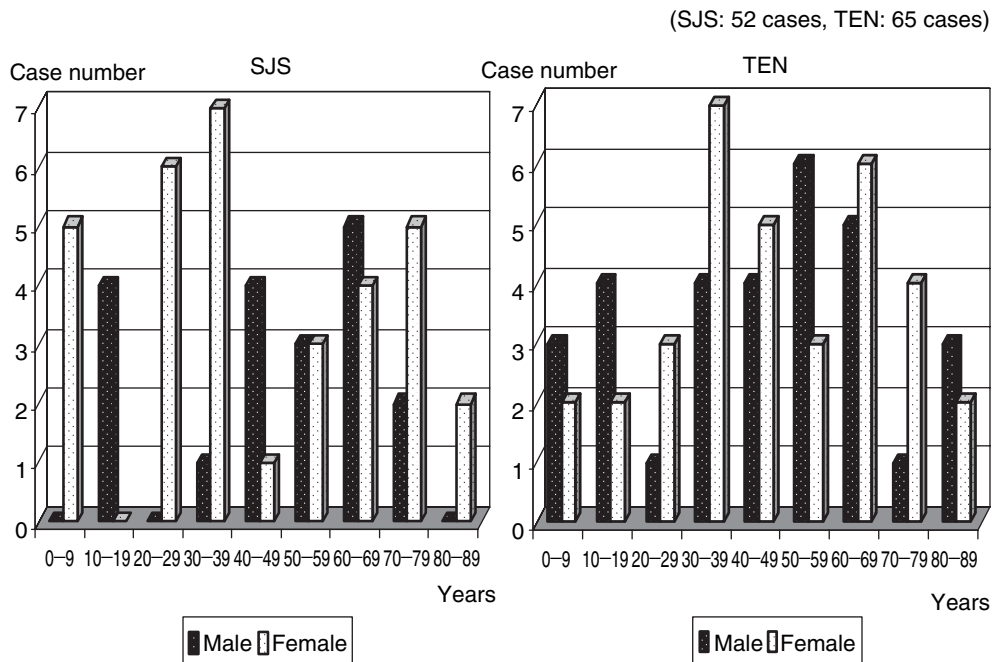
(SJS: 52 cases, TEN: 65 cases)

Fig. 1 Age of Patients with SJS and TEN

The reported mortality varies from 3% to 10% for SJS and from 20% to 40% for TEN.[11,12] Several treatments have been reported to be beneficial but there are no clear indications for the optimal treatment. Systemic administration of corticosteroids is still controversial in many countries,[13] but this form of treatment has become the mainstream of treatment in Japan. High-dose immunoglobulin therapy[10,14-16] and plasma apheresis[17-19] are also considered effective in some reports.

The aim of this study is to present the current clinical characteristics and treatments of SJS and TEN in Japan. We retrospectively analyzed reports of SJS and TEN published in medical journals from 2000 to 2006.

METHODS

We collected reports on SJS and TEN in Japan, which were published in medical journals between January 2000 and December 2006, using the Japana Centra Revuo Medicina. Clinical reports were selected when they contained enough information to make a credible diagnosis. For SJS, symptoms should include acute conditions characterized by mucous membrane erosions and skin lesions (described as macules, atypical target-like lesions, bulla, erosions) with less than 10% of maximum detachment of the skin surface area; and for TEN the symptoms should include more than 10% of maximum skin detachment in addition to the symptoms above. Therefore, SJS without description of mucous involvement and TEN with less than 10% of maximum skin detachment were excluded from this study, even if they were reported as SJS or TEN. Cases reported as overlap of SJS/TEN

were included in TEN.

The following data were collected: Demographic information (age, sex), relevant past medical history, antecedent use of medications, time between the first causative drug intake and the onset of symptoms, presence and extent of mucous membrane involvement, laboratory data, treatment including corticosteroid therapy, high-dose immunoglobulin therapy and plasmapheresis, complications and mortality. The reference numbers of the items analyzed often differed from case to case because they were specified differently in each report.

RESULTS

AGE AND SEX (Fig. 1)
Fifty two cases of SJS and 65 cases of TEN were analyzed in this study. In patients with SJS, comprising 19 males and 33 females, the ages were between 2 and 89 years (mean, 45.2 years). In patients with TEN, comprising 31 males and 34 females, the ages were between 1 and 88 years (mean, 45.7 years).

ETIOLOGY
In SJS, 36 cases (69.2%) were considered to be caused by drugs, and five cases (10.4%) were suspected to be caused by *Mycoplasma pneumoniae*, or *Mycoplasma pneumoniae* and/or drugs. The causes of the other cases were not determined. In contrast, all TEN cases had received drugs and were suspected to be caused mainly by drugs. In both SJS and TEN, antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs) and cold medicines were the major causative drugs (Table 1).

Table 1 Causes of SJS and TEN

	Number of cases	
	SJS	TEN
Antibiotics	8	12
Penicillins	1	2
Cephems	6	5
Pyridone carboxylic acid	0	2
Sulfamethoxazole・trimeathoprim	0	1
Tetracycline	0	1
Polypeptides (vancomycin)	1	1
NSAIDs[†] and cold medicine	4	18
NSAIDs	3	12
Cold medicine	1	6
Anticonvulsants	10	11
Antipodagric (Alopurinol)	2	3
Antitussive	2	0
Anti-arrhythmics (Mexiletine Hydrochloride)	2	0
Protease (serrapeptase)	2	0
Contrast medium	1	1
Others	7[‡]	10[§]
Not determined	10	17
Total	48	72

[†] NSAIDs; nonsteroidal anti inflammartory drugs

[‡] Include each case of; Peplomycin, glibenclamide, azathioprine, spironolactone, dihydrocodeine phosphate, mizoribine, acetazolamide

[§] Include each case of; Cyanamide, amelaxanox, D-penicillamin, imatinib mesylate, digestive enzymes, omeprazole, lysozyme chloride, haloperidol, bromelain, bucillamine

Cephalosporins were the most frequent causative drugs among antibiotics (10 cases in SJS and TEN) and carbamazepine was the most frequent among anticonvulsants (8 cases in SJS and TEN). Many other kinds of drugs were also presumed to be the causes in SJS and TEN, although the frequencies of these cases were much lower than those mentioned above.

INTERVAL BETWEEN THE FIRST DRUG INTAKE AND ONSET OF SYMPTOMS

The intervals between the first drug intake and the onset of symptoms in 34 cases of SJS and 35 cases of TEN are shown in Figure 2. More than half (67.6% of SJS, 80.0% of TEN) of the patients developed symptoms within 2 weeks. Due to the fact that the symptoms appeared within 3 days in 18 cases (51.4%) of TEN and in 9 cases (26.5%) of SJS, TEN thus seemed to develop earlier than SJS.

MAXIMUM SKIN DETACHMENT IN TEN

The maximum skin detachment was specified in 44 cases of TEN. The range was 10% to 100% and the mean was 49.6 %. Eleven cases showed 70% or more detachment of the body surface area and 6 of these showed expansion of the skin detachment even after
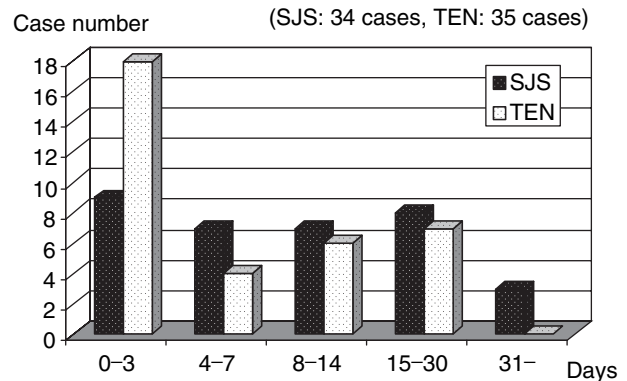
Fig. 2 Time Between the First Causative Drug Intake and Onset of Symptoms

starting steroid therapy.

ORGAN INVOLVEMENT AND COMPLICATIONS

Many patients showed organ involvement and other complications (Table 2). In both SJS and TEN, hepatitis was the most common complication. Twenty four cases (46.2%) of SJS and 41 cases (63.1%) of TEN had hepatitis. In 2 cases of SJS, alanine aminotransferase (ALT) was elevated more than 1,000 IU/ml, but no case of TEN showed such a conspicuous elevation of ALT. This might suggest that SJS could cause more severe hepatitis than TEN.

Respiratory disorders were shown in 11 cases (21.2%) of SJS and 19 cases (29.2%) of TEN. They included mucous membrane damage of trachea or bronchus, bronchiolitis obliterans, pneumonia, respiratory failure, subcutaneous emphysema, mediastinal emphysema and others.

Five cases (9.6%) of SJS and 18 cases (27.7%) of TEN showed renal dysfunction. Haemodialysis was performed in one case of SJS and 3 cases of TEN. Encephalopathy, gastro-intestinal disorder and myocarditis were also reported in both SJS and TEN. Sepsis was more frequent in TEN than in SJS.

Eleven cases of SJS and 9 cases of TEN developed late sequelae ophthalmic disorders, skin disorders, respiratory disorders, and hepatitis. In SJS, 8 cases developed ophthalmic symptoms such as corneal ulceration, adhesions of the eye ball, dry eye and other symptoms. One of these cases underwent an amnion transplantation. On the other hand, fewer TEN cases (6 cases) developed ophthalmic symptoms, and no case needed cornea grafting.

TREATMENT

Major systemic treatments adopted in addition to supportive care were classified into systemic administration of corticosteroids, high-dose immunoglobulin therapy, and plasmapheresis. The treatments performed are shown in Table 3. Only a few cases (4 cases of SJS and 2 cases of TEN) were treated with-

Table 2 Organ Involvement and Complications in Patients with SJS and TEN

Number of cases (%)

	SJS	TEN	Total
Hepatitis	24 (46.2%)	41 (63.1%)	65 (55.6%)
T-bil > 2 mg/dl	1	6	6
ALT[†] Not described	3	5	8
100 IU/l >	6	20	26
500 IU/l > , ≧ 100 IU/l	11	13	24
1000 IU/l > , ≧ 500 IU/l	2	3	5
> 1000 IU/l	2	0	2
Renal dysfunction[‡]	5 (9.6%)	18 (27.7%)	23 (19.7%)
Haemodialysis	1	3	4
Respiratory disorder	11 (21.2%)	19 (29.2%)	30 (25.6%)
Encephalopathy	5 (9.6%)	8 (12.3%)	13 (11.1%)
Gastro-intestinal disorder	5 (9.6%)	9 (13.8%)	14 (12.0%)
Myocarditis	1 (1.9%)	1 (1.5%)	2 (1.7%)
Sepsis	1 (1.9%)	7 (10.8%)	8 (6.8%)
DIC [§]	1 (1.9%)	1 (1.5%)	2 (1.7%)

[†] ALT; alanine aminotransferase

[‡] Cr ≧ 2 and/or Albuminuria and/or enforced Haemodialysis

[§] DIC; disseminated intravenous coagulation

Table 3 Treatment for SJS and TEN

Number of cases

			SJS	TEN
No corticosteroids			4	2 (1)
Steroid therapy			42	39
	PSL[†] equiv	PSL: < 10	0	1
		PSL: 10−29	2	0
		PSL: 30−59	11	8
		PSL: ≧ 60	9	8
		not described	4	3
	mPSL[‡] 1 g/day×3 days		7	8
	mPSL 125−600 mg/day×3 days		7 (1)	10
	pulse dose not described		2	1
Steroid and immunoglobulin therapy			6	12 (2)
	High dose immunoglobulin (400 mg/kg/day)		0	4 (1)
Steroid therapy and plasmapheresis			0	8 (1)
Steroid and immunoglobulin therapy and plasmapheresis			0	4
	High dose immunoglobulin (400 mg/kg/day)		0	2
	Total		52 cases (1)	65 cases (4)

[†] PSL; prednisolone

[‡] mPSL; methylprednisolone

( ): deceased cases

out corticosteroids. Forty-two (80.8%) cases of SJS and 39 cases (60.0%) of TEN were treated with corticosteroids alone. Of these, 16 cases (30.8%) of SJS and 19 cases (29.2%) of TEN were treated with steroid pulse therapy (methylprednisolone (mPSL) 125~1000 mg/ day for 3 days).

A combination of plasmapheresis and corticosteroid therapy without immunoglobulin was chosen in 8 cases of TEN. A combination of high-dose immunoglobulin therapy and corticosteroid therapy was performed in 4 cases of TEN. Two cases were treated with corticosteroid, high-dose immunoglobulin and

Table 4 Mortality for SJS and TEN

Case No./ age/sex	Causative drugs	Maximum skin detachment (%)	Severe complications	Treatments	Time to death[†]
SJS					
1 76/M	Cefcapene pivoxil? NSAIDs[#]?	8%	MRSA[¶] sepsis Hemophagocytosis DIC[‖]	mPSL 250 mg/day×3 days	31 days
TEN					
2 74/F	Piperacillin	70%	Septic shock	No Corticosteroids? Immunoglobulin?	20 days
3 72/F	Allopurinol?	> 90%	Sepsis, DIC Intestinal bleeding Respiratory disorder	mPSL[‡] 1000 mg/day×7 days (3 days + 4 days), immunoglobulin 2.5 g×5 days	62 days
4 53/F	NSAIDs	90%	Septic shock Multiorgan failure	mPSL 500 mg/day×3 days, PA[§] 6 days	73 days
5 3/F	Cefditren pivoxil? Acetoaminofen?	> 90%	Respiratory disorder	mPSL 125 mg/day×3 days, immunoglobulin 5 g×4 days (0.4 g/kg/day)	24 days

[†] Time between the onset of eruption and death

[‡] mPSL; methylprednisolone

[§] PA; plasmapheresis

[¶] MRSA; Methicillin-resistant staphylococcus aureus

[#] NSAIDs; nonsteroidal anti inflammartory drugs

[‖] DIC; disseminated intravenous coagulation

plasmapheresis. In most cases, plasmapheresis was performed using double filtration methods, and human immunoglobulin was administered as high-dose therapy at a dose of 400 mg/kg of body weight per day for 3 days. These combination therapies were chosen for patients in whom corticosteroid therapy alone was not effective enough or when rapidly progressing symptoms were observed.

MORBIDITY AND MORTALITY

One patient with SJS (mortality rate, 1.9%) and 4 patients with TEN (mortality rate, 6.2%) died. A summary of the deceased cases is shown in Table 4. The deceased SJS case was a 76 year-old man. He developed hemophagocytotic syndrome, MRSA pneumonia and MRSA sepsis, and died 33 days after onset of the illness.

As for TEN, all deceased cases were females. Their ages varied from 3 years to 74 years, with a mean age of 50.5 years. The skin detachment was 70% or more of the body surface area. Except for one case, mPSL was administered, and plasmapheresis was also performed in one of them. Three cases developed sepsis, and it appeared that control of the infections affected the outcome of the treatment.

DISCUSSION

SJS and TEN are rare but serious disorders with significant mortality. The pathogenesis is not fully elucidated, although there have been recent developments in the understanding of the apoptotic pathways of keratinocytes and in the immunological changes that are related to adverse drug reactions in these diseases. There is no definite specific treatment for SJS or TEN, and establishment of adequate and more effective therapy is needed.

To clarify the current manifestations and management of these diseases, we reviewed the clinical characteristics and treatments of patients with SJS and TEN that were reported in the literature from 2000 to 2006.

The ages of patients with SJS and TEN ranged from infants to the elderly. The mean age was approximately 45 years in both diseases, which is as high as those reported from other countries.[20] The major causative drugs were antibiotics, anticonvulsants, and NSAIDs and cold medicines. The predominance of these drugs in causing the diseases is unchanged as compared with a study of 269 cases of SJS and 287 cases of TEN, which were reported from 1981 to 1997 in Japan.[21]

In addition to the severe skin symptoms, the patients often had complications involving other organs such as the liver, kidneys, lungs, and gastro-intestinal tract. In addition to multi-organ involvement, another major problem in the clinical course was secondary infections, especially sepsis.

The mortality of both SJS and TEN decreased as compared with the previous data of 1981−1997 (SJS, from 6.3% to 1.9%; TEN, from 21.6% to 6.2%),[21] even though many patients developed organ involvement and, in TEN, extensive skin detachment. These differences might depend on differences in the numbers of analyzed cases, but it could also be due to the cur-

rent improvement of treatment for these diseases.

The use of corticosteroids is based on the idea that corticosteroids can effectively suppress an excessive immune response. However, their use is still controversial. In 1983, Kim *et al.* suggested that treatment with glucocorticoids in SJS and TEN is associated with increased morbidity and mortality mainly due to secondary infections.[22] However, one should be aware that the administration of steroids to patients in their report often was delayed relative to disease onset and usually given in moderate doses and with prolonged duration. In many studies after the 1980s, the authors stated that corticosteroids not only enhanced the risk of sepsis[23,24] but also delayed epithelialization. In contrast, in 2000, Tripathi *et al.* reviewed 67 patients with SJS, and found that 66 of these patients recovered with steroid therapy (1 died due to causes unrelated to steroid therapy).[25] These authors recommended the prompt use of high-dose systemic corticosteroids for a relatively brief period for the treatment of SJS. Corticosteroids have also been recommended for TEN by other authors.[26-28] In our study, corticosteroids were administered in most of the patients, and many of these patients were treated with steroid pulse therapy. This might be one of the reasons why the mortality of both SJS and TEN decreased during these years, because steroid pulse therapy had been rarely chosen for the treatment of SJS and TEN before 2000.

In addition to steroid therapy, plasmapheresis and high-dose immunoglobulin therapy were performed in some patients with TEN. Insufficient improvement of the symptoms with steroid therapy seems to be a big factor in choosing additional treatments. The skin lesions and general conditions were aggravated even after starting the steroid therapy in these patients.

Plasmapheresis has been reported to be effective in several studies of TEN after the middle of the 1980s.[18,19] The mechanism underlying the effectiveness remains speculative but most likely involves removal of drug and drug metabolites, antibodies, and chemical mediators. In Japan, some patients with TEN were treated with plasmapheresis after 1988. However, the optimal method of use and the relevant effects have not yet been established. In this study, only one patient died among 8 patients treated with plasmapheresis and steroids.

The effect of intravenous high-dose immunoglobulin therapy has been investigated by several groups[14-16] after Viard *et al.*[10] published a study of patients with acute TEN in 1998. The mechanisms are suspected to involve inhibition of Fas-mediated keratinocyte death by naturally occurring Fas-blocking antibodies in the administered immunoglobulin and inhibition of inflammatory cytokines. 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 in reducing the mortality associated with TEN.[14] In our study, less immunoglobulin (0.4 g/kg/days for 3 days) was administered together with steroid in 4 patients, and one of these patients died. Two seriously ill patients underwent plasmapheresis and received high-dose immunoglobulin therapy in combination with steroid therapy, with no mortality. These results suggest that the combination of these 3 treatments might be useful in seriously affected patients. More experience is needed to confirm the effect.

Five deceased cases were reported in the seven years of our review. Four of the cases developed sepsis and three of these cases were treated with steroid pulse therapy. According to our previous study, multiorgan involvement and DIC was observed in many deceased patients without sepsis who had been treated only with a moderate dose of corticosteroids.[21] Therefore, the remarkable improvement of the mortality of both SJS and TEN suggests that the use of steroid pulse therapy decreased the risk of the fetal organ involvement, although there is a possibility that the use of steroid pulse therapy enhanced the risk of infection.

Our review of the literature leads us to conclude that steroid therapy with high-dose corticosteroids is effective in SJS and that treatment combinations may be useful in extensive and aggravated TEN, although the selection of cases was biased because we were limited to evaluating published cases.

In France and Germany, a registry of patients with SJS and TEN has already been established since the mid-1990s, and a large-scale epidemiologic study is ongoing. A similar registry system is needed in Japan to evaluate the efficacy of therapies. In addition, such a system might be useful for analysis of genetic markers.

ACKNOWLEDGEMENTS

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