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 death2. 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 SJS5.

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

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 synonyms, 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). 

**Epidemiology**

SJS annual incidence is 1.2-6 cases per million inhabitants, with 0.4-2 cases per million inhabitants for TEN, 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%. 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.

Alopurinol and carbamazepine are SJS and TEN most frequent causal agents, but penicillins and cephalosporins have also been implied; causal agents vary according to the prescription trends. 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. 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). 

**Pathogenesis**

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

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

Adapted from Auquier-Dunant et al. 62.
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.

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 allopurinol has been described in the Chinese population with the HLA-B in allele 5801 and to carbamazepine with HLA-B1502. 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. Other cytokines and substances involved in this pathogenesis include the tumor necrosis factor alpha (TNF-\(\alpha\)), interferon \(\gamma\), interleukin 8 and nitric oxide, which are present in epidermal lesions and some have the capacity to bind to receptors that will induce apoptosis.

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. CD8 T cells and NK cells activation takes place after the drug is bound to the major histocompatibility complex (MHC I) and to the T cell receptor. 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. 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.

**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. Signs and symptoms start with a prodrome of onset with little involvement of palms and soles. The extent of skin involvement is what defines the clinical diagnosis and, hence, the prognosis of the patient. 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. 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.

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. Papular lesions develop later and, in case of progression, flaccid blisters are formed, which acquire a grayish color. 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. 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. 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
symptoms progression evolution to epidermal loss is 6-9 days\textsuperscript{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\textsuperscript{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\textsuperscript{39}.

Pulmonary involvement can occur as obliterant bronchiolitis or interstitial diffuse pneumonitis\textsuperscript{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\textsuperscript{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\textsuperscript{42}.

The factors that have been correlated with worse prognosis include old age of the patient, hematological abnormalities such as thrombocytopenia, neutropenia
and lymphopenia, in addition to serum creatinine elevation. 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. 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.

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. 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. 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.

### Diagnosis

The diagnosis requires clinico-histopathological correlation. Histopathological characteristics vary, but the most important include apoptotic 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. CD8+ lymphocytes are predominant on the epidermis and CD4+ in the papillary dermis.

Serum granulysin is useful for the diagnosis of SJS and TEN at early phases since it is elevated before mucosal involvement and epidermal loss. 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. 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.

Another test that has been proven useful is the measurement of serum High Mobility Group Box1 Protein (HMBG1) by means of an enzyme immunoassay. 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. Nakajima et al. analyzed the HMBG1 assay.

### 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

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Age</td>
<td>≥ 40 years</td>
<td>1</td>
</tr>
<tr>
<td>2 Heart rate</td>
<td>≥ 120 beats/min</td>
<td>1</td>
</tr>
<tr>
<td>3 Malignancy</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>4 Initial epidermolysis</td>
<td>≥ 10% of body surface area affected</td>
<td>1</td>
</tr>
<tr>
<td>5 Serum urea</td>
<td>≥ 10 mmol/l</td>
<td>1</td>
</tr>
<tr>
<td>6 Serum bicarbonate</td>
<td>&lt; 20 mmol/l</td>
<td>1</td>
</tr>
<tr>
<td>7 Serum glucose</td>
<td>≥ 14 mmol/l</td>
<td>1</td>
</tr>
</tbody>
</table>

Adapted from Bastuji-Garin et al.
and demonstrated it had a sensitivity of 45.5% and the advantage, versus granulysin measurement, that HMBG1 levels remain elevated for longer time\textsuperscript{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\textsuperscript{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\textsuperscript{60,61}.

**Differential diagnosis**

A difficult differential diagnosis is EMM, the clinical presentation of which can resemble an early phase SJS\textsuperscript{62}. EMM is a self-limited mucocutaneous condition that doesn’t belong to the SJS and TEN spectrum\textsuperscript{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 apart. Recent studies have demonstrated that differential diagnosis can be established by immunohistochemistry (Table 1)\textsuperscript{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 clinically 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\textsuperscript{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\textsuperscript{67,68}. ALDEN is an algorithm that

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**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 apoptotic keratinocytes.
allows not only finding the causal drug, but also knowing the drugs that might be safely prescribed again to the patient. 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. It has been used and reported in cases of SJS/TEN caused by antibiotics, carbamazepine, pseudoephedrine and trimethoprim-sulfamethoxazole.

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. In 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. Other studies have reported that a high-dose pulse steroid therapy elicits good results and lower incidence of complications. 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.

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

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

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. 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. Its good tolerance and low toxic potential has been shown in some studies. 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. 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. Its good tolerance and low toxic potential has been shown in some studies. 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.

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

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. 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.

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

<table>
<thead>
<tr>
<th>Authors</th>
<th>Gender/age</th>
<th>Dosage</th>
<th>Time to anti-TNF start since symptom onset</th>
<th>Improvement in 24 h</th>
<th>Causal agent</th>
<th>Previous treatment</th>
<th>SCORTEN</th>
<th>Time to re-epithelization after initiation of the biological process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer M (2002)</td>
<td>F/56</td>
<td>5 mg/kg single dose</td>
<td>5 days</td>
<td>Yes</td>
<td>SMX-TMP</td>
<td>None</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Worsnop F (2012)</td>
<td>F/32</td>
<td>5 mg/kg single dose</td>
<td>NR</td>
<td>NR</td>
<td>Sulfasalazine</td>
<td>IVIG 2 g/kg/day x 3 days</td>
<td>2</td>
<td>26 days</td>
</tr>
<tr>
<td>Wójciakiewicz A (2008)</td>
<td>F/17</td>
<td>5 mg/kg single dose</td>
<td>NR</td>
<td>Yes</td>
<td>SMX-TMP</td>
<td>IVIG 0.1 g/kg + dexamethasone</td>
<td>NR</td>
<td>12 days (80% of body surface area)</td>
</tr>
<tr>
<td>Al-Shouli S (2005)</td>
<td>M/67</td>
<td>300 mg single dose</td>
<td>NR</td>
<td>NR</td>
<td>Sildenafil</td>
<td>PDN</td>
<td>NR</td>
<td>10 days</td>
</tr>
<tr>
<td>Hunger R (2005)</td>
<td>F/69</td>
<td>5 mg/kg single dose</td>
<td>3 days</td>
<td>Yes</td>
<td>Diclofenac</td>
<td>NR</td>
<td>NR</td>
<td>5 days</td>
</tr>
<tr>
<td>Kreft B (2010)</td>
<td>M/31</td>
<td>5 mg/kg single dose</td>
<td>NR</td>
<td>Yes</td>
<td>Etoricoxib</td>
<td>PDN</td>
<td>NR</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Zárate-Correa L (2013)</td>
<td>F/51</td>
<td>300 mg single dose</td>
<td>7 days</td>
<td>NR</td>
<td>Ceftriaxone</td>
<td>Methyl-prednisolone</td>
<td>4</td>
<td>7 days</td>
</tr>
<tr>
<td>Zárate-Correa L (2013)</td>
<td>F/17</td>
<td>300 mg single dose</td>
<td>8 days</td>
<td>Yes</td>
<td>Carbamazepine</td>
<td>IVIG 2 g/kg/day x 1 day</td>
<td>3</td>
<td>16 days</td>
</tr>
<tr>
<td>Zárate-Correa L (2013)</td>
<td>F/20</td>
<td>300 mg single dose</td>
<td>NR</td>
<td>NR</td>
<td>Nevirapine, lamivudine and zidovudine</td>
<td>None</td>
<td>2</td>
<td>7 days</td>
</tr>
<tr>
<td>Scott L (2014)</td>
<td>M/7</td>
<td>5 mg/kg single dose</td>
<td>NR</td>
<td>Yes</td>
<td>Carbamazepine</td>
<td>IVIG 2 g/kg/day x 1 day</td>
<td>NR</td>
<td>10 days</td>
</tr>
<tr>
<td>Gubinelli E (2009)</td>
<td>F/59</td>
<td>25 mg/day Twice*</td>
<td>NR</td>
<td>In 48 h</td>
<td>Phenobarbital</td>
<td>Methyl-prednisolone</td>
<td>NR</td>
<td>20 days</td>
</tr>
<tr>
<td>Famularo G (2007)</td>
<td>M/59</td>
<td>25 mg/day Twice (days 4 and 8)*</td>
<td>NR</td>
<td>Yes</td>
<td>Ciprofloxacin</td>
<td>PDN</td>
<td>NR</td>
<td>6 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/57</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Carbamazepine</td>
<td>None</td>
<td>6</td>
<td>12 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>M/70</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Ofloxacin</td>
<td>None</td>
<td>3</td>
<td>8 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/28</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Lansoprazole/azathioprine</td>
<td>None</td>
<td>2</td>
<td>8 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/82</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Methyl-prednisolone</td>
<td>None</td>
<td>3</td>
<td>12 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>M/73</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Ciprofloxacin</td>
<td>None</td>
<td>4</td>
<td>8 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>M/78</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Carbamazepine</td>
<td>None</td>
<td>5</td>
<td>8.5 days (7-21)</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/72</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Phytotherapy</td>
<td>None</td>
<td>2</td>
<td>8 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/50</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Carbamazepine</td>
<td>None</td>
<td>6</td>
<td>20 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>M/71</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Carbamazepine</td>
<td>None</td>
<td>2</td>
<td>9 days</td>
</tr>
<tr>
<td>Paradisi A (2014)</td>
<td>F/55</td>
<td>50 mg single dose*</td>
<td>NR</td>
<td>NR</td>
<td>Diclofenac</td>
<td>None</td>
<td>3</td>
<td>9 days</td>
</tr>
</tbody>
</table>

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. 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. 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.

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 monitor the evolution and start supportive and specific treatment that allows for the remission, cure and prevention of complications and sequelae of the disease.

References


