DERMATOLOGICA SINICA 31 (2013) 191–195

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

REVIEW ARTICLE

French referral center management of Stevens–Johnson syndrome/toxic epidermal necrolysis

Laurence Valeyrie-Allanore [1,*], Saskia Ingen-Housz-Oro [1], Olivier Chosidow [1,2], Pierre Wolkenstein [1,2]

[1] Department of Dermatology, French Referral Center for Toxic Bullous Disease, Henri Mondor Hospital, Créteil, France
[2] Université Paris-Est Créteil Val de Marne, Créteil, France

ARTICLE INFO

Article history:
Received: Aug 21, 2013
Accepted: Sep 25, 2013

Keywords:
sequelae
Stevens–Johnson syndrome
toxic epidermal necrolysis
wound care

ABSTRACT

Drug-induced adverse reactions represent major health problems, with the skin being one of the most common targets. Approximately 2% of all drug-induced skin reactions are considered serious. Stevens–Johnson syndrome/toxic epidermal necrolysis corresponds to rare and acute life-threatening mucocutaneous reactions characterized by extensive necrosis and epidermal detachment. This review focuses on the management of these severe cutaneous reactions in the French Referral Center for Toxic Bullous Diseases. Early referral to a specialized unit, early diagnosis of severe cutaneous adverse reactions, prompt withdrawal of the culprit drug, improved symptomatic management, and specific dermatological care have contributed to better survival in the past 10 years and also has limited sequelae.

Introduction

Drug-induced adverse reactions represent major health problems,[1] with the skin being one of the most common targets.[2] Approximately 2% of all drug-induced skin reactions are considered *serious* according to the World Health Organization definition.[3] In 1994, Roujeau and Stern[4] estimated that one in every 1000 hospitalized patients experienced severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reactions with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. The SJS/TEN corresponds to rare and acute life-threatening mucocutaneous reactions characterized by extensive necrosis leading to epidermal detachment. The incidence of SJS/TEN is approximately one to two cases/million people/year.[5,6] Overall, in-hospital European mortality is estimated to be greater than 22%.[7]

This review focuses on the management of these severe cutaneous reactions in the French Referral Center for Toxic Bullous Diseases, which was established in 2004 by the French Ministry of Health.

Early diagnosis

Early diagnosis of SJS/TEN based on initial clinical symptoms is often difficult and delayed. However, prompt recognition, specific transfer, and early withdrawal of the culprit agent(s) may help in decreasing mortality.[8]

Clinically, SJS/TEN begins 4–28 days after starting drug(s)[7] and may continue for a few days even after the drug(s) has been withdrawn. For approximately 30% of cases, no causative drug is identified, and for 15%, drug responsibility is considered unlikely.[9]

General physical deterioration; fever; flu-like syndrome; ocular symptoms; ear, nose, and throat events; and skin pain precede dermatological manifestations and are key signs that contribute to early diagnosis. Atypical target lesions with a dark center may often be observed, without the typical three concentric rings of erythema multiforme major, mainly localized on the trunk and proximal limbs. Lesions evolve into confluent flaccid blisters leading to extensive erythema and skin detachment. Based on the extent of body surface area (BSA) involved, the disease is classified as follows: SJS, <10% BSA; SJS/TEN, 10–30% BSA; and TEN, >30% BSA.[6] The Nikolsky sign is a helpful clinical indicator of epidermal necrolysis. More than 80% of cases involve at least two mucous membranes, leading to painful erosions and can often precede skin lesions.[10]

The SJS/TEN visceral involvements include elevated liver and/or renal enzymes or bronchial and digestive-tract epithelial necrosis with sloughing of epithelia similar to epidermal detachment.[11,12]

* Corresponding author. Department of Dermatology, 51 Avenue du Maréchal de Lattre de Tassigny, F-94010 Créteil Cedex, France.
E-mail address: laurence.allanore@hmn.aphp.fr (L. Valeyrie-Allanore).

1027-8117/$ – see front matter
http://dx.doi.org/10.1016/j.dsi.2013.09.008

The differential diagnoses may include linear immunoglobulin A (IgA) bullous dermatosis, erythema multiforme major, pemphigus, generalized bullous fixed drug eruption, staphylococcal scaled-skin syndrome and, depending on the context, acute graft-versus-host disease and methotrexate-related skin necrosis, etc.

When to suspect the diagnosis

No specific score or test is available for SJS/TEN diagnosis. The diagnosis mainly relies on a broad spectrum of the following clinical signs or symptoms: (1) *severe prodromal illness:* fever up to 39°C, malaise, mucous membrane pain; (2) *clinical examination*: severe skin pain, mucous membrane erosions, atypical targets as described earlier, vesicles, and/or bullous lesions, Nikolsky sign; and (3) rapidly extensive rash and/or mucous membrane lesions. Diagnosis can be secondarily confirmed based on results of histological tests.[13]

The association of these three signs should lead to contacting the referral center for a transfer and beginning the best supportive care, which is explained in the "Management in a Dermatological Intensive Care Unit" section.

How to manage the disease initially

Management at the acute stage is sequential as follows (Table 1): (1) Evaluation of the severity and prognosis of the disease [SCORe of Toxic Epidermal Necrosis (SCORTEN) severity-of-illness scale, lung involvement][14–16]; (2) Prompt identification of the culprit drug; and (3) Rapid initiation of supportive care.

Table 1 Mandatory indications to correctly refer a patient with Stevens–Johnson syndrome/toxic epidermal necrolysis in an emergency to a dermatological intensive care unit.

Clinical examination	• *Vitals:* blood pressure, pulse/minute, temperature, SaO_2, and respiratory frequency • Evaluation of body surface area involved (Wallace's Rule of Nines) • Respiratory involvement
Biological investigations	• Full blood count • Urea and electrolytes, bicarbonate, glycemia • Blood gas (systematic analysis) • Chest X-ray • Photographs
Initial symptomatic management	• Peripheral venous access • Urinary catheter (with urogenital involvement and for evaluation of renal function) • Oxygen therapy, if necessary • Fluid resuscitation • Parenteral pain management • Isolated and heating room • No immunomodulating treatment before agreement of the referral team
Discontinue the offending agent without delay	• Molecule usually introduced between 4 and 28 days before disease onset • Maintain nonsuspected drugs (taken at least 2 months without any adverse effect) • *With major treatment:* replace the molecule with another from another pharmacological class
SCORTEN evaluation[13,14] (1 point is attributed to each of the following)	• Age >40 years • Presence of malignancy • Heart rate >120 beats/minute
Life threatening if total score ≤1	• Percentage of epidermal detachment >10% • Urea level >10 mmol/L • Serum glucose >14 mmol/L • Bicarbonate level <20 mmol/L
Contact referral center and organize transfer	• Intensive care unit transfer with SCORTEN score >1

Management in a dermatological intensive care unit

Early referral to a specific unit is associated with good survival.[4] The mean delay between disease onset and management in our department is estimated to be >3.5 days[17] and the overall mortality rate was >8% between 2005 and 2009, irrespective of the percentage of BSA involved (unpublished data). Until now, treatment of SJS/TEN has been mainly symptomatic, consisting of specific nursing care, maintenance of fluid and electrolyte balance, and nutritional support.

Early withdrawal of the culprit drug

Accurately documenting the medication history during the previous 2 months is mandatory to determine the index day, which is defined as the date of onset of SCAR-related symptoms or signs that progressed within 3 days.[7–9] The suspected drug(s) should be withdrawn as soon as possible after establishing the precise chronology of each drug. The usual practice is to maintain drugs with long-term use and discontinue all drugs that are nonessential. However, in some cases, the risk versus benefit for each drug must be weighed and whether a similar acting but non-cross-reactive drug is available as a substitute should be investigated. An algorithm for assessment of drug causality in epidermal necrolysis (ALDEN or algorithm of drug causality for EN), specifically developed for this disease, is systematically followed.[9]

Symptomatic management

Patients transferred to a dermatological intensive care unit are managed symptomatically as follows: (1) SJS/TEN is associated with significant fluid loss due to evaporation from erosions, edema, and blisters, resulting in hypovolemia and electrolyte imbalance. Fluid replacement must be started as soon as possible and adjusted daily. Peripheral venous access is preferentially established on nonlesional skin. Central venous lines are not routinely inserted because of septic risk.[18] (2) Patients are in a special intensive care room (Figure 1). Environmental temperature should be maintained at 28 °C to decrease energy consumption. (3) Enteral nutritional hypercaloric and hyperprotidic support is initiated most of the time using a nasogastric tube to prevent protein loss and promote healing. Parenteral nutrition is not recommended because it is frequently poorly tolerated and associated with increased risk of sepsis. (4) Antibiotic prophylaxis is not recommended. In order to prevent the risk of sepsis, patients are carefully handled. Bacterial and fungal cultures of skin, blood, and urine are performed at least two times a week. Antibiotics are initiated when clinical infection is diagnosed or strongly suspected and confirmed by a positive bacterial sample. (5) Standard prophylactic anticoagulation therapy is provided. (6) Management of pain is a major point, often underestimated, and necessitates respiratory monitoring. Pain is systematically assessed on a 10-point visual analog scale (VAS) every 4 hours and based on the VAS score obtained, the treatment is modified if necessary. If the VAS score is >4, morphine is initiated by patient-controlled analgesia mechanisms.[19] An intravenous (IV) pulse of dexamethasone (1 mg/10 kg) can be added when the patient is transported for a bath.[20] (7) Anxiety is systematically evaluated by a psychiatrist and specific treatment is initiated if necessary. (8) Systematic invasive mechanical ventilation is performed only with severe sepsis or life-threatening visceral failure. (9) Skin histology is systematically performed by direct and indirect

Figure 1 Dermatological intensive care unit room.

immunofluorescence assay to confirm the diagnosis and eliminate differential diagnoses.

Specific dermatological care

Wounds are cared for once a day, with minimal manipulation to prevent skin detachment. Wounds are treated conservatively, without large and aggressive skin debridement.[20] Detached epidermis acts as a natural biological dressing, which likely favors reepithelialization.

Bathing

Once a day, patients receive a bath containing a solution of chlorhexidine (1/5000). If bathing is not possible, the solution is sprayed two or three times/day. A morphine IV pulse (0.1 mg/10 kg) is recommended 30 minutes before the bath and/or an equimolar mix of oxygen and nitrogen monoxide (MEOPA) is preferred during the bath. The water temperature is systematically controlled (between 37 and 39 °C).

Skin care

Blister fluid is aspirated while maintaining the blister roof to protect the underlying dermis. Vaseline is systematically applied widely over all detached skin areas. Topical sulfa-containing medications should be avoided. Hydrocellular or absorbent nonadhesive dressings are applied at least once a day to cover pressure points, particularly on the back.

Mucous membrane management

Ocular, oral, nasal, genitalia, anal mucosa lubrication with emollient is mandatory to prevent and limit adhesion formation and sequelae. Crusts are cleaned daily using an isotonic sterile sodium chloride solution and covered with Vaseline.

Prevention of long-term ocular sequelae is a major challenge. Eyes should be regularly examined by an ophthalmologist. Antibiotic eyedrops, vitamin A, and antiseptic agents are instilled every 2 hours during the acute phase; adhesions are broken down using a glass rod at least two times a day. The mouth should be rinsed several times a day with an antiseptic or antifungal solution.

Specific systemic treatment

A specific immunomodulating treatment for SJS/TEN is still being debated. A number of immunosuppressive and/or anti-inflammatory therapies such as corticosteroids,[20,21] calcineurin inhibitors,[17,22] antitumor-necrosis-factor (TNF) therapies,[23,24] IVIg,[25–27] plasmapheresis,[28] and cyclosphosphamide[29] associated with supportive care have been evaluated, largely in small uncontrolled studies.

Thalidomide

Thalidomide could have been an interesting strategy because of its anti-TNF-α activity. Wolkenstein et al conducted a double-blind randomized, placebo-controlled trial, which was stopped because mortality was increased in the thalidomide group, thus suggesting that thalidomide has a detrimental effect in the treatment of TEN.[24]

IVIg

A possible effect of IVIg is that Fas-mediated cell death might be abrogated by monoclonal antibodies against the Fas ligand or the soluble form of the Fas receptor.[25] In fact, the benefit-to-risk ratio of IVIg is still debated. Bachot et al conducted a prospective monocentric noncomparative trial showing the lack of benefit of IVIg for mortality or progression of the disease.[26]

Ciclosporin

We conducted an open Phase II trial to evaluate the safety and possible interest of antiapoptotic and immunomodulating ciclosporin (3 mg/kg/day for 10 days, tapered over a month).[17] The results show that ciclosporin is well tolerated. While the SCORTEN predicted three deaths, none actually occurred ($p = 0.01$). Currently, if possible, based on medical history, patients receive ciclosporin (3 mg/kg/day for 10 days). However, further prospective studies are needed to confirm the benefits and the absence of significant adverse effects.

Follow-up

After the acute phase, SJS/TEN carries a non-negligible risk of severe sequelae, especially ocular and psychiatric events.[30–33] A specific multidisciplinary approach is routinely applied for their early detection and treatment.[34] Patients are examined at least at 2, 6, and 12 months after the acute stage (Figure 2). Specific sequelae may require monthly evaluation.

Patch testing with several suspected drugs can be proposed at 1 year, and a specific drug allergy card is used to definitively exclude the potential causative agent(s) and all members of the same pharmacological family but not the entire therapeutic group.

Conclusion

Prompt transfer of patients with SJS/TEN and management in a specific expert centre such as the French Referral Center for Toxic

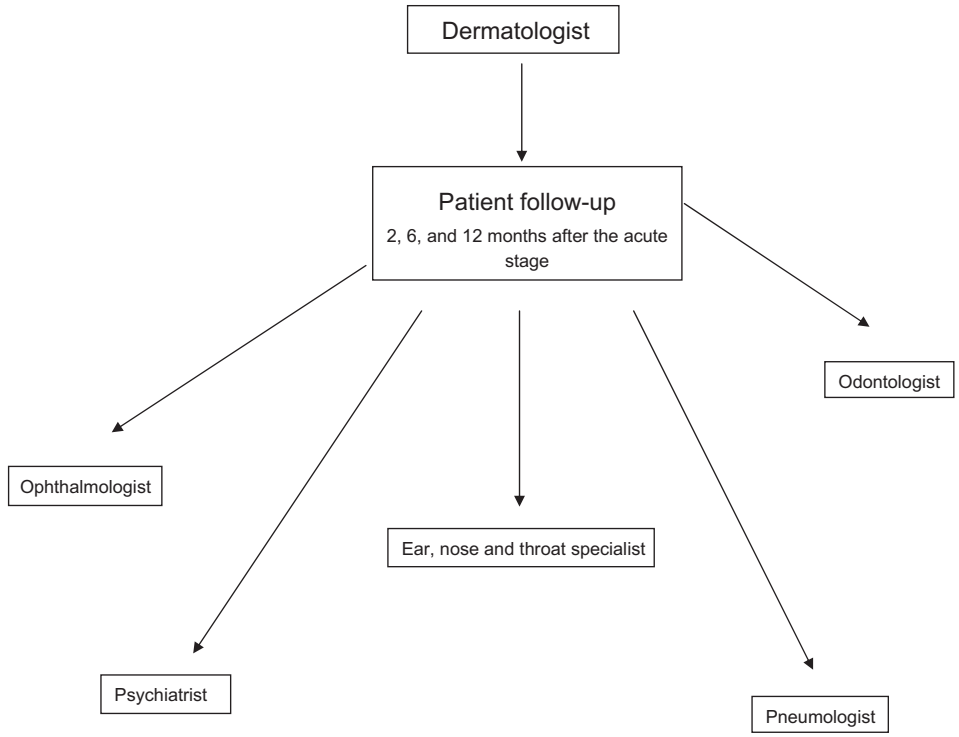

Figure 2 Multidisciplinary follow-up for Stevens–Johnson syndrome/toxic epidermal necrolysis.

Bullous Diseases have helped in early diagnosis, withdrawal of the culprit drug, and decreased mortality in these diseases. Symptomatic treatment and specific nursing care are of utmost importance in preventing and limiting sequelae. In addition, systematic long-term follow-up by an expert physician should be organized.

References

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;**279**:1200–5.
2. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy* 1997;**52**:388–93.
3. Ives TJ, Bentz EJ, Gwyther RE. Dermatologic adverse drug reactions in a family medicine setting. *Arch Fam Med* 1992;**1**:241–5.
4. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;**331**:1272–85.
5. 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**:92–6.
6. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. 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**:1019–24.
7. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J Invest Dermatol* 2008;**128**:35–44.
8. 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**:323–7.
9. 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**:60–8.
10. 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**:539–43.
11. Blum L, Chosidow O, Rostoker G, Philippon C, Revuz J, Roujeau JC. Renal involvement in toxic epidermal necrolysis. *J Am Acad Dermatol* 1996;**34**:1088–90.
12. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med* 1997;**23**:1237–44.
13. Haute Autorité de la Santé. *Nécrolyse épidermique toxique syndrome de Stevens–Johnson et de Lyell*. Protocole national de soins; 2010. http://www.has sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_1012781.
14. 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**:149–53.
15. Guégan S, Bastuji-Garin S, Poszepczynska-Guigné 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**:272–6.
16. de Prost N, Mekontso-Dessap A, Valeyrie-Allanore L, et al. Acute respiratory failure in patients with toxic epidermal necrolysis: clinical features and factors associated with mechanical ventilation. *Crit Care Med* 2013 in press.
17. 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**:847–53.
18. de Prost N, Ingen-Housz-Oro S, Ta Duong, et al. Bacteremia in Stevens–Johnson syndrome and toxic epidermal necrolysis: epidemiology, risk factors, and predictive value of skin cultures. *Medicine (Baltimore)* 2010;**89**:28–36.
19. Valeyrie-Allanore L, Ingen-Housz-Oro S, Colin A, Thuillot D, Sigal ML, Binhas M. Pain management in Stevens–Johnson syndrome, toxic epidermal necrolysis and other blistering diseases. *Ann Dermatol Venereol* 2011;**138**:694–7 [Article in French].
20. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens–Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol* 2007;**87**:144–8.
21. Lee HY, Dunant A, Sekula P, et al. The role of prior corticosteroid use on the clinical course of Stevens–Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. *Br J Dermatol* 2012;**167**:555–62.
22. Reese D, Henning JS, Rockers K, Ladd D, Gilson R. Cyclosporine for SJS/TEN: a case series and review of the literature. *Cutis* 2011;**87**:24–9.
23. 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**:923–4.
24. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998;**352**:1586–9.
25. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;**282**:490–3.
26. 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**:33–6.
27. 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**:424–32.
28. Furubacke A, Berlin G, Anderson C, Sjöberg F. Lack of significant treatment effect of plasma exchange in the treatment of drug-induced toxic epidermal necrolysis? *Intensive Care Med* 1999;**25**:1307–10.
29. Heng MC, Allen SG. Efficacy of cyclophosphamide in toxic epidermal necrolysis. Clinical and pathophysiologic aspects. *J Am Acad Dermatol* 1991;**25**:778–86.
30. Gueudry J, Roujeau JC, Binaghi M, Soubrane G, Muraine M. Risk factors for the development of ocular complications of Stevens–Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol* 2009;**145**:157–62.
31. Gaultier F, Rochefort J, Landru MM, et al. Severe and unrecognized dental abnormalities after drug-induced epidermal necrolysis. *Arch Dermatol* 2009;**145**:1332–3.
32. Meneux E, Wolkenstein P, Haddad B, Roujeau JC, Revuz J, Paniel BJ. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol* 1998;**91**:283–7.
33. Woo T, Saito H, Yamakawa Y, et al. Severe obliterative bronchitis associated with Stevens–Johnson syndrome. *Intern Med* 2011;**50**:2823–7.
34. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol* 2013;**69**:187 e1–e16.