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REVIEW ARTICLE

News in severe clinical adverse drug reactions: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

*Sylvia Aide Martínez-Cabriales, Minerva Gómez-Flores and Jorge Ocampo-Candiani**
Department of Dermatology, Hospital Universitario Dr. José Eleuterio González, Monterrey, N.L., México

Abstract

Stevens-Johnson syndrome and toxic epidermal necrolysis are life-threatening conditions associated with significant morbidity and mortality. They are considered to be part of a spectrum of cutaneous drug reactions, differing only by their extent of skin detachment due to keratinocyte apoptosis. Drugs are assumed as the main cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in most cases. The pathophysiology is incompletely understood; however, current pathogenic models involve Fas ligand, granulysin, and cytokines. Diagnosis relies mainly on clinical signs together with the histological analysis, and treatment requires early cessation of the causative drug and supportive care. Of these conditions, herein we will review the advances in clinical, pathogenesis, and management. (Gac Med Mex. 2015;151:721-31)

Corresponding author: *Jorge Ocampo Candiani, jocampo2000@yahoo.com.mx?*

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Introduction

The skin is one of the target organs most affected by adverse drug reactions, with an approximate incidence of 19% in hospitalized patients. About 2-5% of drug-induced adverse skin reactions are considered severe cutaneous adverse reactions (SCAR)[1]. The World Health Organization (WHO) defines severe drug reaction as any that requires hospitalization or prolongation of pre-existing hospitalization, that causes persistent or significant disability, and that puts life in danger or causes death[2]. Drug-induced skin conditions of this category include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome and acute generalized exanthematous pustulosis (AGEP)[3,4].

History

In 1922, Stevens and Johnson described two cases of children with fever, severe stomatitis, serious eye involvement and disseminated rash with erythematous macules, sometimes with a necrotic core, and were recognized with the name SJS[5].

In 1956, A. Lyell described four patients with a rash with chafed-looking lesions that he named TEN, since he believed the patients' systemic symptoms were caused by a toxin. Later he identified the association between a higher frequency of these cases with the use of medications,

Correspondence:
*Jorge Ocampo-Candiani
Departamento de Dermatología
Hospital Universitario Dr. José Eleuterio González
Av. Madero y Gonzalitos, s/n
Col. Mitras Centro, C.P. 64460, Monterrey, N.L., México
E-mail: jocampo2000@yahoo.com.mx

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Table 1. SJS and TEN key clinical and immunohistochemical characteristics

	EMM	SJS	SJS/TEN	TEN
Morphology	Typical lesions on target (3 rings)	Atypical lesions on target (2 rings/ blisters). Maculopapular evanescent rash. Blisters and epidermal denudation in < 10% of body surface area	Blisters and epidermal loss in 10-30% of body surface area	Blisters and epidermal loss in > 30% of body surface area
Topography	Face and limbs	Predominates in the trunk	Trunk, face and limbs	Trunk, face and limbs
Mucosal membranes	Present. Less than 10% of body surface area	Present	Present	Present
CD4	Intense interface pattern	Diffuse pattern	Diffuse pattern	Diffuse pattern
CD8	Mild	Intense	Intense	Intense
CD56	Mild	Intense	Intense	Intense
CD68	Mild	Intense	Intense	Intense
CD1a	Normal	Absent	Absent	Absent
Granulysine	Mild and diffuse	Intense epidermal pattern and blister	Diffuse on necrosis area	Diffuse on necrosis area
Foxp3	Intense pattern on epidermis and dermis	Mild	Mild	Mild

Adapted from Auquier-Dunant et al.[62].

especially sulfonamides, pyrazolones and antiepileptic drugs. He used the term *necrolysis* to name the histopathologically observed epidermal necrosis[6].

SJS and TEN are currently accepted as being part of a spectrum of adverse drug reactions and are differentiated by the extent of affected skin. Although SJS and erythema multiforme major (EMM) were once considered to be sinonyms, they are currently regarded as two clinically and etiologically different conditions. EMM is mainly caused by the herpes simplex virus (HSV) and its prognosis is better than that of SJS (Table 1)[7].

Epidemiology

SJS annual incidence is 1.2-6 cases per million inhabitants, with 0.4-2 cases per million inhabitants for TEN[8], an incidence that increases with age. In certain ethnic groups there is higher genetic predisposition for developing these adverse events.

Mortality in SJS is 5% and in TEN, 30-50%[9]. Medications are responsible for 80% of TEN cases and 50% of SJS cases. Other associated causes are hypersensitivity reactions to contrast agents and infections; cases of SJS and TEN have also been described in association with *Mycoplasma pneumonia,* cytomegalovirus and dengue[10,11].

Alopurinol and carbamazepine are SJS and TEN most frequent causal agents, but penicillins and cephalosporins have also been implied[12,13]; causal agents vary according to the prescription trends[13]. More than 100 associated drugs have been recently described, including non-steroid anti-inflammatory drugs, sulfonamides, aminopenicillins, antiretrovirals, antiepileptic drugs such as phenytoin, lamotrigine and barbiturates, among others[14,15]. Drugs with a longer half-life entail an increased risk for triggering this type of adverse reactions. Some patients treated with phenytoin and radiotherapy develop EM, in the syndrome known as erythema multiforme associated with phenytoin and cranial radiation therapy (EMPACT)[14,16].

Pathogenesis

Certain groups of patients are more susceptible to experience these severe adverse drug reactions due to genetic predisposition[17]. The incidence is higher

in the female gender, at older age, due to the consumption of multiple drugs and in states of immunosuppression[18-20].

Three pathogenic mechanisms causative of drug adverse reactions are considered to exist: immune, non-immune and idiosyncratic mechanisms. Non-immune mechanisms include drug adverse effects (e.g., mucositis with chemotherapeutic agents), cumulative effects (e.g., hepatic toxicity with methotrexate), and the effect of delayed toxicity, drug interactions and drug metabolism alterations. The idiosyncratic mechanism is considered to be the result of the combination of an immune component and the genetics of the individual (e.g., DRESS syndrome and TEN). In the case of SJS and TEN, the causal mechanism is of the immune adaptive type due to a class IV delayed hypersensitivity response according to the Gell and Coombs classification[21].

The genetic aspect plays a fundamental role in the pathophysiology of TEN. Evidence indicates that patients with TEN express HLA-B12; recently, a genetic predisposition to alopurinol has been described in the Chinese population with the HLA-B in allele 5801 and to carbamazepine with HLA-B1502[22]. Another study has demonstrated that the presence of HLA-DQB1 0601 is associated with eye complications in patients with SJS.

SJS and TEN causal immune mechanism is a delayed cell response that entails keratinocyte apoptosis. Two theories have been proposed as mechanism of action. The first one consists in a FAS-FASL (Fas ligand) signaling pathway that produces caspase 8 activation, which induces keratinocyte apoptosis[23,24]. Other cytokines and substances involved in this pathogenesis include the tumor necrosis factor alpha (TNF-α), interferon γ, interleukin 8 and nitric oxide, which are present in epidermal lesions and some have the capacity to bind to receptors that will induce apoptosis[25].

The second theory, more widely accepted, maintains that cell apoptosis is caused by cytotoxic T cells (CD8) and natural killer (NK) cells (CD56) after being activated by the drug[26]. CD8 T cells and NK cells activation takes place after the drug is bound to the major histocompability complex (MHC I) and to the T cell receptor[27]. Another theory is that the drug becomes immunogenic after its binding with a peptide, thus stimulating the immune system.

Keratinocyte apoptosis is caused by a 15 kDa cytolytic protein named granulysine that is present in the CD8 T cells and NK cells granules together with perforin and granzyme B. The levels of these molecules are elevated in TEN blisters, but are unable to cause the lesion of this condition by themselves[28]. Granulysin is secreted by exocytosis together with a perforin, which enables for it to enter in the keratinocyte and cause cell death by means of damage to the cell membrane and disruption of the mitochondrial transmembrane potential[29].

Clinical manifestations

Cutaneous involvement appears 7-21 days after the start of the medication if it is the first exposure; on subsequent cases, the cutaneous lesions time of onset after the intake of medications can be as short as a few hours[30]. Signs and symptoms start with a prodrome of general malaise with fever, anorexia and rhinorrhea[31].

The lesions start in the trunk, with later involvement of the neck, face and upper limbs, at their proximal portion, with bilateral and symmetric distribution. Usually, distal portions of the limbs remain free of lesions, with little involvement of palms and soles[32]. The extent of skin involvement is what defines the clinical diagnosis and, hence, the prognosis of the patient[33]. SJS corresponds to less than 10% involvement of body surface area; TEN corresponds to more than 30% involvement; the cutaneous involvement range from 10 to 30% is known as SJS-TEN overlapping[34]. The affected skin areas must be considered to define the percentage of extension and its classification; they are those lacking epidermis, without taking into account erythematous areas[35].

The morphology of the lesions varies according to disease evolution. They start as irregular and confluent purplish erythematous macules. They are characterized for being pruriginous, painless and evanescent with digitopressure[32]. Papular lesions develop later and, in case of progression, flaccid blisters are formed, which acquire a grayish color (Fig. 1).

Mucosal involvement is present in 90% of patients and can be found at early stages, which would lead to suspect higher risk of SJS progression to TEN[33]. Genital region mucosal involvement occurs in 40-60% of the cases and ocular mucosa is involved in 85%, and it can range from hyperemia and keratitis to corneal rupture[36]. Oral, ocular and genital mucosal involvement has been described in nearly 50% of patients.

The blister is the result of epidermal keratinocytes necrosis, which causes subepidermal detachment; multiple lesions appear over a few hours. Epidermal denudated areas show a shiny erythematous dermis with a bleeding appearance. Average time of initial

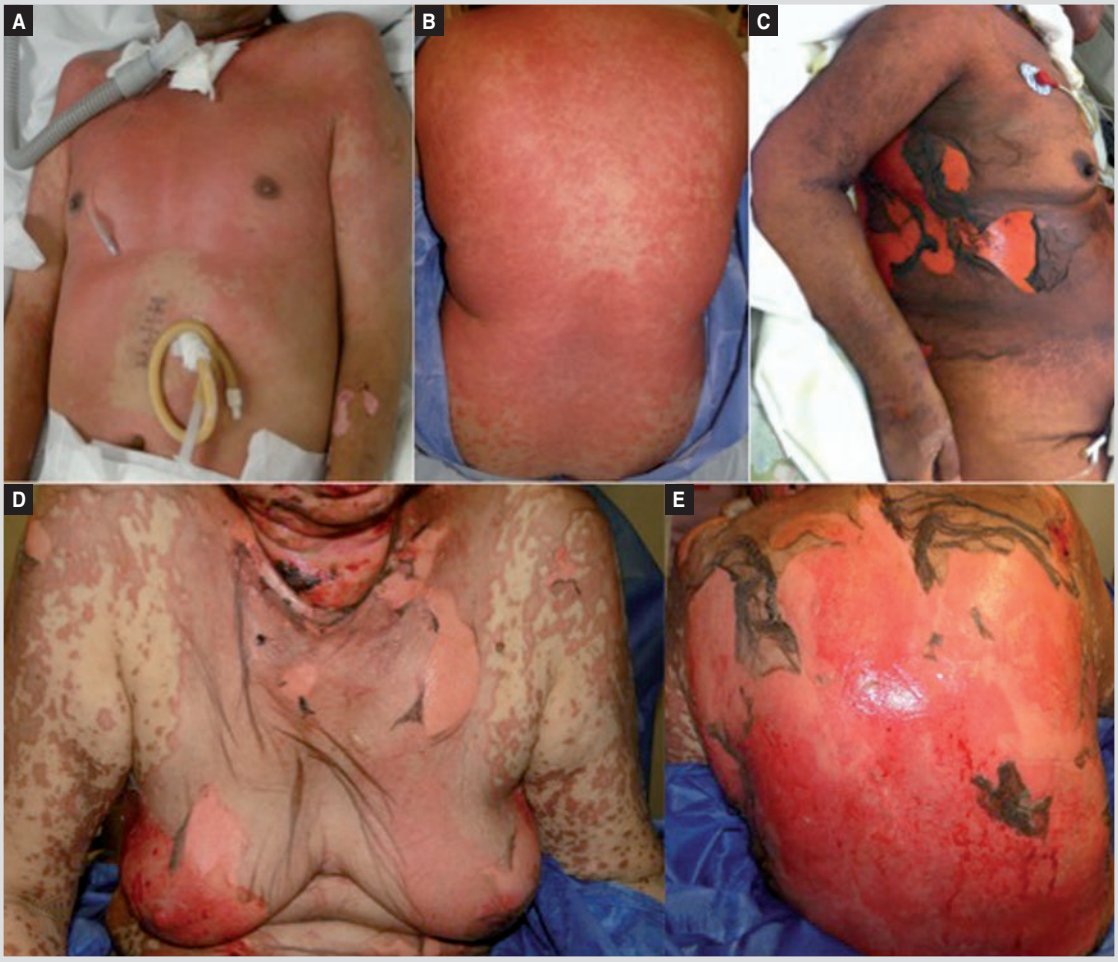

Figure 1. *SJS clinical characteristics and its evolution to TEN.* ***A*** *and* ***B****: multiple confluent erythematous macules, evanescent upon digitopressure.* ***C-E:*** *multiple areas with epidermal loss; erythematous dermis has a shiny appearance.*

symptoms progression evolution to epidermal loss is 6-9 days[37].

When the Nikolsky sign is performed, presence or absence of epidermal detachment is demonstrated after tangential pressure of the blister or on erythematous skin with blister formation. The Asboe-Hansen sign is produced after exerting pressure on the central portion of the blister causing for its size to increase towards the periphery.

Complications are produced by organ implication with respiratory, cardiovascular, gastrointestinal and renal systems involvement. Renal damage symptoms include electrolyte imbalances, prerenal hyperazotemia, tubular necrosis and development of acute renal failure[38]. Renal dysfunction pathogenesis is the consequence of a series of factors, including the nephrotoxic properties of some cytokines involved in SJS and TEN, hypovolemia and cardiac output decrease[39].

Pulmonary involvement can occur as obliterant bronchiolitis or interstitial diffuse pneumonitis[40]. Respiratory symptoms surveillance is recommended to be maintained during the disease evolution even if chest X-rays are normal, in order to enable for opportune care to be provided[40,41]. As a consequence of the hypermetabolic state with hypoalbuminemia and hypogammaglobulinemia presented by the patient and failure of the protecting function of the epidermis, a risk for the development of sepsis is generated, which is the first cause of death[42].

The factors that have been correlated with worse prognosis include old age of the patient, hematological abnormalities such as thrombocytopenia, neutropenia

Table 2. SCORTEN scale. Possible results vary from 0 to 7. Mortality prediction depends on the score as follows: 1, 2, 3, 4 and more than 5 predict 3.2, 12.1, 35.8, 58.5 and 90% mortality, respectively

Variables		Values	Score
1	Age	≥ 40 years	1
2	Heart rate	≥ 120 beats/min	1
3	Malignancy		1
4	Initial epidermolysis	≥ 10% of body surface area affected	1
5	Serum urea	≥ 10 mmol/l	1
6	Serum bicarbonate	< 20 mmol/l	1
7	Serum glucose	≥ 14 mmol/l	1

Adapted from Bastuji-Garin et al.[44]

and lymphopenia, in addition to serum creatinine elevation[43]. Currently, there is a severity scale for TEN known as Severity-of-illness Score for Epidermal Necrolysis (SCORTEN), where seven parameters are assessed in order to predict patient mortality[44,45]. The factors included are: age ≥ 40 years, heart rate ≥ 120 bpm, history of cancer or hematologic malignancies, involvement of > 10% of body surface area, serum urea > 10 mmol/l, serum bicarbonate < 20 mmol/l, serum glucose > 252 mg/dl (14 mmol/l); each positive value is assigned one point (Table 2). This scale was validated by Campione et al. in 2003, by Trent et al. on the same year and by Brown et al. in 2004. The scale should be applied within the first 24 h and at day 3 to obtain higher accuracy of the mortality rate[46].

The lesions start healing through re-epitelization by migration of keratinocytes from their reservoir in hair follicles, with recovery in three weeks. As sequels, residual hyperpigmentation, nail dystrophy and diffuse hair loss may occur, as well as vaginal synechiae, conjunctival synechiae, entropion and blindness[37].

Finkelstein et al. analyzed SJS and TEN recurrence in a cohort of 581 patients and found a mean time to the second episode of 315 days in 7.2% of the patients[47]. Probable causes of relapse include genetic susceptibility and use of drugs likely to have cross-reactivity due to chemical structure similarity with the drugs that caused the first episode. Patients with a history of adverse drug reactions to carbamazepine should avoid taking phenytoin and phenobarbital; in the case of antibiotics such as β-lactams, penicillins, cefalosporins and carbapenems should be avoided, and in the case of sulfones, sulfamethoxazole, sulfadiazine, sulfapyridine and sulfamethizole[48-50].

Diagnosis

The diagnosis requires clinico-histopathological correlation. Histopathological characteristics vary, but the most important include apoptosic keratinocytes in the epidermal basal layers with basement membrane vacuolization (Fig. 2). The adnexa may be affected by the presence of mild inflammation around the eccrine glands. Lymphocytic inflammatory infiltrate is accompanied by multiple eosinophils and, at late phases, subepidermal blisters with necrosis on the overlying epidermis are found[51]. CD8+ lymphocytes are predominant on the epidermis and CD4+ in the papillary dermis[27].

Serum granulysin is useful for the diagnosis of SJS and TEN at early phases since it is elevated before mucosal involvement and epidermal loss[52]. This marker is not SJS-specific, since it can be found in other drug-induced skin conditions, such as the DRESS syndrome, as well as in graft-versus-host disease and viral infections[53]. Fujita et al. have developed an immunochromatography assay that enables the detection of serum granulysin. If this test is performed 2-4 days before the bullous lesions, SJS and TEN can be distinguished from non-severe drug-induced skin conditions with 80% sensitivity and 95.8% specificity[54].

Another test that has been proven useful is the measurement of serum High Mobility Group Box1 Protein (HMBG1) by means of an enzyme immunoassay[55]. HMBG1, with an approximate molecular weight of 30 kDa is the main component of the group of non-histone nuclear proteins that acts as nuclear transcription regulator on its intracellular mechanism. Its extracellular function consists in activating the inflammatory cascade[56,57]. Nakajima et al. analyzed the HMBG1 assay

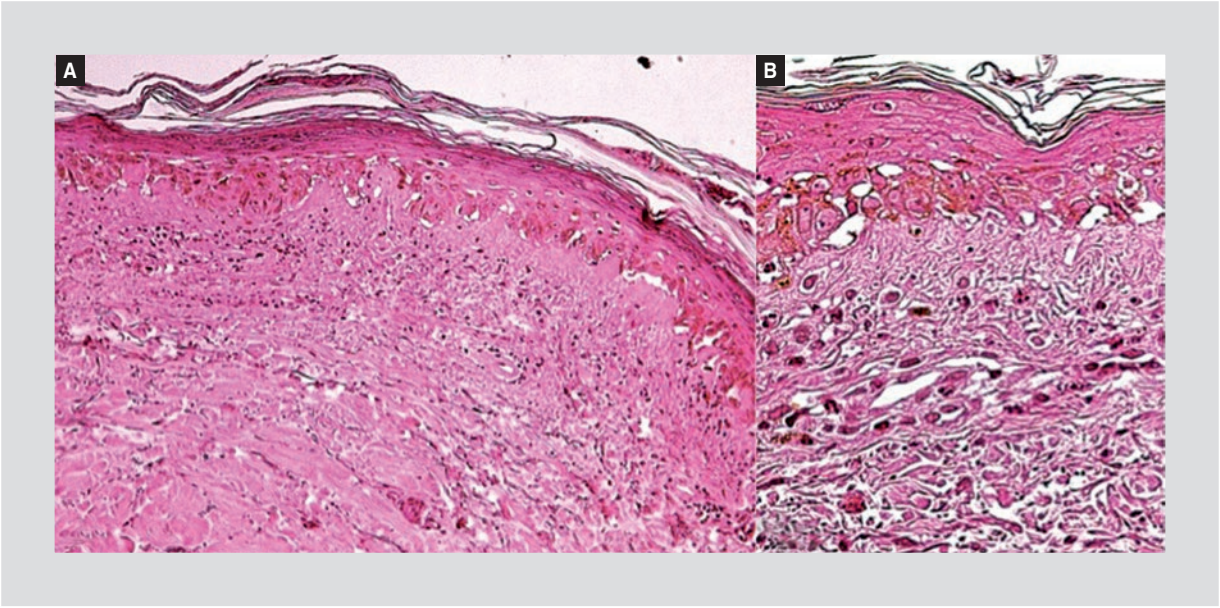

Figure 2. *Histopathology stained with hematoxylin and eosin.* ***A:*** *intraepidermal spongiosis and basement membrane vacuolization with inflammatory infiltrate of diffuse lymphocytic predominance is observed in the dermis.* ***B:*** *the biopsy shows multiple apoptosic keratinocytes.*

and demonstrated it had a sensitivity of 45.5% and the advantage, versus granulysin measurement, that HMBG1 levels remain elevated for longer time[55]. In other diseases, such as lupus erythematous and cancer, an elevation of HMBG1 serum levels has been reported, as well as their correlation with disease prognosis[58,59].

As a preventive method, the Food and Drug Administration (FDA) recommends HLA-B1502 typification in the Asian population or their descendants prior to starting the treatment with carbamazepine[60,61].

Differential diagnosis

A difficult differential diagnosis is EMM, the clinical presentation of which can resemble an early phase SJS[62]. EMM is a self-limited mucocutaneous condition that doesn't belong to the SJS and TEN spectrum[7,63]. EMM can be caused by medications, but its etiology is mostly an infectious agent. Numerous cases associated with HSV and *Mycoplasma* have been described. In EMM, necrosis of smaller extension is expected to be found by histopathology with hematoxylin and eosin, but it is difficult to tell them appart. Recent studies have demonstrated that differential diagnosis can be established by immunohistochemistry (Table 1)[64,65].

With regard to other bullous conditions, SJS and TEN should be differentiated from acute generalized pustulosis (AGEP), which is caused by an adverse drug reaction and is clinically characterized by multiple non-follicular pustules with predisposition for body folds and the face and 20% mucosal involvement. Histopathology reveals the presence of a subcorneal pustule with neutrophilic intradermal infiltrate without epidermal detachment.

The scalded skin syndrome occurs in adult patients with renal damage or immunosuppressed states. It is caused by the *Staphylococcus aureus* exotoxin that targets desmoglein 1, with the ensuing formation of flaccid subcorneal blisters with epidermal sphacelation. Histopathological differentiation is sometimes required.

Other diseases with subepidermal blisters include paraneoplastic pemphigus, acute graft-versus-host disease, coma blisters, blisters by burns, that clincally are not easy to differentiate and therefore require history taking and histopathological correlation.

Treatment

Discontinuation of the causative drug as soon as possible is important, since delayed withdrawal is associated with increased mortality[66]. Identification of the causative drug can be carried out using established algorithms such as the Algorithm of Drug causality for Epidermal Necrolysis (ALDEN) and lymphocyte transformation tests in vitro if they are made within the first week of disease onset[67,68]. ALDEN is an algorithm that

allows not only finding the causal drug, but also knowing the drugs that might be safely prescribed again to the patient[68]. The patch test is another low risk diagnostic option that allows for the delayed sensitivity response caused by the drug responsible of SJS or TEN to be reproduced[69]. It has been used and reported in cases of SJS/TEN caused by antibiotics, carbamazepine, pseudoephedrine and trimethoprim-sulfamethoxazole[29,70,71].

Primary approach of these patients consists in supportive treatment with an adequate supply of fluids and electrolytes, nutritional support and body temperature management, in addition to management of infections or other complications that may occur. Hospital admission is recommended to be carried out in isolation conditions that allow for monitoring and infection prevention.

With regard to topical treatment of lesions, the wounds should be treated with isotonic sodium chloride solutions and then covered with petroleum jelly at the sites of pressure until re-epitelization; the use of mupirocin is recommended in periorificial areas. Consultation with ophthalmology, urology or gynecology departments is necessary in order to assess organ damage and prevent sequels.

The use of systemic steroids was the standard treatment until 1990, but some authors have reported that no benefit has been proven[72]. Ghislain, in a study of 2002, reported that they did not decrease time to recovery and were associated with an increased risk for complications, in particular sepsis and gastrointestinal tract bleeding[73]. Other studies have reported that a high-dose pulse steroid therapy elicits good results and lower incidence of complications[74,75]. Steroids have been used with controversial results, since they have been associated with both increased morbidity and mortality and improvement when used early.

One of the used regimens is dexamethasone in 100 mg boluses for three days, which manages to reduce mortality; the recommendation is to prescribe them initially at high doses for short periods in order to reduce the possibility of infection and wound healing delay.

Dexamethasone is a potent glucocorticoid (seven times more than the prednisolone equivalent dose), with a long half-life of 36 to 54 h, which allows for continuous high serum levels. It strongly suppresses the release of cytokines such as TNF-α and inhibits activated T-cell, interferon γ and FasL-mediated apoptosis. Although there is no consensus on its use, if used at TEN early stages at high doses and for short time periods, the negative impact on wound healing and infections can be prevented[75].

Other therapeutic measures that have been used are cyclophosphamide and plasmapheresis[76]. Cyclophosphamide has shown favorable results when administered at 100-300 mg/day[77]. Plasmapheresis has been used in patients that have not shown improvement with supportive and steroid therapy, offering favorable results in short time[78-82]. Some studies suggest that plasmapheresis should be considered as first-line adjuvant therapy[82,83].

Some case series have reported disease remission and mortality decrease with cyclosporine, owing to its effect on granulysine[84]. The recommended dose is 3 mg/kg/day for 10 days or weaned over 14 days[72,85,86].

Intravenous immunoglobulin (IVIG) was used for the first time in 1998 in 10 patients with TEN who were successfully treated with 0.75 mg/kg/day for four consecutive days[87]. IVIG is obtained from multiple donor serum, and it corresponds to immunoglobulin G. Its immune effects are pleiotropic; in SJS and TEN it is used under the hypothesis that the interruption of the Fas ligand interaction with its receptor will prevent keratinocyte apoptosis[88]. Its good tolerance and low toxic potential has been shown in some studies[89]. The immunoglobulin dose that has demonstrated a mortality decrease by preventing disease deterioration is higher than 2 g/kg total dose administered in 2-4 days[90,91]. However, its use remains, so far, controversial, since recent studies have failed to substantiate a favorable effect on patient survival[90,92-94].

The combination of corticosteroids with IVIG provides better therapeutic effect than the administration of corticosteroids alone[95]. There are few reported cases of IVIG and infliximab combined treatment with satisfactory results[96,97].

Another treatment option for which disease remission and early re-epitelization have been reported is N-acetylcysteine (NAC). NAC is a cysteine derivative that intervenes in the production of glutathione and therefore has antioxidant properties, in addition to the capacity to inhibit TNF-α and interleukin 1β in vitro. The dose at which improvement has been reported is 300 mg/kg/day every 6 h[98,99]. However, recent studies have compared NAC 150 mg/kg intravenously administered in 20 h with the combination of NAC with the same regimen and infliximab 5 mg/kg intravenously administered in 2 h with no better results than supportive treatment and no evidence of disease remission[100].

There is little evidence on the use of anti-TNFs as treatment in SJS and TEN; there are only anecdotal cases reported in the literature[101-110]. They are considered an emerging and promising therapy based on the selective blockage of TNF-α, which plays a fundamental role on pathogenesis (Table 3)[111,112]. Other drugs

Table 3. Summary of infliximab and etanercept-treated SJS and TEN cases reported in the literature in English language

Authors	Gender/ age	Dosage	Time to anti-TNF start since symptom onset	Improvement in 24 h	Causal agent	Previous treatment	SCORTEN	Time to re-epithelization after initiation of the biological
Fischer M (2002)	F/56	5 mg/kg single dose	5 days	Yes	SMX-TMP	None	NR	NR
Worsnop F (2012)	F/32	5 mg/kg single dose	NR	NR	Sulfasalazine	IVGI 2 g/kg/day x 3 days	2	26 days
Wojtkiewicz A (2008)	F/17	5 mg/kg single dose	NR	Yes	SMX-TMP	IVIG 0.1 g/kg + dexamethasone	NR	12 days (80% of body surface area)
Al-Shouli S (2005)	M/67	300 mg single dose	NR	NR	Sildenafil	PDN	NR	10 days
Hunger R (2005)	F/69	5 mg/kg single dose	3 days	Yes	Diclofenac	NR	NR	5 days
Kreft B (2010)	M/31	5 mg/kg single dose	NR	Yes	Etoricoxib	PDN	NR	5 weeks
Zárate-Correa L (2013)	M/76	300 mg single dose	NR	NR	Furosemide	NR	2	9 days (95% of body surface area)
Zárate-Correa L (2013)	F/51	300 mg single dose	7 days	NR	Ceftriaxone	Methyl-prednisolone	4	7 days
Zárate-Correa L (2013)	F/17	300 mg single dose	8 days	Yes	Carbamazepine	IVGI 2 g/kg/day x 1 day	3	16 days
Zárate-Correa L (2013)	F/20	300 mg single dose	NR	NR	Nevirapine, lamivudine and zidovudine	None	2	7 days
Scott L (2014)	M/7	5 mg/kg single dose	NR	Yes	Carbamazepine	IVGI 2 g/kg/day x 1 day	NR	10 days
Gubinelli E (2009)	F/59	25 mg/day Twice*	NR	In 48 h	Phenobarbital	Methyl-prednisolone	NR	20 days
Famularo G (2007)	M/59	25 mg/day Twice (days 4 and 8)*	NR	Yes	Ciprofloxacin	PDN	NR	6 days
Paradisi A (2014)	F/57	50 mg single dose*	NR	NR	Carbamazepine	None	6	12 days
Paradisi A (2014)	M/70	50 mg single dose*	NR	NR	Ofloxacin	None	3	8 days
Paradisi A (2014)	F/28	50 mg single dose*	NR	NR	Lansoprazole/ azathioprine	None	2	8 days
Paradisi A (2014)	F/62	50 mg single dose*	NR	NR	Methyl-prednisolone	None	3	12 days
Paradisi A (2014)	M/73	50 mg single dose*	NR	NR	Ciprofloxacin	None	4	8 days
Paradisi A (2014)	M/78	50 mg single dose*	NR	NR	Carbamazepine	None	5	8.5 days (7-21)
Paradisi A (2014)	F/72	50 mg single dose*	NR	NR	Phytotherapy	None	2	8 days
Paradisi A (2014)	F/50	50 mg single dose*	NR	NR	Carbamazepine	None	6	20 days
Paradisi A (2014)	M/71	50 mg single dose*	NR	NR	Carbamazepine	None	2	9 days
Paradisi A (2014)	F/55	50 mg single dose*	NR	NR	Diclofenac	None	3	9 days

NR: not reported in the case; F: female; M: male.
*Etanercept; all other dosings correspond to infliximab.

that share the anti-TNF mechanism of action are thalidomide and pentoxifylline[113]. However, thalidomide is not recommended due to the risk of paradoxically increasing the levels of that cytokine, with a subsequent increase in mortality, which was demonstrated in 1996 by Wolkenstein et al. in a placebo controlled double-blind clinical trial[114]. Another theory that would explain the mortality increase in the group of patients treated with thalidomide is the protecting function of TNF-α as activator of the anti-apoptotic pathway of the nuclear transcription factor κB[115].

Conclusions

It is important establishing an early diagnosis of these diseases in order to discontinue the causative drug as soon as possible. In addition, severity markers should be identified to monitior the evolution and start supportive and specific treatment that allows for the remission, cure and prevention of complications and sequels of the disease.

References

1. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA. 1986;256(24):3358-63.
2. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.
3. Phillips EJ, Chung WH, Mockenhaupt M, Roujeau JC, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J Allergy Clin Immunol. 2011;127(3 Suppl):S60-6.
4. Vassallo C, Derlino F, Brazzelli V, D'Ospina RD, Borroni G. Acute generalized exanthematous pustulosis: report of five cases and systematic review of clinical and histopathological findings. G Ital Dermatol Venereol. 2014;149(3):281-90.
5. Stevens A JF. A new eruptive fever associated with stomatitis and ophthalmia. Am J Dis Child. 1992;24:526.
6. Lyell A. Toxic epidermal necrolysis: an eruption resembling scalding of the skin. Br J Dermatol. 1956;68:355-61.
7. Assier H, Bastuji-Garin S, Revuz J, Roujeau JC. Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. Arch Dermatol. 1995;131(5):539-43.
8. Mockenhaupt M, Schopf E. Epidemiology of drug-induced severe skin reactions. Semin Cutan Med Surg. 1996;15(4):236-43.
9. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet J Rare Dis. 2010;5:39.
10. Stevens D, Swift PG, Johnston PG, Kearney PJ, Corner BD, Burman D. Mycoplasma pneumoniae infections in children. Archives of disease in childhood. 1978;53(1):38-42.
11. Fournier S, Bastuji-Garin S, Mentec H, Revuz J, Roujeau JC. Toxic epidermal necrolysis associated with Mycoplasma pneumoniae infection. Eur J Clin Microbioll Infect Dis. 1995;14(6):558-9.
12. Halevy S, Ghislain PD, Mockenhaupt M, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol. 2008;58(1):25-32.
13. Lin YF, Yang CH, Sindy H, et al. Severe cutaneous adverse reactions related to systemic antibiotics. ClinI Infect Dis. 2014;58(10):1377-85.
14. Fernandez FA, Pintor E, Quesada R, Garces FJ. [Toxic epidermal necrolysis induced by phenytoin and whole brain radiotherapy]. Actas Dermosifiliogr. 2007;98(7):483-5.
15. Sanz-Munoz C, Martinez-Moran C, Torrero-Anton MV, Miranda-Romero A. [Indapamide-associated Stevens-Johnson syndrome]. Actas Dermosifiliogr. 2008;99(4):321-2.
16. Khafaga YM, Jamshed A, Allam AA, et al. Stevens-Johnson syndrome in patients on phenytoin and cranial radiotherapy. Acta Oncol. 1999; 38(1):111-6.
17. Phillips EJ, Mallal SA. Pharmacogenetics of drug hypersensitivity. Pharmacogenomics. 2010;11(7):973-87.
18. Blanes M, Belinchon I, Portilla J. [Cutaneous drug reactions in HIV-infected patients in the HAART era]. Actas Dermosifiliogr. 2009;100(4):253-65.
19. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med. 1991;324(6):377-84.
20. Sotelo-Cruz N. [Stevens-Johnson syndrome and toxic epidermal necrolysis in children]. Gac Med Mex. 2012;148(3):265-75.
21. Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. Br J Clin Pharmacol. 2011;71(5):672-83.
22. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A. 2005;102(11):4134-9.
23. Chung WH, Hung SI. Genetic markers and danger signals in stevens-johnson syndrome and toxic epidermal necrolysis. Allergol Int. 2010;59(4):325-32.
24. Choi HJ, Ku JK, Kim MY, et al. Possible role of Fas/Fas ligand-mediated apoptosis in the pathogenesis of fixed drug eruption. Br J Dermatol. 2006;154(3):419-25.
25. Viard-Leveugle I, Gaide O, Jankovic D, et al. TNF-alpha and IFN-gamma are potential inducers of Fas-mediated keratinocyte apoptosis through activation of inducible nitric oxide synthase in toxic epidermal necrolysis. J Invest Dermatol. 2013;133(2):489-98.
26. Henkart PA. Lymphocyte-mediated cytotoxicity: two pathways and multiple effector molecules. Immunity. 1994;1(5):343-6.
27. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139(8):683-93.
28. Nassif A, Moslehi H, Le Gouvello S, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. J Invest Dermatol. 2004; 123(5):850-5.
29. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008;14(12):1343-50.
30. Guillaume JC, Roujeau JC, Revuz J, Penso D, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). Arch Dermatol. 1987;123(9):1166-70.
31. Downey A, Jackson C, Harun N, Cooper A. Toxic epidermal necrolysis: review of pathogenesis and management. J Am Acad Dermatol. 2012;66(6):995-1003.
32. Bolognia J JJ, Rapini R. Drug reactions. Dermatology. 2008;1.
33. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-85.
34. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129(1):92-6.
35. Arndt KA, Feingold DS. The sign of Pyotr Vasilyewich Nikolsky. N Engl J Med. 1970;282(20):1154-5.
36. Wilkins J, Morrison L, White CR, Jr. Oculocutaneous manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum. Dermatol Clin. 1992;10(3):571-82.
37. Becker DS. Toxic epidermal necrolysis. Lancet. 1998;351(9113):1417-20.
38. Hung CC, Liu WC, Kuo MC, Lee CH, Hwang SJ, Chen HC. Acute renal failure and its risk factors in Stevens-Johnson syndrome and toxic epidermal necrolysis. Am J Nephrol. 2009;29(6):633-8.
39. Blum L, Chosidow O, Rostoker G, Philippon C, Revuz J, Roujeau JC. Renal involvement in toxic epidermal necrolysis. J Am Acad Dermatol. 1996;34(6):1088-90.
40. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. Intensive Care Med. 1997;23(12):1237-44.
41. Wallis C, McClymont W. Toxic epidermal necrolysis with adult respiratory distress syndrome. Anaesthesia. 1995;50(9):801-3.
42. Revuz J, Penso D, Roujeau JC, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. Arch Dermatol. 1987;123(9):1160-5.
43. Goens J, Song M, Fondu P, Blum D, Achten G. Haematological disturbances and immune mechanisms in toxic epidermal necrolysis. Br J Dermatol. 1986;114(2):255-9.
44. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-53.
45. Sekula P, Liss Y, Davidovici B, et al. Evaluation of SCORTEN on a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis included in the RegiSCAR study. J Burn Care Res. 2011;32(2):237-45.
46. Guegan S, Bastuji-Garin S, Poszepczynska-Guigne E, Roujeau JC, Revuz J. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol. 2006;126(2):272-6.
47. Finkelstein Y, Macdonald EM, Li P, Hutson JR, Juurlink DN. Recurrence and mortality following severe cutaneous adverse reactions. JAMA. 2014;311(21):2231-2.

48. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet. 1999;353(9171):2190-4.
49. Nassif A, Bensussan A, Boumsell L, et al. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. J Allergy Clin Immunol. 2004;114(5):1209-15.
50. Paquet P, Jacob E, Damas P, Pierard GE. Recurrent fatal drug-induced toxic epidermal necrolysis (Lyell's syndrome) after putative beta-lactam cross-reactivity: Case report and scrutiny of antibiotic imputability. Crit Care Med. 2002;30(11):2580-3.
51. Rzany B, Hering O, Mockenhaupt M, et al. Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 1996;135(1):6-11.
52. Abe R, Yoshioka N, Murata J, Fujita Y, Shimizu H. Granulysin as a marker for early diagnosis of the Stevens-Johnson syndrome. Ann Intern Med. 2009;151(7):514-5.
53. Nagasawa M, Isoda T, Itoh S, et al. Analysis of serum granulysin in patients with hematopoietic stem-cell transplantation: its usefulness as a marker of graft-versus-host reaction. Am J Hematol. 2006;81(5): 340-8.
54. Fujita Y, Yoshioka N, Abe R, et al. Rapid immunochromatographic test for serum granulysin is useful for the prediction of Stevens-Johnson syndrome and toxic epidermal necrolysis. J Am Acad Dermatol. 2011;65(1):65-8.
55. Nakajima S, Watanabe H, Tohyama M, et al. High-mobility group box 1 protein (HMGB1) as a novel diagnostic tool for toxic epidermal necrolysis and Stevens-Johnson syndrome. Arch Dermatol. 2011;147(9):1110-2.
56. Bianchi ME, Manfredi AA. High-mobility group box 1 (HMGB1) protein at the crossroads between innate and adaptive immunity. Immunol Rev. 2007;220:35-46.
57. Sims GP, Rowe DC, Rietdijk ST, Herbst R, Coyle AJ. HMGB1 and RAGE in inflammation and cancer. Ann Revl Immunol. 2010;28:367-88.
58. Wittwer C, Boeck S, Heinemann V, et al. Circulating nucleosomes and immunogenic cell death markers HMGB1, sRAGE and DNAse in patients with advanced pancreatic cancer undergoing chemotherapy. Int J Cancer. 2013;133(11):2619-30.
59. Xiao J, Ding Y, Huang J, et al. The association of HMGB1 gene with the prognosis of HCC. PloS one. 2014;9(2):e89097.
60. Chen Z, Liew D, Kwan P. Real-world efficiency of pharmacogenetic screening for carbamazepine-induced severe cutaneous adverse reactions. PloS one. 2014;9(5):e96990.
61. Ferrell PB, Jr., McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9(10):1543-6.
62. Auquier-Dunant A, Mockenhaupt M, Naldi L, Correia O, Schroder W, Roujeau JC. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. Arch Dermatol. 2002;138(8):1019-24.
63. Watanabe R, Watanabe H, Sotozono C, Kokaze A, Iijima M. Critical factors differentiating erythema multiforme majus from Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Eur J Dermatol. 2011;21(6):889-94.
64. Iwai S, Sueki H, Watanabe H, Sasaki Y, Suzuki T, Iijima M. Distinguishing between erythema multiforme major and Stevens-Johnson syndrome/toxic epidermal necrolysis immunopathologically. J Dermatol. 2012;39(9):781-6.
65. Cho YT, Lin JW, Chen YC, et al. Generalized bullous fixed drug eruption is distinct from Stevens-Johnson syndrome/toxic epidermal necrolysis by immunohistopathological features. J Am Acad Dermatol. 2014;70(3):539-48.
66. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol. 2000;136(3):323-7.
67. Kano Y, Hirahara K, Mitsuyama Y, Takahashi R, Shiohara T. Utility of the lymphocyte transformation test in the diagnosis of drug sensitivity: dependence on its timing and the type of drug eruption. Allergy. 2007;62(12):1439-44.
68. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60-8.
69. Barbaud A, Collet E, Milpied B, et al. A multicentre study to determine the value and safety of drug patch tests for the three main classes of severe cutaneous adverse drug reactions. Br J Dermatol. 2013;168(3):555-62.
70. Barbaud A, Reichert-Penetrat S, Trechot P, et al. The use of skin testing in the investigation of cutaneous adverse drug reactions. Br J Dermatol. 1998;139(1):49-58.
71. Lin YT, Chang YC, Hui RC, et al. A patch testing and cross-sensitivity study of carbamazepine-induced severe cutaneous adverse drug reactions. J Eur Acad Dermatol Venereol. 2013;27(3):356-64.
72. Harr T, French LE. Severe cutaneous adverse reactions: acute generalized exanthematous pustulosis, toxic epidermal necrolysis and Stevens-Johnson syndrome. Med Clin North Am. 2010;94(4):727-42, x.
73. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J. 2002;8(1):5.
74. Araki Y, Sotozono C, Inatomi T, et al. Successful treatment of Stevens-Johnson syndrome with steroid pulse therapy at disease onset. Am J Ophthalmol. 2009;147(6):1004-11, 1011.e1.
75. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol. 2007;87(2):144-8.
76. Roujeau JC. Treatment of severe drug eruptions. J Dermatol. 1999;26(11): 718-22.
77. Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis. Clinical and pathophysiologic aspects. J Am Acad Dermatol. 1991;25(5 Pt 1):778-86.
78. Sakellariou G, Koukoudis P, Karpouzas J, et al. Plasma exchange (PE) treatment in drug-induced toxic epidermal necrolysis (TEN). Int J Artif Organs. 1991;14(10):634-8.
79. Yamada H, Takamori K. Status of plasmapheresis for the treatment of toxic epidermal necrolysis in Japan. Ther Apher Dial. 2008;12(5):355-9.
80. Szczeklik W, Nowak I, Seczynska B, Sega A, Krolikowski W, Musial J. Beneficial therapeutic effect of plasmapheresis after unsuccessful treatment with corticosteroids in two patients with severe toxic epidermal necrolysis. Ther Apher Dial. 2010;14(3):354-7.
81. Narita YM, Hirahara K, Mizukawa Y, Kano Y, Shiohara T. Efficacy of plasmapheresis for the treatment of severe toxic epidermal necrolysis: Is cytokine expression analysis useful in predicting its therapeutic efficacy? J Dermatol. 2011;38(3):236-45.
82. Chaidemenos GC, Chrysomallis F, Sombolos K, Mourellou O, Ioannides D, Papakonstantinou M. Plasmapheresis in toxic epidermal necrolysis. Int J Dermatol. 1997;36(3):218-21.
83. Kostal M, Blaha M, Lanska M, et al. Beneficial effect of plasma exchange in the treatment of toxic epidermal necrolysis: a series of four cases. J Clin Apher. 2012;27(4):215-20.
84. Arevalo JM, Lorente JA, Gonzalez-Herrada C, Jimenez-Reyes J. Treatment of toxic epidermal necrolysis with cyclosporin A. J Trauma. 2000;48(3):473-8.
85. Singh GK, Chatterjee M, Verma R. Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid. Indian J Dermatol Venereol Leprol. 2013;79(5):686-92.
86. Valeyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trial of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol. 2010;163(4):847-53.
87. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. Science. 1998;282(5388):490-3.
88. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med. 2012;367(21):2015-25.
89. Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. Acta Derm Venereol. 2007;87(3):206-18.
90. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139(1):33-6.
91. Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. Eur J Dermatol. 2010;20(6):743-7.
92. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008;58(1):33-40.
93. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis. Br J Dermatol. 2012;167(2):424-32.
94. Lee HY, Lim YL, Thirumoorthy T, Pang SM. The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre. Br J Dermatol. 2013;169(6):1304-9.
95. Yang Y, Xu J, Li F, Zhu X. Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China. Int J Dermatol. 2009;48(10):1122-8.
96. Patmanidis K, Sidiras A, Dolianitis K, et al. Combination of infliximab and high-dose intravenous immunoglobulin for toxic epidermal necrolysis:

successful treatment of an elderly patient. Case Rep Dermatol Med. 2012;2012:915314.
97. Gaitanis G, Spyridonos P, Patmanidis K, et al. Treatment of toxic epidermal necrolysis with the combination of infliximab and high-dose intravenous immunoglobulin. Dermatology. 2012;224(2):134-9.
98. Velez A, Moreno JC. Toxic epidermal necrolysis treated with N-acetylcysteine. J Am Acad Dermatol. 2002;46(3):469-70.
99. Redondo P, de Felipe I, de la Pena A, Aramendia JM, Vanaclocha V. Drug-induced hypersensitivity syndrome and toxic epidermal necrolysis. Treatment with N-acetylcysteine. Br J Dermatol. 1997;136(4):645-6.
100. Paquet P, Jennes S, Rousseau AF, Libon F, Delvenne P, Pierard GE. Effect of N-acetylcysteine combined with infliximab on toxic epidermal necrolysis. A proof-of-concept study. Burns. 2014;40(8):1707-12.
101. Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. Br J Dermatol. 2002;146(4):707-9.
102. Wojtkiewicz A, Wysocki M, Fortuna J, Chrupek M, Matczuk M, Koltan A. Beneficial and rapid effect of infliximab on the course of toxic epidermal necrolysis. Acta Derm Venereol. 2008;88(4):420-1.
103. Hunger RE, Hunziker T, Buettiker U, Braathen LR, Yawalkar N. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. J Allergy Clin Immunol. 2005;116(4):923-4.
104. Al-Shouli S, Abouchala N, Bogusz MJ, Al Tufail M, Thestrup-Pedersen K. Toxic epidermal necrolysis associated with high intake of sildenafil and its response to infliximab. Acta Derm Venereol. 2005;85(6):534-5.
105. Kreft B, Wohlrab J, Bramsiepe I, Eismann R, Winkler M, Marsch WC. Etoricoxib-induced toxic epidermal necrolysis: successful treatment with infliximab. J Dermatol. 2010;37(10):904-6.
106. Famularo G, Di Dona B, Canzona F, Girardelli CR, Cruciani G. Etanercept for toxic epidermal necrolysis. Ann Pharmacother. 2007;41(6):1083-4.
107. Gubinelli E, Canzona F, Tonanzi T, Raskovic D, Didona B. Toxic epidermal necrolysis successfully treated with etanercept. J Dermatol. 2009 36(3):150-3.
108. Scott-Lang V, Tidman M, McKay D. Toxic epidermal necrolysis in a child successfully treated with infliximab. Pediatr Dermatol. 2014;31(4):532-4.
109. Zarate-Correa LC, Carrillo-Gomez DC, Ramirez-Escobar AF, Serrano-Reyes C. Toxic epidermal necrolysis successfully treated with infliximab. J Investig Allergol Clin Immunol. 2013;23(1):61-3.
110. Worsnop F, Wee J, Natkunarajah J, Moosa Y, Marsden R. Reaction to biological drugs: infliximab for the treatment of toxic epidermal necrolysis subsequently triggering erosive lichen planus. Clin Exp Dermatol. 2012;37(8):879-81.
111. Paquet P, Paquet F, Al Saleh W, Reper P, Vanderkelen A, Pierard GE. Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis. Am J Dermatopathol. 2000;22(5):413-7.
112. Napolitano M, Giampetruzzi AR, Didona D, Papi M, Didona B. Toxic epidermal necrolysis-like acute cutaneous lupus erythematosus successfully treated with a single dose of etanercept: report of three cases. J Am Acad Dermatol. 2013;69(6):e303-5.
113. Redondo P, Ruiz de Erenchun F, Iglesias ME, Monedero P, Quintanilla E. Toxic epidermal necrolysis. Treatment with pentoxifylline. Br J Dermatol. 1994;130(5):688-9.
114. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet. 1998;352(9140):1586-9.
115. Nagata S. Apoptosis by death factor. Cell. 1997;88(3):355-65.