ORIGINAL ARTICLE

Efficacy of intravenous immunoglobulins for treatment of Stevens-Johnson syndrome, toxic epidermal necrolysis and their overlap

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ABSTRACT

OBJECTIVE: To evaluate the effect of IVIG in the management of Stevens-Johnson Syndrome (SJS), SJS/TEN (toxic epidermal necrolysis) overlap, and TEN and its possible relation to the outcome in these cases.

PATIENTS & METHODS: Data of patients admitted with the diagnosis of Stevens-Johnson syndrome (SJS), SJS/TEN (toxic epidermal necrolysis) overlap, and TEN were retrieved from the medical database of our hospital. The diagnosis relied on the clinical manifestations. Patients were classified into SJS, SJS/TEN overlap, and TEN on the basis of the body surface area (BSA) that showed epidermal detachment. Age, sex, implicated drug, involved and non-involved sites of the skin and mucous membranes, percentage of BSA involved with tender erythema and/or Nikolsky's sign and skin detachment, and infectious manifestations and complications were recorded. Treatment before and after admission in addition to the outcome of treatment were reviewed.

RESULTS: Thirteen patients [1 male with SJS, 4 with SJS/TEN overlap (3 females and 1 male) and 8 with TEN (5 males and 3 females)] were managed during the period from March 2003 to March 2010. The average age was 48.4 years. Drugs were implicated in all patients (13/13, 100%). The average BSA that showed epidermal detachment was 49%. Five patients (1 with SJS/TEN overlap and 4 with TEN) had received intravenous fluids, corticosteroids, and antibiotics, but not IVIG before admission to our hospital. IVIG were used in an average dose of 3 gm/kg over an average duration of 4.3 days. New blister formation stopped after an average duration of 3.6 days. Complete healing was achieved in 11 (85%) patients after an average duration of 9.2 days. The remaining 2 (15%) patients died because of septicemia while healing of the lesions was going on.

CONCLUSIONS: Drug-induced SJS, SJS/TEN overlap, and TEN are serious conditions that necessitate early therapeutic intervention. We recommend the use of high dose IVIG without using either corticosteroids or prophylactic antibiotics systemically for treating these cases.

KEYWORDS: Adverse cutaneous drug reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, intravenous immunoglobulins.

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INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare acute life-threatening mucocutaneous disorders.[1,2,3] The incidence rates are 1-6 cases/10^6 person-years for SJS and 0.4-1.2 cases/10^6 person-years for TEN.[4] The aetiology of SJS and TEN is usually drug-related (80-95% of patients with TEN and >50% with SJS).[5,6] The commonest drugs triggering TEN are anticonvulsants (phenytoin, barbiturates, and carbamazepine), antibiotics (sulfonamides, ampicillin, and other beta lactam antibiotics), NSAID, and allopurinol.[7,8,9]

SJS and TEN are closely related conditions. They are characterized, in addition to severe constitutional manifestations, by different degrees of sloughing of the skin and erosions of the mucous membrane of the mouth, eyes, and genitalia.[10] Death occurs in up to 18% of patients with SJS.[11] In TEN, mortality is twice as high in elderly patients (51%) than in younger ones (25%).[10]

Treatment consists of discontinuation of the offending drug, admission to a burn unit where intensive supportive care and specialized treatment can be given and attention to the eyes, respiratory tract, fluid and electrolyte balance, nutrition, infection, and pain relief. Adjuvant treatments include plasmapheresis[12], cyclophosphamide[13], cyclosporine,[14,15] corticosteroids,[16,17] tumor necrosis factor-α (TNF-α) inhibitors,[18] and intravenous immunoglobulins (IVIG).[19] The latter was used in several studies and showed promising results in these critical illnesses.[19,20,21]

The aim of this study was to evaluate the effect of IVIG in the management of SJS, SJS/TEN overlap, and TEN and their possible relation to the outcome in these cases.

PATIENTS AND METHODS

The medical database of King Abdullah Medical City (KAMC), the Holy Makkah, Saudi Arabia, was reviewed to retrieve patients with the diagnosis of SJS, SJS/TEN overlap, and TEN who were admitted under the care of dermatology department during the period from March 2003 to March 2010.

The diagnosis based on the clinical findings of acute, widespread epidermal sloughing with/without mucous membrane involvement where the skin looked like a superficial burn. Patients were classified relying on the percentage of the involved BSA; SJS when <10%, SJS/TEN overlap when 10-30%, and TEN when >30% of the epidermis showed detachment; respectively.

Routine laboratory work-up (including complete blood count and chemistry) and repeated cultures of skin, urine, and blood (to look for possible secondary infections) had been performed before and during treatment for all patients.

Data were retrieved for 13 patients. They included: age, sex, causative drug, involved and non-involved sites of skin and mucous membrane, percentage of BSA involved with tender erythema and/or Nikolsky's sign and skin detachment, as well as infectious manifestations and complications.

One patient with SJS/TEN overlap and 4 patients with TEN were referred to our hospital 1-4 days after starting treatment in other hospitals, where they had received intravenous fluids and systemic

Table 1 Age, sex, implicated drug, clinical findings, and disease entity

Patient No.	Sex	Age	Implicated drug	H/O of limited reaction to same drug	ED (%)*	Consistently non-involved skin	MM involvement**	Disease entity
1	Male	62	Ibuprofen	+	70	Scalp	Oral	TEN
2	Male	65	TMP/SMZ	-	60	Scalp	Oral	TEN
3	Male	42	Amoxicillin	-	50	Scalp	None	TEN
4	Male	48	TMP/SMZ	+	75	Scalp	Oral	TEN
5	Male	59	TMP/SMZ	+	90	Scalp	None	TEN
6	Female	15	TMP/SMZ	-	25	Scalp	Oral/ocular	SJS/TEN
7	Female	75	Diclofenac sodium	-	70	Scalp	Oral	TEN
8	Female	49	Phenytoin	+	60	Scalp	Oral	TEN
9	Male	40	Piroxicam	-	15	Scalp	Oral	SJS/TEN
10	Female	17	Allopurinol	-	25	Scalp	Oral/ocular	SJS/TEN
11	Male	38	TMP/SMZ	-	8	Scalp	Oral	SJS
12	Female	58	Allopurinol or Ibuprofen	-	28	Scalp	Oral	SJS/TEN
13	Female	61	TMP/SMZ	-	60	Scalp	Oral	TEN

TMP/SMZ: Sulphamethoxazole/cotrimoxazole

* *ED (%): Epidermal detachment (%)*

***MM involvement: Mucous membrane involvement*

corticosteroids and antibiotics. The remaining 8 patients, 1 with SJS (with severe oral mucosal and pharyngeal involvement), 3 with SJS/TEN overlap, and 4 with TEN, were admitted to our hospital since the start of the disease process without receiving similar treatment as the first 5 patients.

The SJS patient and the 4 SJS/TEN overlap patients (5/13, 38.5%) were managed in the isolation rooms of the internal medicine department. All patients with TEN (8/13, 61.5%) were admitted in the burn-intensive care unit to provide them the best possible chance for management. The causative drugs were immediately discontinued. Patients with TEN and one patient with SJS/TEN overlap received prophylactic heparinization. All patients were managed using intravenous fluids (to maintain the fluid and electrolyte balance), IVIG, a closed-type dressing for the affected areas, and air-fluidized mattresses. Topical antibiotics were used according to the clinical situation. Neither systemic corticosteroids nor systemic antibiotics were used in the eight patients who were admitted without being prescribed any medication before admission. IVIG (Octagam, Octapharma Co., Switzerland) was infused in high doses to all patients according to the manufacturer's protocol. Octagam is a sucrose-depleted IVIG to minimize the risks of renal failure. The duration of IVIG use was determined by the stoppage of appearance of new blisters. Where, IVIG was given for one more day after halting of blistering. Other medications such as H_2-receptor blockers or proton-pump in-

hibitors (as a prophylaxis to stress ulcer to prevent gastrointestinal bleeding), paracetamol, and oral mycostatin suspension mixed with xylocaine and dexamethasone ampoules had been used to relieve oral pain. Consultations to internal medicine, oral medicine, and ophthalmology were done according to the needs.

The time from start of lesions to stoppage of appearance of new ones after initiation of therapy and then, to complete healing of skin and mucous membrane lesions, complications, and the need for mechanical ventilation were recorded.

RESULTS

Thirteen patients [1 with SJS (with severe oral and pharyngeal involvement), 4 with SJS/TEN syndrome overlap (3 females and 1 male), and 8 with TEN (5 males and 3 females)] were managed during the period from March 2003 to March 2010). The average age of the patients was 48.4 years (range: 15-75 years). The male (7 patients) to female (6 patients) ratio is nearly 1:1. Drugs were implicated in all patients (13/13, 100%). The implicated drugs in TEN syndrome patients were trimethoprim/sulphamethoxazole (TMP/SMZ) in 4 patients, amoxicillin/clavulanate in 1 patient, ibuprofen in 1 patient, diclofenac sodium in 1 patient, and phenytoin in 1 patient. TMP/SMZ was implicated in the SJS patient and in one SJS/TEN syndrome overlap patients. Piroxicam and allopurinol were implicated separately in two SJS/TEN overlap patients. The last patient (Fig.1) was receiving 4 drugs at that time. These involved phenytoin (used for epilepsy for 30 years), metronidazole, allopurinol, and ibuprofen. The last three drugs were prescribed in prescription and started together. We continued the patient on phenytoin during and after her hospital stay with no development of new lesions during or after stopping treatment for SJS/TEN overlap. Four out of the 13 (31%) patients had experienced one form of ACDR of limited extent due to the same drug that was implicated in the current condition.

The average BSA that showed epidermal detachment was 49% (range: 8-90%). Scalp was the part that consistently showed no involvement (13/13, 100%). Oral mucosa was involved in 11 patients (11/13, 84.6%); 1 (1/11, 9%) with SJS, 4 (4/11, 36%) with SJS/TEN overlap, and 6 (6/11, 55) with TEN. Ocular mucosa was involved in the patient (1/13, 8%) with SJS and in one patient (1/13, 8%) with SJS/TEN overlap (Table 1).

Five patients (1 with SJS/TEN overlap and 4 with TEN) had received intravenous fluids, and systemic corticosteroids and antibiotics, but not IVIG before admission to our hospital. Eight patients (1 with SJS, 4 with SJS/TEN overlap and 2 with TEN) received 0.5 gm/kg/day and the remaining 6 patients (with TEN) received 1 gm/kg/day. The average duration before starting IVIG was 2.5 days. The average daily dose of IVIG was 0.7gm/kg and the average duration of IVIG use was 3.5 days (range 3-6 days). The average total IVIG dose used was 2.45gm/kg. New blister formation had halted after an average duration of 4.5 days (range: 2-5 days). Complete healing was achieved in 11 patients (85%) after an average duration of 9.2 days (range: 6-13 days) (Fig. 2). The remaining 2 patients (15%) died while healing of the lesions was going on (Table 2).

Serious complications were encountered in 4 (4/13, 30%) patients with TEN. Septicemia

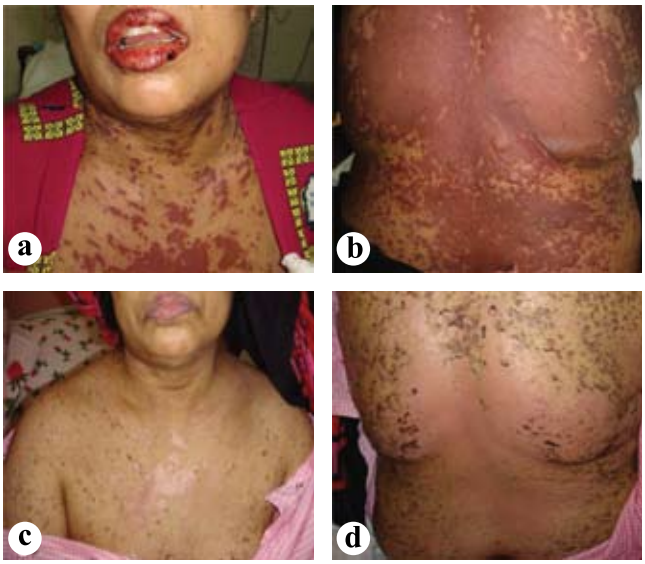

Fig. 1 SJS/TEN overlap in a female patient before (a,b) and after (c,d) treatment with IVIG for 3 days

occurred in all of them and was complicated by septic shock in 3 and by disseminated intravascular coagulation (DIC) in the fourth patient. Two (2/13, 15%) patients required mechanical ventilation, underwent cardiac arrest, and died (Table 3).

DISCUSSION

Most ACDR are benign and transient. Rarely, reactions are serious and potentially life-threatening. The most important of these are SJS, TEN, and drug hypersensitivity syndrome.[21] Recent studies suggest that SJS and TEN are the same disease spectrum with differences in severity and area of involvement.[22,23] Both disorders are of great concern because of their high mortality (25-70%, average: 30%)[24], the pathophysiology of the dramatic death of epidermis which is not fully elucidated, and the lack of a satisfactory treatment to improve disease outcome.[25]

These factors preclude any placebo-controlled studies[26] and mandate early institution of appropriate therapy.

The mechanisms underlying the development of SJS and TEN are not well understood.[27] It has been found that exposure to causative drugs can induce an interaction between the cell-surface death receptor (CD95R/Fas) and its ligand (CD95RL/FasL) which are found to be significantly over expressed in keratinocytes of those patients compared with normal individuals. This ultimately results in extensive keratinocyte apoptosis which is the pathogenic hallmark with subsequent extensive epidermal detachment which is the clinical hallmark of this interaction.[28] Tumor necrosis factor-α (TNF-α) has also been reported to play an important role in the apoptotic pathway that is triggered in TEN.[29,30]

No optimal treatment has been developed for SJS and TEN.[29] It was revealed that antibodies present in pooled purified human immunoglobulins could block this Fas/FasL-mediated apoptosis. Based on this, 10 patients with TEN were treated with 0.2–0.75 gm/kg/d of IVIG for 4 consecutive days with dramatic response. The disease activity was interrupted within 1–2 days of initiating the IVIG therapy and complete re-epithelialization occurred within 4–10 days and no mortality was reported.[25] A single infusion of infliximab (anti-TNF-α) induced rapid and dramatic improvement in a 56-year-old female with TEN.[31]

In this study, it has been noticed that all cases were drug- induced (13/13, 100%). TMP/SMZ was implicated in 6 out of the 13 patients (46%) followed by NSAID (ibuprofen, diclofenac sodium, and piroxicam) in 3 patients (23%). It has been reported that approximately 90% of such cases are caused by an adverse drug reaction.[32] The most commonly im-

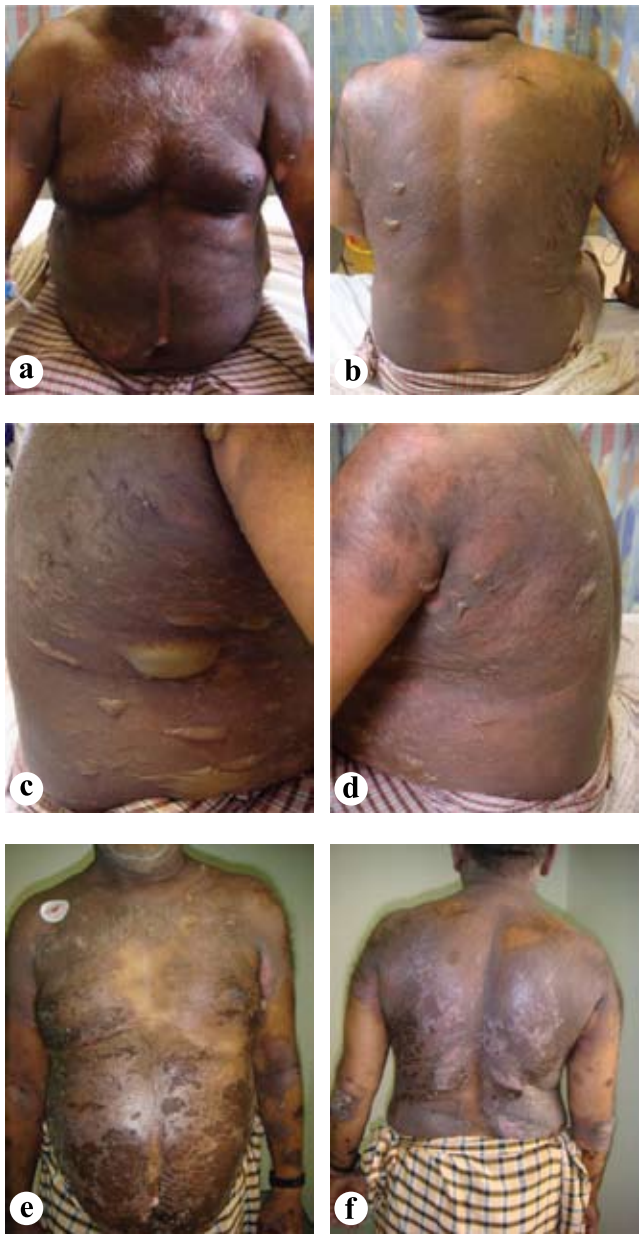

Fig. 2 TEN in a male patient before (a,b,c,d) and after (e,f) treatment with IVIG for 5 days

plicated agents are antibiotics (especially sulfonamides), anticonvulsants (especially carbamazepine and phenytoin) and NSAID.[33,34,35] Less than 5% of cases are linked to other causes such as infection, vaccination, or graft-versus-host disease and in some cases the cause is unknown.[36]

An important clinical finding noted in all our patients (13/13, 100%) was the lack of involvement of the hairy portion of the scalp. This was reported by Roujeau (1993) who stated that "even in extensive disease, the hairy portion of the scalp is generally not affected."[37]

In the current study, the average BSA that showed epidermal detachment was 49% (range: 8-90%). The IVIG infusion was started 1–4 days (average: 2.5 days) after the onset of skin lesions at a dose of 0.5–1.0 gm/kg/day (average: 0.7 gm/kg/day) and continued for 3-6 days (average: 3.5 days). About 2-5 days (average: 4.5 days) passed before stoppage of new blister formation. Eleven patients (85%) showed complete healing within 6 to 13 days (average: 9.2 days) after starting IVIG. Two patients (15%) died before complete healing of skin lesions, but the lesions improved well before death. Four (4/13, 31%) patients developed septicemia. Septicemia occurred as a complication of chest infection in 3 patients and urinary tract infection in the fourth. Two of them developed septic shock and died, and 1 patient had DIC, but improved well. No side effects to IVIG treatment were observed.

The results of the current study and those of other studies are shown in Table (4). Our study is among those studies with small number of patients (n=13). The average age of patients (48.4 years) was higher than that in 7 studies[19,21,29,38,39,42], but lower than that in 3 other studies.[41,343,44] IVIG was used in different doses (0.2-2gm/kg/day) and for different durations (2-6 days) in various studies. In this study, IVIG dose was from 0.5 to 1 gm/kg/day and the range was from 3-6 days. The latter is comparable to that in the other studies. The range of time from the onset of the disease to

Table 2 Medications used and duration for stoppage of new blister formation after IVIG

Patient No.	Use of drugs*	Weight (kg)	Duration before IVIG (days)	IVIG dose (gm/kg/day)	Duration of IVIG infusion (days)	IVIG to stoppage of blister formation (days)	IVIG to complete healing (days)
1	+	95	1	0.5	5	4	Died
2	+	97	2	0.5	5	4	Died
3	-	82	1	1	4	3	7
4	+	75	4	1	6	5	13
5	+	101	4	1	5	4	9
6	+	47	4	0.5	4	3	11
7	-	70	2	1	5	3	8
8	-	49	2	1	5	3	7
9	-	82	1	0.5	4	3	6
10	-	60	2	0.5	3	2	10
11	-	65	2	0.5	3	2	8
12	-	78	3	1	4	3	10
13	-	67	4	0.5	5	4	12

**Use of systemic corticosteroids and antibiotics before and after starting IVIG*

start of IVIG as reported was shorter than most of the studies (1-4 days). Both the time for halting of new blister formation and the time to complete healing were variable among different studies with the first ranging from 1 to 17 days and the second ranging from 3 to 40 days for studies with available data. In the current study, the time for halting of new blister formation and the time to complete healing ranged from 2 to 5 days and 6 to 13 days; respectively, for the 11 alive patients. These are among the lowest ranges for both parameters.

Seven of the previously carried out studies considered IVIG effective in treating SJS and TEN as they had no mortality or low mortality rate.[19,21,29,38,40,41,43] Additionally, the University of Florida (USA) provided its practical guidelines for the management of TEN and SJS including high dose IVIG.[45] However, 3 studies considered it ineffective because of the high mortality rates (32%[39], 41.7%[42], and 25%[44]) despite using adequate doses of IVIG. This is mostly because the titers of Fas inhibitory antibodies vary from batch to batch to a similar extent as the antimicrobial antibodies.[46, 47]

Although each study has its potential bias and that the studies are not strictly comparable, it appears that IVIG at total doses of more than 2 gm/kg during three to five consecutive days is a safe and potentially useful treatment for TEN.[45,48,49] In this study, the average total IVIG dose used was 2.45gm/kg which corroborates the data of the

Table 3 Complications, need for mechanical ventilation, and outcome of SJS, SJS/TEN overlap, and TEN patients

Patient No.	Disease entity	Complications	Ventilation	Outcome
1	TEN	Septicemia/Septic shock	Yes	Death
2	TEN	Septicemia/Septic shock	Yes	Death
3	TEN	None	No	Alive
4	TEN	Septicemia/DIC*	No	Alive
5	TEN	Septicemia	No	Alive
6	SJS/TEN	None	No	Alive
7	TEN	None	No	Alive
8	TEN	None	No	Alive
9	SJS/TEN	None	No	Alive
10	SJS/TEN	None	No	Alive
11	SJS	None	No	Alive
12	SJS/TEN	None	No	Alive
13	TEN	None	No	Alive

**Disseminated intravascular coagulation*

previous authors.

Serious septic complications were encountered in 4 patients (31%) with TEN in the current study. This could be related to systemic corticosteroids and antibiotics before admission to our hospital. The mortality rate (15%) is close to that of the studies which indicated ineffectiveness of IVIG in treating TEN. This study has a smaller number of patients and we believe that IVIG had an effective role in treating our patients in general, particularly those for whom neither corticosteroids nor prophylactic antibiotics were used systemically. An evidence for this is the rapid and smooth healing of the skin and mucous membrane lesions in patients who did not use the latter drugs. The cause of death was septicemia that was complicated by septic shock and subsequent multiorgan failure. The non-judicious use of systemic corticosteroids and antibiotics had possibly a major role in inducing the emergence of the multidrug resistant Gram-negative strains that were implicated in the irreversible complications and death.

Systemic corticosteroids have been used in the management of these conditions. Their use is controversial and studies have demonstrated increased mortality in corticosteroid-treated patients.[50,51] This is possibly because corticosteroid-induced down-regulation of nuclear factor kappa beta (NFκβ) in the presence of elevated TNF-α levels may be proapoptotic and may account for these observations.[52] Another possibility is that their immunosuppressive activity promoted the appearance of infectious complications and masked the early signs of a possible septic picture, thus postponing the beginning of treatment with all its subsequent risks. Additionally, their use results in

Table 4 Some studies of intravenous immunoglobulins (IVIG) therapy in patients with SJS/TEN overlap and TEN

Study (y)	No. of patients	Age (y); mean (range)	Disease entity	IVIG dose (gm/kg/ day)	Duration (days)	Duration before starting IVIG; mean (range)	Time to stoppage of blister formation; mean (range)	Time to complete healing; mean (range)	Mortality (%)
1. Tristani-Firouzi et al., (2002)[19]	8	8.1 (22m-21y)	TEN	0.5-0.75	4	3.2 (2-5)	2.1 (1-4)	8.1 (3-14)	0
2. Al-Mutairi et al., (2004)[21]	12	27.2 (7-50)	TEN	0.5-1	4	1-3 (1.58)	1-5 (2.83)	7.33 (5-13)	0
3. Viard et al.,(1998)[29]	10	39.4 (11-88)	SJS or TEN	0.2-0.75	4	2-5	1-2	6.9 (4-12)	0
4. Prins et al.,(2003)[38]	48	43 (4-95)	SJS/TEN or EN	0.4-0.7	4±0.9	2-30	1-6	15±9.5 (4-40)	12
5. Bachot et al.,(2003)[39]	34	47 (13-88)	SJS or TEN	1-2	2-5	1-9	1-6	3-75	32
6. Trent et al.,(2003)[40]	16	42.8 (19-62)	TEN	1	4	3.5 (1-17)	3.75 (1-17)	8.5 (4-23)	6.25
7. Campione et al., (2003)[41]	10	49	TEN	0.4	5	NAD	NAD	NAD	10
8. Brown et al., (2004)[42]	24	45	TEN	0.4	4	NAD	NAD	9.2	41.7
9. Stella et al.,(2001)[43]	9	54.0 (27-68)	SJS or TEN	0.6-0.7	4	6 (1-15)	6.2 (3-10)	12.2 (7-17)	11
10. Shortt et al., (2004)[44]	16	53 (32-74)	TEN	0.5-0.9	3-5	4.8	NAD	11 (7-16)	25
11. The current study	13	48.4 (15-75)	SJS, SJS/TEN, or TEN	0.5-1	3-6	2.5 (1-4)	4.5 (2-5)	9.2 (6-13) (for 11 patients)	15

SJS: Stevens-Johnson syndrome; SJS/TEN overlap: Stevens-Johnson syndrome/toxic epidermal necrolysis overlap; TEN: toxic epidermal necrolysis; NAD: no available data

delaying the healing process and an increased risk of gastrointestinal hemorrhage. Therefore, several researchers advocate suspension of any such therapy.[53,54]

The prophylactic use of systemic broad-spectrum antibiotics must be discouraged in such patients,[53,55] unless there is leucopenia[56] or there are symptoms of septic complications (fever or hypothermia, oliguria, change in mental state, and paralysed ileum).[55]
SCORTEN as a scoring system was not used in this study to estimate the possible mortality rate among TEN patients because of lack of some parameters that are used to predict mortality among TEN patients such as serum bicarbonate level. Two recent studies showed controversies about the accuracy of SCORTEN as a scoring system in predicting the mortality rate among TEN patients treated in a burn center setting.[57, 58]

CONCLUSIONS

SJS, SJS/TEN overlap and TEN are life-threatening conditions that are usually drug-induced. They necessitate early therapeutic intervention. Based on the available data from the current study and other studies, we recommend the use of IVIG in a dose 0.5gm/kg/day for patients with SJS and SJS/TEN overlap and in a dose of 1gm/kg/day without using either corticosteroids or prophylactic antibiotics systemically for the treatment of these conditions. Further studies need to be done in the form of randomized controlled trials.

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