ORIGINAL ARTICLE

Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine

Mark G. Kirchhof, MD, PhD,[a] Monica A. Miliszewski, MD,[a] Sheena Sikora, MD,[b] Anthony Papp, MD, PhD,[b] and Jan P. Dutz, MD[a,c]
Vancouver, British Columbia, Canada

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous reactions, typically to medications, that are associated with a high patient mortality. Controversy exists over which systemic treatments decrease mortality associated with SJS/TEN.

Objective: In this study we sought to determine whether intravenous immunoglobulin (IVIg) or cyclosporine use for SJS/TEN results in better patient outcomes.

Methods: We undertook a retrospective chart review of 71 patients admitted between 2001 and 2011 for SJS/TEN at a tertiary care center of which 64 cases were included in the data analysis. Predicted severity-of-illness score for TEN mortality was compared with actual mortality for patients treated with either cyclosporine or IVIg.

Results: Our cohort demonstrated a relative mortality benefit to the use of cyclosporine in the treatment of SJS/TEN with a standardized mortality ratio of 0.43, over the use of IVIg with a standardized mortality ratio of 1.43.

Limitations: This is single-center retrospective study.

Conclusions: The use of cyclosporine over IVIg may offer a greater mortality benefit in the treatment of SJS/TEN. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2014.07.016.)

Key words: cyclosporine; intravenous immunoglobulin; Stevens-Johnson syndrome; toxic epidermal necrolysis.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous reactions, typically to drugs, that are the result of immune activation and keratinocyte death.[1] Patients with SJS/TEN present with a spectrum of symptoms including conjunctivitis, mucocutaneous ulcers, and a macular exanthema that can progress with the formation of flaccid bullae and epidermal sloughing. Patients who present with epidermal sloughing involving less than 10% of their body surface area (BSA) are classified as having SJS, whereas patients with 10% to 30% BSA are in the SJS/TEN overlap group, and patients with more than 30% BSA are classified as having TEN.[2,3] The mortality of SJS/TEN can be quite high with rates for SJS estimated to be between 1% and 5%, whereas

Abbreviations used:

BSA:	body surface area
IVIg:	intravenous immunoglobulin
SCORTEN:	severity-of-illness score for toxic epidermal necrolysis
SJS:	Stevens-Johnson syndrome
SMR:	standardized mortality ratio
TEN:	toxic epidermal necrolysis

From the Department of Dermatology and Skin Science,[a] Division of Plastic Surgery, Department of Surgery,[b] and Child and Family Research Institute,[c] University of British Columbia.
Funding sources: None.
Conflicts of interest: None declared.
Accepted for publication July 9, 2014.
Reprint requests: Mark G. Kirchhof, MD, PhD, Department of Dermatology and Skin Science, University of British Columbia, 835 W 10th Ave, Vancouver, BC, V5Z 4E8 Canada. E-mail: kirchhof.mark@gmail.com.
Published online July 30, 2014.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2014.07.016

rates for TEN are between 25% and 30%.[2,4] To assess patients with SJS/TEN, the severity-of-illness score for TEN (SCORTEN) has been developed and is used to predict mortality.[5-8] Given the difficulty in designing and implementing randomized trials for therapeutic interventions for SJS/TEN, clinicians have assessed the efficacy of treatments using the SCORTEN-predicted mortality and comparing this with actual mortality.[9-12]

Treatment for SJS/TEN consists primarily of identification and cessation of the offending medication along with supportive measures.[1,13] Systemic treatments have also been used. Systemic corticosteroids, intravenous immunoglobulin (IVIg), and cyclosporine have been the most studied therapies for SJS/TEN.[1,13,14] Unfortunately, studies regarding the efficacy of these systemic medications for SJS/TEN have provided mixed and often conflicting results. Some studies have found that systemic corticosteroids are associated with increased rates of infection, longer hospital stays, and higher mortality, whereas others have found some benefit to the use of corticosteroids.[9,15-17] Because of these conflicting results and the possible risk of increased mortality with corticosteroids, IVIg and cyclosporine use has increased among clinicians treating SJS/TEN. However, even the mortality benefit of IVIg has been questioned with some studies showing an increased risk of mortality.[11,18-20] Conversely, the use of cyclosporine has been supported by relatively few case reports and case series, which have shown a benefit including halting progression of disease and decreasing the overall mortality.[21-27] In this retrospective study we examined the mortality of patients with SJS/TEN treated with cyclosporine or IVIg. The results from this study provide evidence for systemic treatments for SJS/TEN and may help guide clinicians in their treatment choices.

CAPSULE SUMMARY

- Stevens-Johnson syndrome/toxic epidermal necrolysis can be a life-threatening mucocutaneous reaction and is often systemically treated with intravenous immunoglobulin.
- In this retrospective chart review, patients treated with intravenous immunoglobulin had a higher mortality than predicted by the severity-of-illness score for toxic epidermal necrolysis algorithm, whereas those treated with cyclosporine had a lower mortality.
- Our study suggests a potential therapeutic benefit to cyclosporine vs intravenous immunoglobulin in the treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis.

METHODS

The procedures and protocols of this study were reviewed and approved by the Clinical Research Ethics Board of the University of British Columbia. Using the *International Classification of Diseases Version 9* codes for SJS/TEN, we were able to identify 62 patients admitted from January 2001 to December 2011 to Vancouver General Hospital, British Columbia, Canada, for SJS/TEN. Vancouver General Hospital serves as a referral center for the majority of SJS/TEN cases in the province as it has a dermatology service on call and the largest burn treatment center in British Columbia. In addition, to these 62 patients a further 9 patients with SJS/TEN were identified from our dermatology consult service database. In total, 71 patients with possible SJS/TEN were identified. The charts of these 71 patients were reviewed and evaluated for inclusion in our study. Exclusion criteria included: (1) incompatible clinical assessment, (2) incompatible biopsy results, and (3) clinical history of autoimmune bullous disease or other diagnoses that might mimic SJS/TEN. Patients with SJS/TEN were managed according to treatment protocols established at our hospital, which included involvement of a variety of specialists (eg, dermatologists, ophthalmologists, plastic surgeons). In general, treatment involved withdrawal of the suspected drug if it had not been stopped earlier, and supportive care, which included wound dressing, fluid and electrolyte resuscitation, nutritional supplementation, and antibiotics if warranted. In severe cases, patients were transferred to the burn department or the intensive care department for ongoing high acuity care. The primary end point of this study was in-hospital mortality of patients treated with either cyclosporine or IVIg.

Data collected from the reviewed charts included patient demographics (age, sex), comorbid medical conditions, time of onset of symptoms, time to hospital presentation, length of stay in hospital, BSA detachment at admission, maximal BSA, dose and timing of IVIg or cyclosporine, corticosteroid administration before admission, and mortality outcomes. SCORTEN values were calculated at time of admission to hospital, as was done in the initial SCORTEN derivation.[3,5,7] According to the SCORTEN, 1 point is given for each clinical or biochemical risk factor, which included age greater than 40 years, presence of malignancy, heart rate over 120 beats per minute, BSA detachment

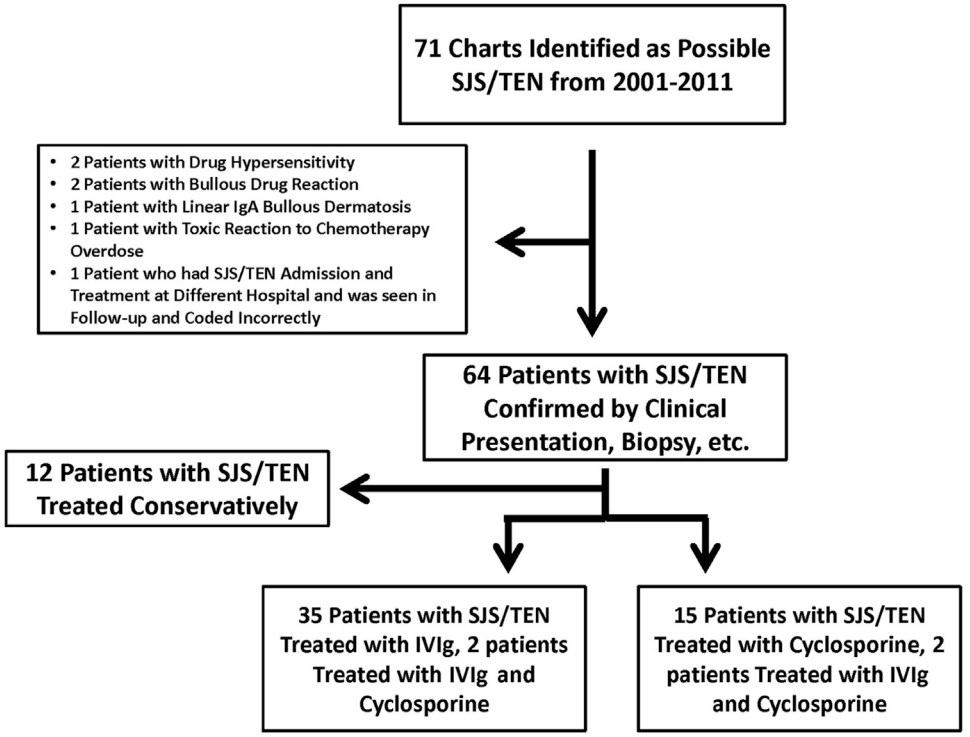

Fig 1. Flow diagram showing patient evaluation and assignment for inclusion in this retrospective study of cyclosporine versus intravenous immunoglobulin (*IVIg*) treatment for Stevens-Johnson syndrome (*SJS*)/toxic epidermal necrolysis (*TEN*).

more than 10%, serum glucose higher than 14 mmol/L (252 mg/d), serum urea higher than 10 mmol/L (28 mg/dL), and serum bicarbonate less than 20 mmol/L (20 mEq/L).[5,7,10] Predicted mortality according to SCORTEN is 3.2% for a score of 0 or 1, 12.1% for 2, 35.3% for 3, 58.3% for 4, and 90.0% for patients scoring 5 or more points.[5,7,10] The predicted mortality was compared with the actual mortality. The standardized mortality ratio (SMR) was calculated for patients (sum of observed deaths/sum of expected deaths). The 95% confidence interval was determined using the Fisher exact test for SMR. Further statistical analysis included the calculation of percentages or means with SD. Statistical significance was determined using the Student 2-tailed *t* test for quantitative variables whereas qualitative variables were compared using the χ^2 test. *P* values less than .05 were considered significant.

RESULTS

We identified 71 patients admitted with a possible diagnosis of SJS/TEN between January 2001 and December 2011 (Fig 1). After chart review, 7 patients were excluded from further evaluation because of an alternate diagnosis. The 64 remaining patient charts were classified according to the systemic treatment received, either IVIg or cyclosporine or supportive measures only. It should be noted that none of the patients received glucocorticoids after evaluation by the dermatology service, however a significant portion were treated with glucocorticoids before admission or dermatologic evaluation. Of the 64 patient, 12 patients were treated with supportive measure only, 35 with IVIg, 15 with cyclosporine, and 2 were treated with both IVIg and cyclosporine. Based on the maximal BSA epidermal detachment, 28 were given a diagnosis of SJS, 19 of SJS/TEN overlap, and 17 of TEN (Fig 2). We also determined the yearly variation in the use of cyclosporine and IVIg (Fig 3). The use of IVIg has been fairly consistent, however, cyclosporine use has shown a dramatic increase particularly from 2009 to 2011. The average dose of IVIg was 1 g/kg/d for 3 days whereas the dose for cyclosporine varied between 3 and 5 mg/kg/d orally or intravenously for an average of 7 days.

The 35 patients treated with IVIg and 15 patients treated with cyclosporine were evaluated for mortality benefit. The 2 patients treated with cyclosporine and IVIg were included in both arms of the study so that any negative or positive effect would be equalized among both treatment groups. Demographic analysis (Table I) showed patients treated with IVIg had a slightly higher average age (54.6 vs 53.2 years) and had a higher proportion of

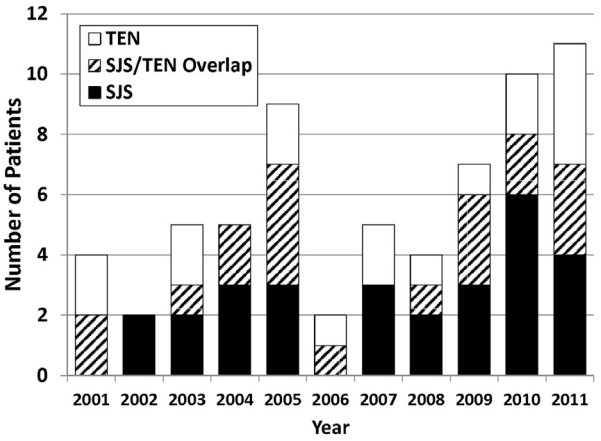

Fig 2. Number of patients with Stevens-Johnson syndrome (*SJS*), SJS/toxic epidermal necrolysis (*TEN*) overlap, and TEN by year of admission.

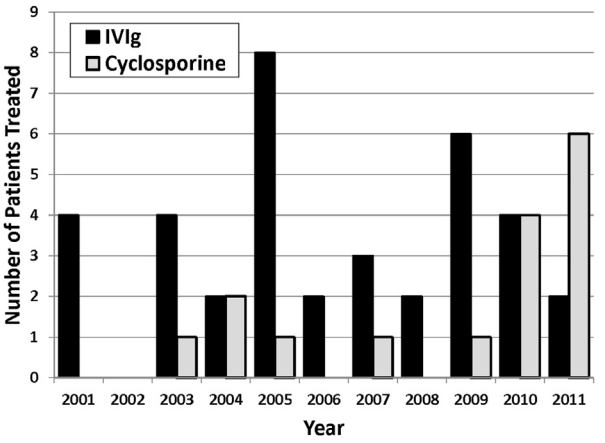

Fig 3. Number of patients receiving either intravenous immunoglobulin (*IVIg*) or cyclosporine by year of admission.

males (48.6% vs 41.2%), although neither were significant differences ($P > .05$). On average, patients treated with IVIg had more severe disease as they had a higher SCORTEN at admission, a greater percentage were classified as SJS/TEN overlap or TEN, and they had a greater maximum BSA of epidermal detachment. Most of these differences were not statistically significant, although the difference in the proportion of patients with SJS was significant ($P = .04$). However, it should be noted that at time of admission, 17 of the patients treated with IVIg (46%) had less than 10% BSA involvement and would have been classified as SJS, in comparison with 11 of the patients treated with cyclosporine (64.7%) and this difference was not statistically significant ($P = .20$). This shows that patients treated with IVIg had progression of epidermal detachment during admission. Furthermore, consideration can be given to using the Bonferroni correction as multiple variables are being compared, which would reduce the P value below .05 and render all demographics between the cyclosporine and IVIg groups insignificant. We also recorded information about corticosteroids administration before admission and show that a similar proportion of patients treated with IVIg or cyclosporine received corticosteroids. One of the reasons IVIg is chosen over cyclosporine is because of the renal toxicity of cyclosporine and we do see that a greater number of patients treated with IVIg had pre-existing renal disease, although this was not significant.

The SCORTEN of patients treated with IVIg or cyclosporine was recorded and based on this the predicted mortality was calculated (Table II). For the 37 treated with IVIg, one would expect a mortality of 20.8% (N = 7.4) and for the 17 patients treated with cyclosporine one would expect a mortality of 14.1% (N = 2.4). The observed morality was 29.7% (N = 11) for IVIg- and 5.9% (N = 1) for cyclosporine-treated patients. The SMR for IVIg-treated patients was 1.43, whereas the SMR for patients treated with cyclosporine was 0.42. The calculated SMR suggests a survival benefit to cyclosporine use and an increased mortality associated with IVIg use. The majority of patients, 66.7% (8 of 12), died because of sepsis and/or multiorgan failure.

DISCUSSION

The systemic treatment of SJS/TEN remains controversial. To date, much of the information regarding IVIg and cyclosporine use has come from case reports, case series, or small open prospective trials. In this retrospective study of IVIg versus cyclosporine, we show a mortality benefit to cyclosporine use and possible increased mortality with IVIg use.

One of the major points of contention between studies examining IVIg has been the discrepancy between low-dose IVIg (0.2-0.5 g/kg) and high-dose IVIg (2-3 g/kg) and the assertion that high doses are necessary to actualize the mortality benefit of IVIg. The total dose of IVIg for patients in this study ranged from 2 to 5 g/kg, which is consistent with previous studies that have shown mortality benefit.[10,14,28-31] A number of studies have shown no mortality benefit to IVIg use even with higher doses,[11,17-20] supporting our findings. In addition, the average time from onset of disease to administration of IVIg was 6 days, which is similar to several studies that show a benefit to IVIg use.[31,32] A recent meta-analysis of IVIg use for SJS/TEN did not show a mortality benefit, except among pediatric patients.[19] Some may criticize the heterogeneity of studies examining IVIg use, with variations in dosing and timing of administration and

Table I. Demographics of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis treated with intravenous immunoglobulin or cyclosporine

	IVIg (N = 37)	Cyclosporine (N = 17)	*P* value
Average age, y	54.6, SD 20.6	53.2, SD 22.2	.83
Male sex	48.6% (N = 18)	41.2% (N = 7)	.61
Average SCORTEN on day 1	2.08, SD 1.23	1.65, SD 1.22	.24
Causative drug withdrawn within 24 h of hospital presentation	81.1% (N = 30)	64.7% (N = 11)	.19
Disease classification based on initial BSA involvement			
SJS	45.9% (N = 17)	64.7% (N = 11)	.20
SJS/TEN overlap	32.4% (N = 12)	23.5% (N = 4)	.51
TEN	21.6% (N = 8)	11.8% (N = 2)	.39
Disease classification based on maximum BSA involvement			
SJS	29.7% (N = 11)	58.8% (N = 10)	.04
SJS/TEN overlap	37.8% (N = 14)	23.5% (N = 4)	.30
TEN	32.4% (N = 12)	17.6% (N = 3)	.26
Average maximum BSA involvement	28.7%, SD 26.6%	16.3%, SD 19.6%	.06
Average time from onset of symptoms to hospital presentation, d	4.3, SD 5.9	8.2, SD 13.2	.25
Average time from admission to initiation of systemic treatment, h	50.1, SD 98.7	26.8, SD 25.3	.19
Average length of hospital stay, d	26.6, SD 28.0	16.8, SD 8.2	.06
Patients receiving corticosteroids before IVIg or cyclosporine	46% (N = 17)	47% (N = 8)	1.00
Patients with pre-existing renal dysfunction	14% (N = 5)	6% (N = 1)	.41

BSA, Body surface area; *IVIg*, intravenous immunoglobulin; *SCORTEN*, severity-of-illness score for toxic epidermal necrolysis; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

Table II. Predicted mortality of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis using severity-of-illness score for toxic epidermal necrolysis versus observed mortality for patients treated with intravenous immunoglobulin or cyclosporine

	No. of patients	
SCORTEN	IVIg	Cyclosporine
0	2	3
1	12	6
2	11	3
3	6	4
4	5	1
5	1	0
Predicted mortality	7.7	2.4
Observed mortality	11	1
Standardized mortality ratio	1.43 (95% CI 0.71-2.56)	0.42 (95% CI 0.11-2.32)

CI, Confidence interval; *IVIg*, intravenous immunoglobulin; *SCORTEN*, severity-of-illness score for toxic epidermal necrolysis.

comorbid conditions of the patient populations, but overall there seems to be enough data to question the benefit of IVIg use for SJS/TEN. Ultimately, a randomized multicenter trial with a significantly large cohort of patients for robust statistical analyses would be necessary to address the continued use of IVIg.

Although the data regarding the use of IVIg have been contradictory, the mortality benefit of cyclosporine is supported by several case reports, case series, and open trials.[11,21,22,24-27] The 2 recent open trials of cyclosporine for SJS/TEN had a combined predicted mortality of 2.86 patients based on SCORTEN, but neither study had any observed deaths.[11,27] In our study, 1 patient died after cyclosporine use and this patient had a complex history with up to 4 months of intermittent allopurinol use and associated rash with oral ulcers. This patient presented to our hospital cachectic from lack of oral intake, intubated and with 40% BSA epidermal detachment. With cyclosporine administration the patient's mucocutaneous condition improved dramatically but this was not sufficient to prevent a deterioration of the patient's overall condition and eventual death from sepsis. The remaining patients treated with cyclosporine survived and this includes 2 patients initially treated with IVIg and then switched to cyclosporine. One of the patients treated with IVIg had a myocardial infarction after 1 dose and was subsequently treated with cyclosporine and recovered. This patient had pre-existing renal disease and the risks of IVIg use in patients with renal disease has been highlighted by a previous study.[18]

There are several limitations to our study that need to be addressed. This is a single-center retrospective study with inherent disadvantages when compared with the ideal multicenter double-blind and controlled trial. However, a double-blind randomized controlled trial comparing IVIG and

cyclosporine is not realistic because of the rarity of the condition resulting in an inability to recruit sufficient patients. The other major criticism of our study is the heterogeneity of the systemic treatment, as dosing and timing of IVIg or cyclosporine was not uniform. In addition, we did not exclude patients based on pre-existing comorbid conditions. Although none of our patients was HIV positive (some studies exclude HIV-positive patients), our IVIg treatment group did have a greater proportion of patients with pre-existing renal dysfunction. Finally, some may criticize the mixing of patients with different disease states of SJS/TEN. Including patients with mild or early SJS considers the fact that clinically we treat patients at all stages of SJS/TEN and as early as possible to prevent progression of the disease. In fact, from our data we show that 6 patients treated with IVIg progressed from SJS to a more severe disease state.

In conclusion, our study suggests a potential therapeutic benefit to cyclosporine use in the treatment of SJS/TEN and questions the purported benefits of IVIg. Although we cannot comment on the actual efficacy of cyclosporine because of the limitations of this study, the data presented here add to reports that suggest cyclosporine use in the setting of SJS/TEN increases the probability of patient survival. There are obvious limitations to this study, but these are inherent to the study of a rare and potentially deadly disease that is difficult to study using controlled and randomized trial methodology.

Dr Dutz is a senior scientist at the Child and Family Research Institute. We thank Boris Kuzeljevic for review of the statistical analysis.

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