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A Retrospective Study into Causes and Treatments of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Iranian Patients

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ABSTRACT

Aims Stevens-Johnson syndrome and toxic epidermal necrolysis are serious severe cutaneous adverse reactions with high mortality and morbidity induced by medications. In this cross sectional study, we investigated, suspected drugs, and potential treatments of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

Methods A cross- sectional descriptive study was conducted on 60 patients admitted with a diagnosis of Stevens-Johnson Syndrome (47 patients) or Toxic Epidermal Necrolysis (13 patients). Except for the therapeutic procedure, data related to pharmacological causes and treatment was obtained from electronic medical records. They were treated daily with either co-administration of intravenous immunoglobulin (1-2mg/kg) and corticosteroid (Prednisolone Forte 1-2mg/kg; maximum 60mg/kg) or exclusive corticosteroid.

Findings Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis were more frequent among females (56.7%) and young people (73.4%). Sepsis was observed in 11.8% of Stevens-Johnson Syndrome patients treated with intravenous immunoglobulin and corticosteroid (mean hospitalization days 2.2±0.6) but not in those who were treated with a corticosteroid (mean hospitalization days 1.6±0.5 days), though all Stevens-Johnson Syndrome patients improved after treatment. In Toxic Epidermal Necrolysis patients, 76.9% of the them showed sepsis that received intravenous immunoglobulin and corticosteroid. The mortality rate was 5%. Antibiotics and anticonvulsant drugs were found to be the main causes of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

Conclusion Either intravenous immunoglobulin and corticosteroid or corticosteroid treatments seem to be effective for Stevens-Johnson Syndrome improvement. Potential drug Causes of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis included Antibiotics and anticonvulsant drugs.

Keywords Anticonvulsants; Adrenal Cortex Hormones; IVIG; Phenobarbitals; Lyell's Syndrome

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare drug-associated mucocutaneous disorders with severe morbidity and mortality [1]. They are determined by the conditions like necrotic epidermis detachment and mucous membranes erosions. Body surface detachment occurs in less than 10% of SJS patients while in TEN patients, the involvement of skin detachment is more than 30%. SJS/TEN overlap is defined by 10-30% of skin area detachment [2, 3]. 1.2 to 6 patients per million develop SJS annually worldwide with morbidity and mortality rates less than 10%. The global incidence of TEN is 0.4 to 1.2 patients per million per year with a mortality rate of approximately 50% [2, 4]. The mortality rate for SJS/TEN overlap is approximately 30%. Age, underlying diseases as well as the severity of skin detachment, and the time of onset reaction, are considered the effective factors in SJS/TEN development and mortality rate [4].

Although reactions to some medicines are known to be the main cause of SJS (50-80%) and TEN (about 80%) [1, 5], infections are known as the main cause of SJS/TEN in children [1]. The pathogenesis of drug-induced SJS/TEN may be rooted in the presentation of major histocompatibility complex (MHC) in response to drugs or their metabolites leading to active T cell production [6]. The interaction of drugs and MHC molecules is mediated through two mechanisms: the direct binding of drugs to MHC molecules, a complex that is recognized by the T cell receptor (TCR). The second mechanism involves the intermediary role of TCR. Both structures stimulate the activation of immune responses [4, 7].

Although no absolute therapy has been fully established for SJS and TEN, the disease progression can be managed by the early diagnosis and withdrawal of agents inducing SJS/TEN as well as supportive care. The specific pharmacological therapies for SJS/TEN consist of systemic steroids due to their immunosuppressive effects [8, 9]. Other treatments like tumor necrosis factor α (TNF-α) antagonist, thalidomide, and cyclosporine are considered so far. However, the exclusive use of these medicines or in combination with each other has been controversial [10, 11].

Sekula in the study of such patients confirmed high in-hospital mortality and revealed a remarkable number of deaths after discharge, which could mainly be attributed to severe comorbidities and older age, whereas the impact of severity of reaction on the risk of death was limited to the first few weeks [2].

In various studies, most cases of SJS syndrome, especially TEN, are attributed to pharmacological causes. Given the severe side effects and even mortality that may occur following these drug reactions, it is important to identify the most common drugs that cause these reactions. Therefore, this study aimed to investigate risky medicines inducing SJS/TEN, and the potential therapeutic effects of corticosteroids and a combination of IVIG+corticosteroid treatment.

Instrument & Methods

This is a cross-sectional study. The Census sampling method was used. The participants were 60 patients diagnosed with SJS and TEN from 2010 to 2018 in Namazi Hospital of Shiraz University of Medical Sciences, Shiraz, Iran. Patients were classified according to their illnesses, either SJS or TEN, based on the most widely accepted consensus defined by Bastuji-Garin *et al.* [12]. Patients with an epidermal detachment of less than 10% and more than 30% were considered SJS and TEN, respectively [13]. Inclusion criteria were the presence of medication, laboratory and treatment orders in the electronic file of patients.

This study has been proposed and approved by the ethics committee in the research of Shiraz University of Medical Sciences. The information was extracted from electronic medical records and gathered using a designed form by researchers. This information included: demographic data, possible drug cause, disease complications, incubation period, type of treatment, associated laboratory disorders, history of underlying disease, length of hospital stay, the season of onset of disease, and previous history of SJS or TEN. Moreover, symptoms, laboratory tests, underlying allergic diseases, medical background in taking medicines, the interval between symptom manifestation and development, and treatment outcome were obtained by reviewing electronic medical records. Laboratory tests that determined the patient's response to treatment were also extracted from patients' electronic medical records. They included ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) as inflammation markers. Kidney function had been assessed by measuring BUN (blood urea nitrogen) and Cr (creatinine). Moreover, dysfunctional liver had been diagnosed relying on the levels of serum SGOT glutamic-oxaloacetic transaminase (aspartate transaminase, AST) and SGPT (glutamic-pyruvic transaminase (alanine transaminase, ALT). To assess whether drugs are probably or very probably responsible for SJS/TEN (based on the ALDEN algorithm [14]), and have a different impact on mortality, patients without and with identified drug causes were distinguished. In addition to underlying factors in SJS/TEN occurrence, the effectiveness of the therapeutic procedure was also investigated. A unique treatment regimen was provided over the 8 years so that SJS patients received a simultaneous treatment of IVIG (1-2mg/kg) and corticosteroid (oral prednisolone; 1-2g/kg, maximum 60mg/kg), while TEN patients underwent corticosteroid treatment (oral prednisolone; 1-2mg/kg, maximum

60mg/kg). White Blood Cell (WBC) counts were assessed before and after administration. After having stable clinical indices and no lesion, either in the oral cavity or on genital and conjunctival mucosa, patients were discharged.

Quantitative variables were expressed by percentage and mean±SD and median (range) used for normal and non-normal distribution data, respectively. The data analysis was performed by GraphPad Prism software V6.01 (GraphPad Software, Inc., San Diego, CA, USA) and SPSS 21 software. A p-value ≤ 0.005 was considered significant.

Findings

The age range of patients was between 3-67 years and the mean±SD age was 17.15±2.68 years old. Overall, females showed disorders more than males (Table 1).

Table 1) Results of frequency demographic data of patients (the numbers in parentheses are in percent)

Variables	SJS (n=47)	TEN (n=13)	All (n=60)
Age Groups (Years)			
1-10	20 (42.6)	5 (38.5)	25 (41.7)
11-20	16 (34.0)	3 (23.1)	19 (31.7)
21-30	5 (10.6)	1 (7.7)	6 (10.0)
31-40	5 (10.6)	2 (15.4)	7 (11.7)
41-50	0	1 (7.7)	1 (1.7)
51-60	1 (2.1)	0	1 (1.7)
61-70	0	1 (7.7)	1 (1.7)
Gender			
Male	19 (40.4)	6 (46.2)	26 (43.3)
Female	28 (59.6)	7 (53.8)	34 (56.7)

Most of the patients had one or more prodromal symptoms such as cough (46.7%), headache (61.7%), and fever (86.7%, as the most frequent manifestation). Ocular complications were exhibited in 75% of the population, making it the second highly occurring symptom. Moreover, oral mucosa detachment involved approximately as many patients as headache, with 35% frequency compared to 37%, respectively. Also, underlying allergic diseases such as rhinitis (26.7%), asthma (15%), and urticaria (15%) whose frequencies were of the lowest occurrences before death (with only three casualties) were observed among patients. Among SJS patients that were treated with the only corticosteroid, no sepsis was reported, while 4 (11.8%) of SJS patients who have been treated with the combination of IVIG+corticosteroid, had sepsis (Figure 1).

Based on medical records, SJS/TEN sufferers showed abnormal paraclinical manifestations. In SJS patients, 4 (6.7%) and 2 (3.3%) people had varicella-zoster virus (VZV) infection and herpes simplex virus-1 (HSV-1) infection, respectively. A total percentage of 23% of the patients had sepsis, with a greater frequency in TEN patients compared with the SJS group (76.9% vs 8.5% for TEN and SJS). Two TEN patients with sepsis died (Table 2).

The second major drugs were anticonvulsants with a mean day of drug intake of 13.05±6.08 ranging from 6 to 28 days. They included phenobarbital (16.7%), sodium valproate (8.3%), lamotrigine (8.3%), and carbamazepine (5%). Its mean day of intake was 12.3±5.9 days. Three patients used other medicines including imipramine, hydrochlorothiazide, and vitamin C with mean day intakes of 12, and 5 days for the two first medicines. This item was not available for vitamin C (Table 2).

During the therapeutic days, an increase from 5400 to 6700 was seen in the median number of T cells. In contrast, patients' leukocytosis and leukopenia reduced after treatment with 9 (15%) and 17 (28.3%), cases before the treatment and 2 (3.3%) and 1 (1.7%) after medical prescription suggesting the beneficial effects of the treatments (Table 2).

In an attempt to find the medicine which is probably responsible for the incidences of SJS and TEN, we monitored the history of underlying diseases of patients. The majority of patients had received antibiotics (45%), followed by anticonvulsant drugs (38.3%) and other drugs (5%). In addition, three (5%) patients had received two antibiotic drugs together. Although co-trimoxazole, penicillin, cefixime, and azithromycin were among the frequently used drugs, their frequencies lessen when they were used accompanying another medicine. The patients that had been administered antibiotics showed the symptoms of SJS or TEN after a mean duration of 13.5±4.6 with a range of 6-21 days (Table 3).

More precisely, it had taken a mean duration of 13.6±5.4 days ranging from 5 to 28 days for SJS to manifest its symptoms. This period was 9.5±4.3 days with a range of 3-18 days for TEN. Most of the patients showed SJS after 10-20 days they had taken antibiotics while most TEN cases were diagnosed ten days after antibiotics treatment (Figure 2).

After preventing all patients from taking suspected drugs, either IVIG+corticosteroid or corticosteroid treatments began. All TEN patients received IVIG+corticosteroid with a mean day of 3.5±0.9 ranging from 2 to 6 days. Although 72.3% of SJS patients had taken IVIG+corticosteroid (with mean days of 2.2±0.6 with a range of 1-4), others (27.7%) had been exclusively treated with a corticosteroid with mean days of 1.6±0.5 and ranging from 1 to 2 days (Figure 3).

Clinical signs of all patients were improved except for 3 of the TEN patients who died during treatment. The mortality rate was 5% among SJS/TEN patients. T cell numbers were counted before and after treatment (Figure 4). Some SJS patients (n= 44) were treated with IVIG and prednisolone treatment however 11 SJS patients had received only prednisolone. 8 Of 13 TEN patients were treated with IVIG/prednisolone. Any data on the WBC of others was not available.

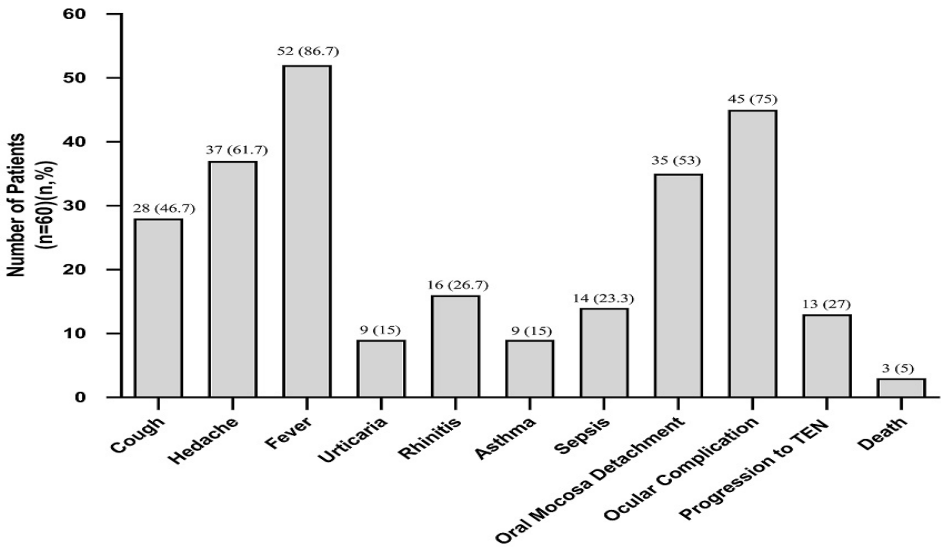

Figure 1) Clinical features of patients

Table 2) Results of laboratory analysis of patients (the numbers in parentheses are in percent)

Laboratory Indices		SJS (n= 47)	TEN (n=13)	Total (n= 60)
ESR (mm/h)				
Normal[1]		5 (10.6)	1 (7.7)	6 (10.0)
Abnormal		41 (87.3)	7 (53.9)	48 (80.0)
NA*		1 (2.1)	5 (38.5)	6 (10.0)
CRP (mg/dl)				
Normal (<10)		1 (2.1)	5 (38.5)	6 (10.0)
Abnormal		45 (95.8)	4 (30.8)	49 (81.7)
NA		1 (2.1)	4 (30.8)	5 (8.3)
Kidney Dysfunction		28 (59.6)	8 (61.5)	36 (69.0)
BUN (mg/dl) Abnormality		8 (17)	0	8 (13.3)
Cr (mg/dl) Abnormality		20 (42.6)	7 (53.8)	27 (45)
Both BUN and Cr Abnormality		0	1 (7.7)	1 (1.7)
Healthy kidney[2]		18 (38.3)	5 (38.5)	23 (38.3)
NA		1 (2.1)	0	1 (1.7)
Liver Dysfunction		21 (42.7)	1 (7.8)	22 (36.5)
SGPT (unit/l); Abnormal		7 (14.9)	0	7 (11.7)
SGOT (unit/l); Abnormal		1 (2.1)	0	1 (1.7)
Both SGPT/SGOT Abnormal		13 (27.7)	1 (7.8)	14 (23.3)
Healthy Liver[3]		24 (51.1)	6 (46.2)	30 (50.0)
NA		2 (4.3)	6 (46.2)	8 (13.3)
Eosinophil				
Normal (<400 ml)		46 (97.9)	8 (61.5)	54 (90.0)
NA		1 (2.1)	5 (38.5)	6 (10.0)
Neutrophil				
Normal (1500- 6000 /ml)		30 (63.8)	7 (53.8)	37 (61.7)
Neutrophilia (>6000/ml)		3 (6.4)	1 (7.7)	4 (6.7)
Neutropenia (<1500 ml)		13 (27.7)	0	13 (21.7)
NA		1 (2.1)	5 (38.5)	6 (10.0)
Lymphocyte				
Normal		24 (51.1)	6 (46.2)	30 (50.0)
Lymphocytopenia (<2500/µl)		22 (46.8)	3 (23.1)	25 (41.7)
NA		1 (2.1)	4 (30.8)	5 (8.3)
Sepsis				
Positive		4 (8.5)	10 (76.9)	14 (23.3)
Negative		41 (87.2)	3 (23.1)	44 (73.3)
NA		2 (4.3)	0	2 (3.3)
WBCs[4]				
Normal (4000- 10000/ml)	Before	25 (53.2)	8 (61.5)	33 (55)
	After	41 (87.2)	8 (61.5)	49 (81.7)
Leukocytosis (>10000/ml)	Before	7 (14.9)	2 (15.4)	9 (15)
	After	2 (4.3)	0	2 (3.3)
Leukopenia (<4000/ml)	Before	14 (29.8)	3 (23.1)	17 (28.3)
	After	1 (2.1)	0	1 (1.7)
NA	Before	1 (2.1)	0	1 (1.7)
	After	3 (6.4)	5 (38.5)	8 (13.3)

*NA: Not Applicable; [1](Male: 0-22, Female: 0-29); [2](BUN: 7-20, Cr: male: 0.6 to 1.**2,** female: 0.5 to 1.1); [3](SGOT:5-40), (SGPT:7-56); [4]the number of WBCs (Median, Range) before of treatment was 4750 (1000- 2800), 6400 (3600- 14600), 5400 (2800-16400) for SJS, TEN, and total patients, respectively, and after of treatment it was 6700 (1000-110000), 6800 (4700- 8200), and 6700 (1000- 10000) for SJS, TEN, and total patients, respectively.

Table 3) The comparison of different drugs in terms of the time it took for SJS and TEN to appear after taking each medicine, and the frequencies of different medical measures as well as the time the illness started to improve (n=60)

Drugs	Patients n (%)	Duration of Appearance (Mean of Days ±SD)	Treatment		Duration of Improvement (Mean of Day±SD)
			IVIG+Corticosteroid n (%)	Corticosteroid n (%)	
Antibiotic Drugs	27 (45)	13.5±4.6	0	0	0
Co-trimoxazole	5 (8.3)	11.2±4.3	6 (100)	0	13.3±5.5
Penicillin	4 (6.7)	15.5±1.2	4 (80)	1 (20)	9.4±3.5
Cefixime	4 (6.7)	11±6.8	2 (50)	2 (50)	10.25±6.8
Cefalexin	3 (5.0)	10±2.8	3 (100)	0	10±3.5
Ciprofloxacin	2 (3.3)	17±1.4	1 (50)	1 (50)	7.5±0.7
Amoxicillin	2 (3.3)	11±6.8	1 (50)	1 (50)	10.25±6.8
Azithromycin	2 (3.3)	11±7.0.7	2 (100)	2 (100)	8.5±2.1
Ofloxacin	2 (3.3)	19.5±2.1	0	2 (100)	6.5±0.7
Rifampin+Co-trimoxazole	1 (1.7)	18.0±0.0	1 (100)	0	19.0±0.0
Penicillin+Cefixime	1 (1.7)	15.0±0.0	1 (100)	0	8.0±0.0
Acyclovir+Azithromycin	1 (1.7)	14.0±0.0	1 (100)	0	12.0±0.0
Anticonvulsant Drugs	23 (38.3)	13. 5±6.4	0	0	0
Phenobarbital	10 (16.7)	12.3±5.9	9 (90)	1 (10)	11.1±3.8
Sodium valproate	5 (8.3)	10.5±3.1	4 (80)	1 (20)	9.4±3.3
Lamotrigine	5 (8.3)	16.6±7.5	4 (80)	1 (20)	10.6±4.2
Carbamazepine	3 (5.0)	16.3±9.2	3 (100)	0	10.6±3.1
Others	3 (5.0)	13.2±8.2	0	0	0
Imipramine	1 (1.7)	12.0±0.0	1 (100)	0	12.0±0.0
Hydrochlorothiazide	1 (1.7)	5.0±0.0	1 (100)	0	2.0±0.0
Vitamin C	1 (1.7)	0	1 (100)	0	15.0±0.0
NA*	7 (11.7)	0	0	0	18.0±0.0

*NA: Not Applicable

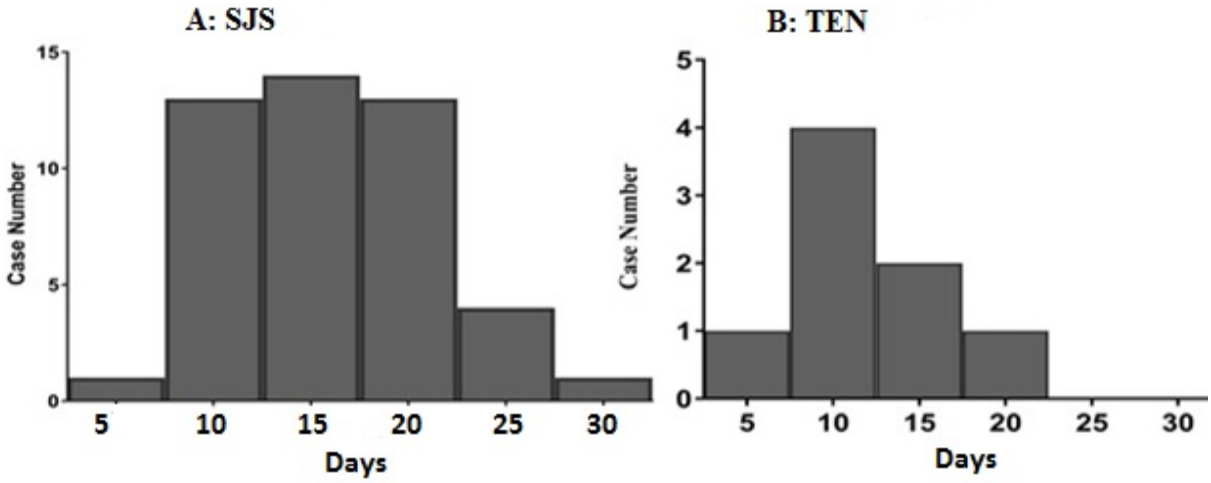

Figure 2) The first day of drug causality SJS and TEN intake and first symptoms (A and B)

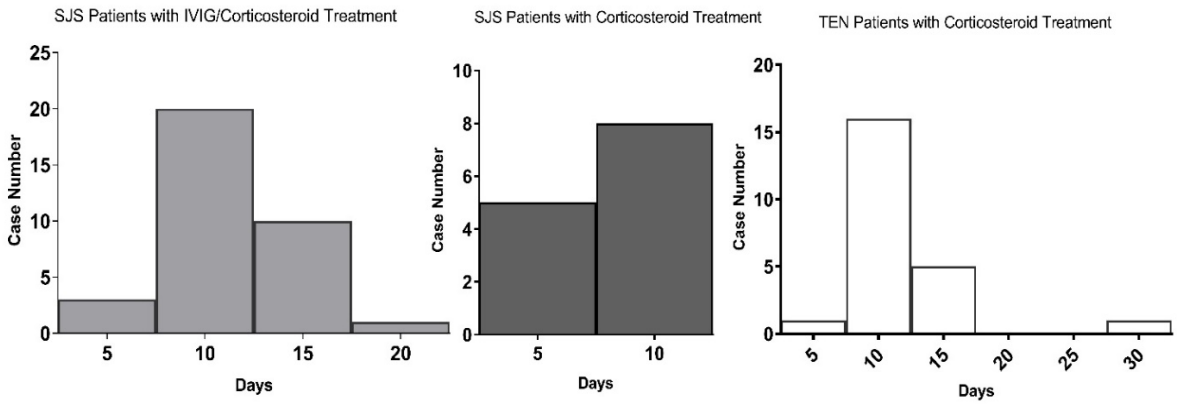

Figure 3) Total days of SJS and TEN treatment

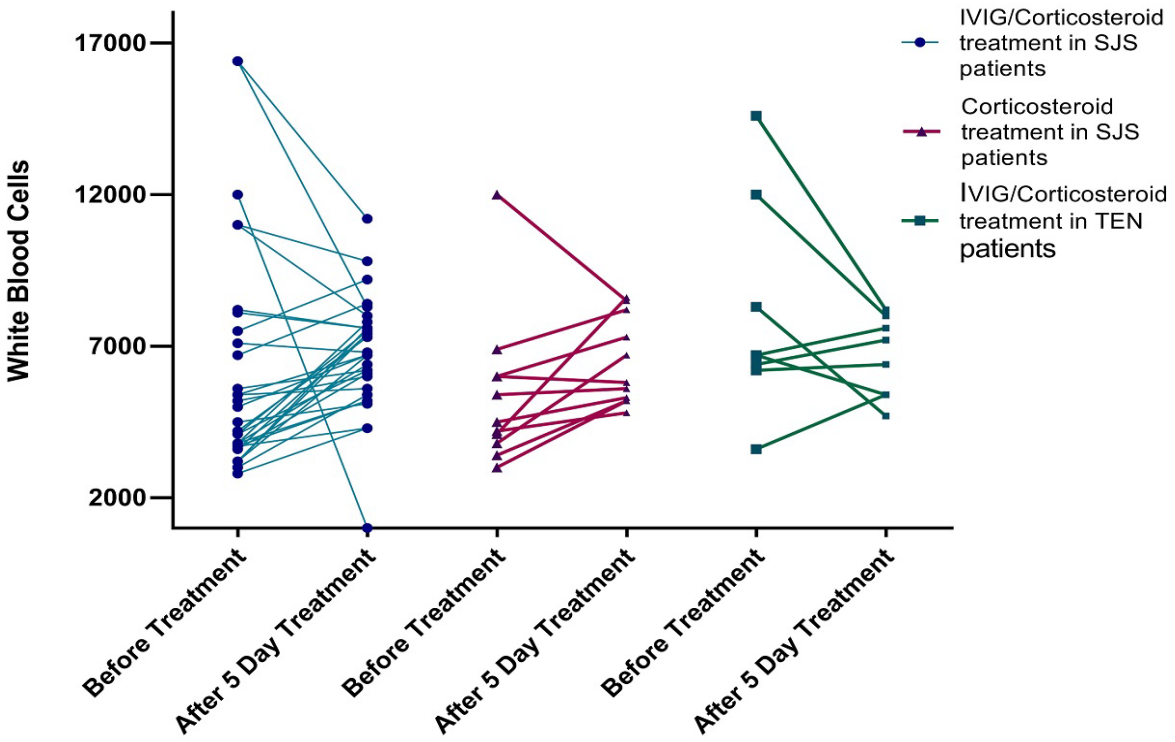

Figure 4) White Blood Cell counts before and 5 days after treatments

Discussion

In the present study, the causes of SJS and TEN syndrome in patients referred to Namazi Hospital in Shiraz in Iran for 8 years were investigated. In various studies, most cases of SJS syndrome, especially TEN, are attributed to pharmacological causes. Given the severe side effects and even mortality that may occur following these drug reactions, it is important to identify the most common drugs that cause these reactions. SJS and TEN are characterized as complex diseases whose etiologies are affected by various factors such as genetic background, infections, autoimmune diseases, and drugs [1].

In the present study, apart from three casualties in TEN patients, all patients were cured of either SJS and TEN most of them were young between 3 to 20 years old. Since corticosteroids and IVIG have immunosuppression actions [8, 9], this result shows that the reduction of immunologic competence in young people may lead to a reduction in drug reactions [15]. Various studies have reported gender effects in SJS and TEN occurrences in which females were more prone to SJS/TEN [16-18]. However, a study conducted in India was in contrast with our results [19]. Furthermore, some other studies found equal effects for both genders which may be due to differences in sample size. Therefore, no elicit conclusion can be made unless a separate study is carried out using a greater population with diverse nationalities [15, 20, 21].

In addition to the severe skin symptoms, the involvement of other organs has been reported by various studies. For instance, it has been reported that ocular implications are common in SJS (40%) and TEN (75 %) patients [22]. Similar to our study in which ocular complication was seen in 75% of total patients, 74% and 89% of SJS/TEN cases in France and South Africa had mild ocular complications [23, 24]. However, a fewer rate of ocular involvement has been observed in the Korean population (12.2%) [18]. What is more, based on our results, the ocular complication was more frequent than oral problems (53%). Liver and kidney dysfunctions were observed in our patients as in Japanese, Indian, and Korean populations [18, 19, 21, 25]. In addition, neutrophilia (6.7%), neutropenia (21.7%), and lymphocytopenia (41.7%) were observed among patients. Some patients complained of various symptoms such as fever (86.7%), headache (61.7%), and cough (46.7%). Sepsis is an important issue in SJS and especially in TEN. In this study, sepsis was observed more frequently in TEN patients, akin to Japanese patients [25]. However, sepsis was equally reported in both SJS and TEN cases in Thailand [21].

In the present study, the main drugs which induce SJS and TEN were antibiotics (40%) and anticonvulsants (38.3%) drugs (Table 4). This is consistent with several studies that confirmed the major role of antibiotics and anticonvulsants [20, 25-27]. To be more specific, co-trimoxazole (8.3%) had the greatest potential among antibiotics to induce SJS/TEN

followed by penicillin (6.7%) and cefixime (6.7%). Compared to our result, the incidence of co-trimoxazole-induced SJS/TEN has been 1-3 cases per 100,000 white users. It has been demonstrated that the special alleles of HLA and haplotype are important genetic risk factors for carriers who intake co-trimoxazole. The risk of susceptibility in co-trimoxazole-induced SJS/TEN with HLA-B*15:02, HLA-C*06:02, and HLA-C*08:01 alleles and HLA-B*15:02-C*08:01 haplotype is approximately 3–11-fold and 14-fold, respectively [28]. Moreover, penicillin and co-trimoxazole were identified as major drug-related causes of SJS/TEN in Thailand (21). Similarly, penicillin was the pivotal causative drug in other countries [29, 30].

The second major drug related to SJS/TEN in the present study was anticonvulsant (table 4), similar to north India and Japan results [19, 25]. It is believed that patients with convulsion defeats, neurogenic pains, and bipolar disorder show SJS/TEN frequently since anticonvulsant drugs are prescribed with higher dosages for these conditions. Therefore, anticonvulsant drugs are often the main SJS/TEN causative drugs [25]. Among anticonvulsant drugs, phenobarbital approved a greater possibility (16.7%) to cause SJS/TEN. Similarly, phenobarbital has been known as a culprit of SJS/TEN in the Philippines with an approximately equivalent frequency of 14.3%, while in Thailand phenobarbital was taken in only 2.8% of patients [26].

It was demonstrated that drugs that have the carbamazepine-like aromatic ring, such as lamotrigine, phenytoin, and oxcarbazepine, are risk factors in HLA-B*1502 carriers for SJS/TEN [6]. In addition to the important role of genetic predisposition in SJS/TEN pathogenesis, this matter is in agreement with our results since carbamazepine and lamotrigine were of causative roles in SJS/TEN (Table 4). While lamotrigine has been known as a high-risk drug for SJS/TEN in Asian countries such as Taiwan (5.4%), Japan (36%), Malaysia (8.3%), Hong Kong (10.3%), and mainland China (Fujian) (6.1%), in European countries it has not been identified as a major susceptible drug for SJS/TEN [26]. In our study, the frequency of lamotrigine was 8.3%, which is a close number to Malaysia's. Carbamazepine had less frequency than anticonvulsant drugs. Moreover, sodium valproate (8.3%) was one of the offending drugs in our study, similarly to the Indian population, where it was reported as a rarely causative drug [19, 31-33].

Although a specific treatment for SJS and TEN has not been completely found because of their complex pathogenesis, corticosteroids and IVIG therapies are reported to have beneficial effects in SJS/TEN treatment despite their controversial administration [16, 18]. IVIG antibodies are considered a potential treatment for SJS/TEN since they can sequestrate keratinocytes' Fas-mediated necrosis, one of the possible pathological mechanisms of SJS/TEN [18]. Furthermore, corticosteroids have been used for various diseases such as inflammatory bowel disease and rheumatoid arthritis due to their immunosuppressive and anti-inflammatory properties [34]. Corticosteroids exert their influences through the inhibition of a variety of pathways including cytokine production, interferon-gamma-mediated apoptosis, and cytotoxic T lymphocyte functions, all of which result in suppression of immunological responses [21, 35]. However, corticosteroid consumption has been controversial. While some studies reported that the early treatment of a suitable dose of corticosteroids could improve SJS and TEN [16, 36], other researchers emphasized that corticosteroids may lead to an increase in infectious complications and result in poorer prognosis as well as delayed epithelialization [16, 18].

Despite inconsistent beneficial effects of exclusive administration of IVIG and corticosteroids, their simultaneous prescription has been recommended as an effective treatment [37, 38]. Moreover, a case report study indicated that the simultaneous treatment of methylprednisolone (500mg methylprednisolone bolus), infliximab (5mg/kg), and a high dose of IVIG (2g/kg over 5 days) was effective and safe for patients with TEN [39]. In our study, the IVIG+corticosteroid treatment was effective for all SJS and most TEN patients. However, some SJS patients had received corticosteroids alone. The rate of mortality in TEN/SJS patients was 5% which had a lower rate in comparison with the average mortality rate of 20-25% in the public population [18].

The major limitation of this study was the lack of a control group to be compared with our results due to the severity of the disease that does not allow patients to be kept without treatment even for a short time. Moreover, the low occurrence of the disease limits providing a huge sample population. Other limitations can be attributed to causative agents that were not determined by immunological tests but by patients' history.

Conclusion

The most common drugs causing SJS and TEN were antimicrobial (Co-trimoxazole) and anticonvulsants (phenobarbital) drugs. Due to the wide range of severe complications such as eye injuries and the risk of death of patients, physicians, and other medical staff must be familiar with the symptoms of these reactions and provide the necessary information to the public not to use antimicrobial drugs arbitrarily. Furthermore, IVIG+corticosteroids may have an effective role in SJS/TEN treatment, however, TEN treatment needs to be studied more. A broader knowledge of the main causes of SJS/TEN and optimal treatment may help in better management of these diseases.

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