Original Article

The Clinical Characteristics, Putative Drugs, and Optimal Management of 62 Patients With Stevens-Johnson Syndrome and/or Toxic Epidermal Necrolysis: A Retrospective Observational Study

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Abstract

Background: Case reviews of severe cutaneous adverse drug reactions (ADRs) such as SJS/TEN provide useful insights for clinical characteristics, putative drugs, and management protocols. **Patients and Methods:** Medical charts of 62 (m:f- 20:42) patients with SJS/TEN hospitalized between 2010 and 2019 were analyzed retrospectively for clinical attributes, putative drugs and their indications, extracutaneous complications, and therapeutic outcome. The diagnosis was clinical based on established criteria. WHO-UMC scale for reporting ADR and ALDEN algorithm score were used for causality assessment. Therapies were customized based on in-house resources and affordability. **Results:** Cases included were SJS (41.9%), SJS/TEN overlap (33.9%), and TEN (24.2%) aged 4–85 years. Complications included transaminitis (69.4%), lymphadenopathy (15.5%), septicemia (11.3%), and wound infections (4.8%). Aromatic anticonvulsants (37.1%), disease-modifying antirheumatic drugs (25.8%), antiretroviral drugs (12.9%), non-steroidal anti-inflammatory drugs (8.1%), antimicrobials (4.8%), and trihexyphenidyl (3.2%) were major putative drugs. The mean latent period was 16.6 days. The observed 8% mortality was because of primary comorbidities or multiorgan failure. Addition of fresh blood transfusion (BT, n = 11) or IVIg (n = 7) to systemic corticosteroids showed early relief in skin tenderness, improvement in general condition, and re-epithelialization. Only 16% of patients developed sequelae. **Conclusion:** Aromatic anticonvulsants, allopurinol, nevirapine, cotrimoxazole, paracetamol, and diclofenac remain the most implicated drugs. Sulfasalazine, leflunomide, ethambutol, and trihexyphenidyl were uncommon additions. A short course of high-dose dexamethasone in the early stage was useful. Addition of BT or IVIg provided rapid relief. Preexisting HIV disease, kidney disease, and sepsis remain important for in-hospital deaths. Retrospective study design and small number of cases remain major limitations.

Keywords: *Allopurinol, anticonvulsants, corticosteroids, efavirenz, HIV disease, intravenous immunoglobulin, leflunomide, nevirapine, physiological hyperuricemia, SCORTEN, septicemia, severe mucocutaneous adverse drug reactions, sodium valproate, Stevens–Johnson syndrome, sulfasalazine, toxic epidermal necrolysis, trihexyphenidyl*

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe drug hypersensitivity reactions with a propensity for fatal endings.[1,2] *Mycoplasma pneumonia* or *Herpes simplex* virus infection, vaccinations, and allergy to contrast medium are non-drug-related causes.[3,4] Currently, SJS and TEN are considered spectral manifestations (SJS, SJS/TEN overlap, and TEN) of the same entity differing only in extent of mucocutaneous detachment, with TEN being the most severe and potentially life-threatening form.[5] The worldwide estimated annual incidence of SJS-SJS/TEN overlap-TEN is 2–7 cases per million persons; SJS is reported more often than TEN.[3,6] Clinically, patients with first exposure have skin manifestations usually starting 7–21 days after the offending drug is initiated but can be as early as within 2 days after re-exposure to a drug that previously had caused SJS/TEN. A prodrome of fever, malaise, and upper respiratory tract symptoms for 1–3 days precedes eruption of painful, erythematous, dusky or purpuric amorphous patches which evolve into flaccid blisters and hemorrhagic erosions with associated mucosal involvement.[1,3]

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An early diagnosis, withdrawal of the offending drug, and optimum treatment are imperative to prevent systemic complications of fluid and electrolyte imbalance, sepsis, septic shock, hepatitis, renal dysfunction, multiple organ failure, and resultant mortality.[7] However, for want of an ideal treatment protocol, use of systemic corticosteroids, intravenous immunoglobulin (IVIg), cyclosporine, cyclophosphamide, plasmapheresis, and TNFα inhibitors (thalidomide) has remained debatable for variable outcomes.

In practice, the diagnosis is mainly clinical for want of diagnostic criteria, while drug re-challenge test is not recommended. Although apoptotic keratinocytes, partial to full-thickness epidermal necrosis, subepidermal bulla formation, and minimal dermal inflammatory infiltrate are pathognomic, histopathology is rarely performed for diagnosis.[1,2] The exact pathomechanism for such a massive keratinocyte apoptosis in SJS/TEN is poorly understood but considered to be an immune-mediated (type 4c) hypersensitivity reaction among predisposed individuals.[8] Following exposure to the drug(s) or drug metabolites, a potentially antigenic drug-tissue complex forms that triggers the secretion of granulysin, perforin, and granzyme-B by cytotoxic CD8 T-cells and natural killer cells along with increased interaction between FAS ligand and FAS death receptor on keratinocytes, leading to massive keratinocyte apoptosis.[3,9] Genetically susceptible ethnic groups with specific human leukocyte antigen alleles (HLA B*1501, B*5802), old age, immunocompromised state (HIV infection, chemotherapy, hematologic malignancy), polypharmacy, and past hypersensitivity to the drug are common predisposing factors.[10-13] In general, the prognosis is often dictated by the nature of the offending drug(s), local prescription trends, medical infrastructure and treatment policies, and clinical characteristics of patients, which frequently differ across regions. Given the disease-associated high morbidity and mortality, case reviews will provide useful insights for management and devising effective treatment protocols. In this hospital-based retrospective study, we share our experience of 62 patients with SJS/TEN treated and followed-up in our institution.

Patients and Methods

The medical records of all patients with SJS, SJS/TEN overlap, or TEN hospitalized between 2010 and 2019 in this tertiary care hospital were analyzed retrospectively for demographic profile, clinical diagnosis, all medications (indigenous, herbal, or others) taken within 2–3 months prior to the onset of eruptions, putative drug(s) and its indication(s), comorbidities (infections, pulmonary tuberculosis, hepatorenal disease, connective tissue diseases, immunosuppression, diabetes mellitus, hypertension, internal malignancy), extracutaneous complications, and therapeutic outcome.

The diagnosis was primarily clinical based on history of ingestion of putative drug and characteristic mucocutaneous lesions with or without tenderness, positive (pseudo) Nikolsky's sign, and involvement of two or more mucosal surfaces. The spectrum of SJS, SJS/TEN overlap, and TEN was defined as per criteria given by Bastuji-Garin *et al*.,[5] wherein less than 10% body surface area (BSA) involvement was classified as SJS, BSA involvement of 10%–30% was considered SJS/TEN overlap, and BSA involvement (with skin pain/tenderness) more than 30% without spots or 10% with spots defined TEN. All the patients were interviewed for prodromal symptoms, temporal correlation with drug intake, and drug reactions in the past. Causality assessment was done using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale for reporting adverse drug reactions and in cases with a history of polypharmacy, the causative drug was decided based on the *algorithm of drug causality for epidermal necrolysis* (ALDEN) score.[14,15]

Baseline lab investigations included complete blood counts, blood sugar, and hepato-renal function tests, serum uric acid, urinalysis, chest X-rays, and electrocardiogram. Repeated skin swabs and urine and blood samples were subjected to aerobic culture and antimicrobials sensitivity patterns. When indicated, Mantoux test/computed tomography (CT) scan to exclude pulmonary tuberculosis/disease, echocardiography for cardiac fitness, and other tests relevant to medical history were performed.

Treatment protocol and outcome

After the immediate withdrawal of the suspected drug(s), the actual treatment was individualized for all patients based on affordability and in-house resources available for patient care. Pending investigations, all patients were initiated treatment with intravenous (i.v.) dexamethasone 12 mg in the morning and 8 mg in the evening given daily, amoxiclavulanate 625 mg PO or 1 gm intravenously thrice daily (later modified as per antimicrobial sensitivity patterns), wound care by vaseline gauge dressings after cleansing of erosions with normal saline, oral hygiene with frequent saline swishes and applications of lidocaine fortified clotrimazole mouth paint, enteral/parenteral nutrition, and other supportive therapy for fluid and electrolyte maintenance, including 1–2 units of fresh blood transfusions. The fluid (Ringer lactate, 5% dextrose, normal saline) requirement was calculated using the Parkland formula (fluid requirement = 4 ml/kg body weight × percentage of body surface area involved).[13] Half of the calculated amount was administered in the first 8 h and the other half in the next 16 h during the first 24 h. Thereafter, the fluid replacement was titrated to maintain a urine output between 1000 and 1500 ml. Dexamethasone was switched with oral prednisolone 40–60 mg (1 mg/kg body weight) daily in 7–10 days or after the general condition improved. Oral prednisolone was

tapered off by 10 mg every 5–7 days or earlier thereafter depending upon wound re-epithelialization and overall clinical improvement. When affordable, patients were additionally treated with IVIg 0.4 gm/kg body weight/d for 5 days (approximate cost: INR 1.5 lakh). All patients were treated for primary comorbidities with alternate medications by concerned internists. Ocular involvement was managed by ophthalmologist(s) with regular cleaning and lubricant/antibiotic eye drops/ointments.

Patients were monitored daily for vitals, fluid intake and urine output, serum electrolytes, hepatorenal functions, blood glucose, development of complications (sepsis, respiratory distress, hypothermia, and electrolyte imbalance), clinical activity of the disease, and period of hospitalization. They were followed- up until re-epithelialization of skin lesions or hospital discharge and for late complications thereafter.

Statistical methods

MS Office™ Excel® software was used to tabulate and analyze the data. The continuous data are presented as mean, standard deviation (SD), and categorical variables are presented as frequencies and percentages. Median ± IQR was calculated for data with uneven and wide distribution and extreme values.

Results and Observations

Table 1 depicts the baseline characteristics of 62 patients comprising 20 (32.3%) males and 42 (67.7%) females (m:f- 1:2.1) aged 4–85 years (mean ± SD = 41.2 ± 19.4 years). The majority, 40 (64.5%) patients, was aged between 21 and 60 years. There were 20 (19.4%) children and adolescents; the youngest being a 4-year-old boy. These cases included 26 (41.9%) of SJS, 21 (33.9%) of SJS/TEN overlap, and 15 (24.2%) of TEN. Other

Table 1: Baseline characteristics of patients with SJS-TEN

Baseline Characteristics		Number of patients *n*=62 (%)
Gender	Males	20 (32.3)
	Females	42 (67.7)
	Male:Female	1:2.1
Age	<20 y	12 (19.4)
Range (Mean±SD)	21-40 y	22 (35.5)
4-85 (41.2±19.4) y	41-60 y	18 (29.0)
	61-80 y	9 (14.5)
	>80 y	1 (1.6)
Disease profile	SJS	26 (41.9)
	TEN	21 (33.9)
	Overlap	15 (24.2)
Cutaneous and Extra cutaneous complications	Prodrome/Constitutional symptoms*	58 (93.5)
	Lymphadenopathy	9 (14.5)
	Eosinophilia (AEC >450 cells/cmm)	7 (11.3)
	LFT derangement	43 (69.4)
	Bacteremia	7 (11.3)
	Wound infection	3 (4.8)
	Oral candidiasis	2 (3.3)
Latent interval	<10d	21 (33.9)
Range: 1-60 d	10-20d	18 (29.0)
Median±IQR: (15.0±16.0, lower quartile=7, upper quartile=23) d;	21-30 d	19 (30.6)
Mean±SD 16.6±12.6 d	>30 d	4 (6.5)
Primary Comorbidities	Seizure disorder	13 (21)
	Hyperuricemia/Gout	11 (17.7)
	HIV infection	8 (12.9)
	PUO	7 (11.3)
	Major psychiatric disorder	6 (9.7)
	Trauma/Surgery	5 (8.1)
	Seizure prophylaxis in head injury/subdural hemorrhage/meningioma	3 (4.8)
	Others comorbidities**	9 (14.5)

HIV, human immunodeficiency virus; LFT, liver function tests; PUO, pyrexia of unknown origin; SD, standard deviation; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; d, day; y, year; *Prodrome/Constitutional symptoms: fever (*n*=44), malaise (*n*=19), myalgia (*n*=7), arthralgia (*n*=7), sore throat (*n*=7), headache (*n*=5), nausea (*n*=4), diarrhea (*n*=2). **Others comorbidities include: rheumatoid arthritis (*n*=3), chronic kidney disease (*n*=3), toothache (*n*=2), pulmonary tuberculosis (*n*=1)

complications were transaminitis (n = 43, 69.4%), lymphadenopathy (n = 9, 15.5%), elevated eosinophil counts >450 cells/cmm (n = 7, 11.3%), bacteremia (n = 7, 11.3%), and wound infection (n = 3, 4.8%). While coagulase positive *Staphylococcus aureus* was the most common cause of bacteremia (n = 5), methicillin sensitive *S. aureus*, coagulase negative *S. aureus*, and infection with *Escherichia coli* and *Klebsiella* pneumoniae had complicated wounds in one case each. Two (3.3%) patients also had oral candidiasis.

The most common primary comorbidities were seizure disorder (n = 13, 21%), hyperuricemia/gout (n = 11, 17.7%), and HIV infection (n = 8, 12.9%). Pyrexia (n = 7), major psychiatric disorders (n = 6), accidental or surgical trauma (n = 5), and rheumatoid arthritis (n = 3) were other indications for offending drug intake. Three patients each with head injury/meningioma and chronic kidney disease, respectively, were receiving anticonvulsants or allopurinol as prophylaxis. The latent period varied between 1 and 60 days (mean ± SD = 16.6 ± 12.6 days) and the majority, 37 (59.7%) patients, developed constitutional symptoms and skin lesions within 10–30 days of initiating the offending drug intake.

Table 2 illustrates cases based on the most incriminated drugs**.** Anticonvulsants in 23 (37.1%), disease-modifying antirheumatic drugs (DMRDs) in 16 (25.8%), antiretroviral drugs (ART) in 8 (12.9%), non-steroidal anti-inflammatory drugs (NSAIDs) in 5 (8.1%), antimicrobials in 3 (4.8%), and trihexyphenidyl in 2 (3.2%) patients with psychiatric disorder were the major *very probable* culprit drugs. The offending drug(s) remained unidentified in 5 (8.1%) patients who were either taking indigenous formulations or treatment from other medicine system(s).

Phenytoin (n = 9), carbamazepine (n = 9), lamotrigine (n = 3), and phenobarbitone (n = 2) were *very probable* offending drugs among anticonvulsants. Phenytoin had been combined with carbamazepine (n = 2), phenobarbitone (n = 3), sodium valproate (n = 2), or trihexyphenidyl (n = 1). Two patients were taking lamotrigine in combination with sodium valproate. Ten of the 11 (90.9%) patients taking allopurinol had asymptomatic hyperuricemia or arthralgia of unidentified origin. Nevirapine (n = 7) and efavirenz (n = 1) were the *very probable* culprit ART drugs. Among NSAIDs, paracetamol and diclofenac were the *very probable* offending drugs in one case each as evident from subsequent recurrence after retaking the paracetamol unknowingly and past drug rash from diclofenac. Of the 3 (4.8%) cases caused by antimicrobials, 2 were from cotrimoxazole taken for *Pneumocystis jiroveci* prophylaxis by HIV-positive patients before initiating ART. Sulfasalazine and leflunomide caused SJS-TEN overlap in 1 patient each. Trihexyphenidyl was the *very probable* culprit drug in 2 patients. One patient, a 56-year-old male with nevirapine-induced SJS, died of intracranial bleed and deep vein thrombosis (DVT) after he retook the drug mistakenly a few days after hospital discharge. One patient each who had recovered from ethambutol- or trihexyphenidyl-induced TEN developed SJS after retaking the drug by mistake.

With anticonvulsants, the patients developed skin lesions within 18–21 days (average) after initiating the medication. Allopurinol caused skin lesions on an average of 25 days after initiating medication, while this interval was 2–20 days (average) with NSAIDs and 18–21 days with antimicrobials. The interval between initiating treatment and onset of skin lesions was 10 and 13 days with efavirenz and nevirapine, respectively, and it was about 19 days for trihexyphenidyl.

All 62 patients received supportive therapy and i.v. dexamethasone with tapering off as the wound epithelialization started in 6–7 days (mean: 7–10 days) as per protocol. Additionally, IVIg was given to 7 patients (SJS = 2, SJS-TEN overlap = 3 and TEN = 2) 3–9 days after hospitalization. Other 6 patients of TEN and 5 patients with SJS-TEN overlap received two units of fresh blood on days 3–5 after hospitalization. The average hospital stay was 13.2 days (range: 4–27 days) for dexamethasone alone compared to 13 days (range: 6–27 days) for IVIg plus dexamethasone-treated cases. Although no association between treatment used and the outcome could be ascertained in terms of hospital stay or need for prolonged therapy, it was observed that patients treated with IVIg showed immediate relief in skin tenderness and pain on day 1 itself, early improvement in general condition, wound epithelialization, and withdrawal of dexamethasone. To some extent, similar observations were also made in patients who had received blood transfusion. Except for the death of 5 (8.1%) patients (SJS = 3, SJS-TEN overlap = 1, TEN = 1), all patients recovered completely and were off medication when discharged from the hospital. Fatal cases illustrated in Table 3 show that three patients had died of sepsis-associated multiorgan failure complicating nevirapine-induced SJS, sulfasalazine-induced TEN, and SJS-TEN overlap due to unknown drug. One patient with SJS due to nevirapine died of intracranial bleed and DVT 1 week after retaking the drug and developing TEN. The patient with allopurinol-induced SJS died of renal failure despite receiving hemodialysis. Skin dyspigmentation (n = 8), dry eyes (n = 3), telogen effluvium (n = 2), onychomadesis (n = 1), and scarring (n = 1) were late sequelae noted in 10 (16%) patients on subsequent follow-up.

Discussion

SJS/TEN can occur in patients at any age, including children and both genders, albeit women are reportedly affected more often than men with few exceptions, as was also noted in this study, with females outnumbering males by almost two times.[6,16-18] The SJS in 41.9%, SJS-TEN overlap in 24.2%,

Table 2: Description of cases based on most probable culprit drug

Possible causative drug *n*=62		Number of cases	Causality score*	Mean Age (in years)	Gender (M=20, F=42)	Mean Latency period in days	Diagnosis			Remarks
							SJS (*n*=26)	Overlap (*n*=15)	TEN (*n*=21)	
Anticonvulsants 23 (37.1%)	Phenytoin	9	Very probable	29.3	M=5 F=4	20	4	2	3	Two patients each were also receiving carbamazepine and phenobarbitone
	Carbamazepine	9	Very probable	45.3	M=2 F=7	21	5	1	3	Two patients each were also receiving phenytoin and sodium valproate.
	Lamotrigine	3	Very probable	24.5	F=3	18	1	1	1	Two patients were also taking sodium valproate
	Phenobarbitone	2	Very probable	22.3	M=1 F=1	19	1	1	0	Both patients were also taking phenytoin
DMARDs 16 (25.8%)	Allopurinol	14	Very probable	60.2	M=1 F=13	25	5	5	4	Gout (*n*=1), CKD (*n*=1), Arthralgia (*n*=3) Physiological hyperuricemia (*n*=9)
	Leflunomide	1	Very probable	33	F=1	45	1	0	0	-
	Sulfasalazine	1	Very probable	74	M=1	21	0	1	0	-
ART 8 (12.9%)	Nevirapine	7	Very probable	43.3	M=4 F=3	13	3	3	1	ART (SLN and ZLN regimens, *n*=2 each; TLN regimen, *n*=1). 2 SJS patients died; one of them developed TEN after he retook nevirapine mistakenly
	Efavirenz	1	Very probable	35	M=1	10	1	0	0	ART (TLE regimen)
NSAIDs 5 (8.1%)	Paracetamol	1	Very probable	38	F=1	4	0	0	1	One SJS patient had also taken ofloxacin and cefixime. Redeveloped TEN when took PCM again
	Diclofenac sodium	1	Very probable	60	F=1	8	0	0	1	PCM was other drug in combination. There was no history of drug reaction with PCM in the past
	Mefenamic acid	1	Probable	10	F=1	2	1	0	0	None of them had received any other drug
	Lornoxicam	1	Probable	68	F=1	5	0	0	1	
	Etoricoxb	1	Probable	60	F=1	20	1	0	0	
Antimicrobials 3 (4.8%)	Cotrimoxazole	2	Very probable	47	M=2	18	1	1	0	Taken for *Pneumocystis jiroveci* prophylaxis prior to ART
	Ethambutol HCl	1	Very probable	38	M=1	21	0	0	1	Developed SJS after retaking ethambutol by mistake
Antipsychotics 2 (3.2%)	*Trihexyphenidyl*	2	Very probable	51.5	M=1 F=1	19	0	0	2	One patient re-took the drug and developed SJS
Unknown 5 (8.1%)	Indigenous	5	Probable	32.0	M=1 F=4	13	2	0	3	One patient each treated for psychiatric illness, toothache, aches, PUO, and diarrhea

*Causality assessment was based on World Health Organization-Uppsala Monitoring Centre (WHO-UMC) scale and algorithm of drug causality for epidermal necrolysis (ALDEN) score. Drug re-challenge was not performed in any of the patients. ART-, antiretroviral treatment; CKD, chronic kidney disease; DMARDs, disease-modifying anti-rheumatic drugs; F, female; HIV, human immunodeficiency virus; M, male; NSAIDs, non-steroidal anti-inflammatory drugs; PCM, paracetamol; PUO, pyrexia of unknown origin; SJS, Stevens-Johnson syndrome; SLN, stavudine + lamivudine + nevirapine; TEN, toxic epidermal necrolysis; TLE, tenofovir + lamivudine + efavirenz; TLN, tenofovir + lamivudine + nevirapine

Table 3: Description of fatal cases

Diagnosis	Gender	Age in years	Culprit drug(s)	Primary Comorbidities	Latent interval (in days)	Hospital Presentation (in days)	Casualty by ALDEN algorithm score and WHO-UMC scale	Complications	Treatment given as per protocol	Remarks
SJS	M	56	Nevirapine	HIV infection	23	3 days	Very Probable	Intracranial bleed and deep vein thrombosis right arm	Dexamethasone (i.v.) Supportive therapy	Died 1 week after hospital discharge. He had developed TEN after retaking nevirapine.
SJS	M	52	Nevirapine	HIV infection	30	4 days	Very Probable	Pneumonia, Respiratory distress	Dexamethasone (i.v.) Supportive therapy	Died on 2nd day of hospitalization
SJS	F	38	Allopurinol	CKD	19	20 days	Very Probable	Renal failure	Dexamethasone (i.v.) Supportive therapy Hemodialysis	Died on 10th day of hospitalization
TEN	F	26	Unknown	Major psychiatric disorder	Not known	3 days	Probable	Multi-organ failure ? sepsis	Dexamethasone (i.v.) Supportive therapy	Died after 12 days of hospitalization
Overlap	M	74	Sulfasalazine	Rheumatoid Arthritis	21	14 days	Very Probable	Multi-organ failure ? sepsis	Dexamethasone (i.v.) Supportive therapy	Died on 2nd day of hospitalization

*Drug re-challenge was not performed in any of the patients. ALDEN, algorithm of drug causality for epidermal necrolysis; CKD, chronic kidney disease; HIV, human immunodeficiency virus, SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; WHO-UMC, World Health Organization-Uppsala Monitoring Centre

and TEN in 24.2% cases and overall profile of associated extracutaneous complications, and the incriminated drugs such as anticonvulsants, particularly the aromatic compounds (phenytoin, carbamazepine, phenobarbitone, lamotrigine), antimicrobials (sulfonamides), allopurinol, NSAIDs, and nevirapine, and the onset of SJS/TEN in less than 7–21 days with anticonvulsants, and up to 2 months of initiating the other treatments in this study is more or less in sync with the reported literature.[3,6,10,16] Interestingly, lamotrigine has been used frequently in combination with sodium valproate. Whereas the estimated risk of lamotrigine-induced SJS/TEN is 2.5 per 10,000 new users, its co-administration with sodium valproate significantly increases this risk due to inhibition of its glucuronidation, thereby increasing its half-life from 25–30 h to almost 60 h.[10,19-21] This calls for emphasizing the significance of adherence to the updated guidelines for lamotrigine prescription. We note that sulfonamides remain the most common antimicrobial drug, while ethambutol causing SJS/TEN in one of our patients is a rare occurrence.[22-24]

Allopurinol is another commonly prescribed prophylactic drug for gout and CKD-associated hyperuricemia. However, despite being a frequent cause of SJS/TEN across studies, the majority of prescriptions apparently have been for asymptomatic hyperuricemia as was noted in our more than 90% cases taking allopurinol.[16,24-46] In contrast to a previous report of SJS/TEN in 19.6% of patients from paracetamol, ibuprofen, diclofenac, nimesulide, and etoricoxib, only paracetamol and diclofenac had caused TEN in our one case each, perhaps from their comparatively more frequent use in our setup rather than having a higher propensity for toxicity.[16] Among ART drugs, nevirapine has been associated with greater risk for developing SJS/TEN compared to others.[27,28] Nevirapine had caused SJS/TEN in our 7 of 8 patients, accounting for 87.5% of our HIV patients, comparable to 84% of 50 patients in another study.[29] However, efavirenz with one case of SJS in this study remains an uncommon cause for SJS/TEN.[30,31] Trihexyphenidyl appears to be an emerging addition to the ever-evolving list of putative drugs for SJS/TEN.

Maintaining nutrition, fluid and electrolyte balance, care of mucocutaneous ulcerations, and prevention of systemic complications is the mainstay for the management of these patients. Despite being controversial, the use of corticosteroids in high doses for a brief period, and cyclosporine (3–5 mg/kg body weight) early in the course of the disease has shown to stop the progression of epidermal necrosis and reduce morbidity and mortality.[13,32] In addition to withdrawal of the offending drug and supportive treatment, all our patients received i.v. dexamethasone immediately after hospitalization and IVIg in fewer cases. In general, the outcome was not affected with respect to the duration of delay in treatment initiation, the duration of treatment, re-epithelialization time, and mean duration of hospital stay. Studies have

reported decreased mortality in TEN patients treated with intravenous immunoglobulin.[33-35] However, it did not improve mortality compared with the group that received supportive therapy alone in a few studies.[36,37] We feel that this variability could be because of doses used from very low to high. Nevertheless, major beneficial effects noted in our patients were rapid pain relief, reduced healing time, shortened clinical course, and possibly increased survival as has been reported previously.[35,38,39] It is also possible that these additional benefits of IVIg were from its combination with dexamethasone as reported previously as well.[40] Whether fresh blood transfusion besides correcting hypovolemia and anemia will improve outcome in terms of faster disease control and reduced morality in SJS/TEN patients noted in this study and previously perhaps needs validation with more studies.[41]

SJS/TEN is usually associated with significant morbidity and mortality with estimated mortality ranging from 10% in SJS to >40% in TEN with respiratory failure, and sepsis-related multiorgan failure being the most common causes of in-hospital deaths as was also noted in 8.1% of cases in our study.[42-44] The prognosis of individual patients is usually evaluated on days 1 and 3 of hospitalization by SCORTEN.[1,45,46] However, SCORTEN is reportedly overestimates the mortality rates since patients dying of sepsis and other comorbidities such as HIV disease, CKD as noted in this study are not included in the scoring system limiting its utility in practice.[47,48] Cutaneous dyspigmentation, dry eyes, telogen effluvium, onychomadesis, and scarring are well-described late sequelae of the disease.[9]

Limitations

A retrospective study design and a small number of patients for stratification, particularly for the IVIg group, to compare treatment outcomes remain major limitations to make any recommendation. Some of the information was not included in medical charts, limiting data retrieval. We could not quantify the mortality risk for want of all the SCORTEN parameters for analysis due to inconsistent data recorded in case files. The significance of data analysis for efficacy of IVIg or fresh blood transfusion remains limited as only fewer patients had received them. Cyclosporine was not used in any of the patients.

Conclusion

Aromatic anticonvulsants, allopurinol, nevirapine, cotrimoxazole, paracetamol, and diclofenac remain the most common drugs causing SJS/TEN. Sulfasalazine, leflunomide, ethambutol, and trihexyphenidyl appear uncommon additions, further expanding the list of putative drugs. It will be prudent to limit allopurinol prescriptions to symptomatic cases only and not to combine lamotrigine with sodium valproate. Immediate management is targeted toward withdrawal of the offending drug, supportive measures, and prevention of systemic complications. In addition, a short course of systemic dexamethasone in higher doses in the early stage was useful in limiting the progress of the disease in 92% of our patients and faster epithelialization. Combining dexamethasone with fresh blood transfusion or IVIg provides rapid relief in pain, reduced healing time, and shortened clinical course. Pre-existing HIV disease, CKD, and sepsis remain important causes of in-hospital deaths in 8% of patients and perhaps need to be included as additional parameters in the SCORTEN scoring system for estimating mortality. Educating the patient and the caretakers for avoidance of offending drugs in the future by all means is imperative.

Statement of ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. All patients were provided standard medical treatment and care.

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Conflicts of interest

There are no conflicts of interest.

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