

Severe cutaneous adverse reactions to drugs

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Purpose of review

This paper updates the treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis supported by relevant views about the pathogenesis.

Recent findings

Building on the thesis that Stevens–Johnson syndrome and toxic epidermal necrolysis are due to dermal cell apoptosis, molecular pathways that may lead to this have been proposed. Intravenous immunoglobulin is postulated to block apoptosis via the Fas pathway. Most series on the use of intravenous immunoglobulin in toxic epidermal necrolysis have been favourable. Tumour necrosis factor is also thought to be an important mediator of cell death in toxic epidermal necrolysis. There was impressive control of the progression of toxic epidermal necrolysis with intravenous anti-tumour necrosis factor antibody infliximab in two cases. Strong associations between human leukocyte antigen subtypes and severe cutaneous reactions due to allopurinol and carbamazepine have been described.

Summary

To date, there is no established treatment of Stevens–Johnson syndrome/toxic epidermal necrolysis. With advancing knowledge of the pathogenesis, it is hoped that better forms of treatment may result.

Keywords

drug allergy, Stevens–Johnson, toxic epidermal necrolysis, treatment

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and life-threatening cutaneous adverse reactions to drugs. Their incidence ranges from 0.4 to 1.2 and 1.2 to 6 per million person-years respectively [1]. The incidence of SJS and TEN in hospitalized patients was 0.07 per 1000 (data collected over 6 months) in a French hospital [2] and 0.2 per 1000 (data over 9 years) in a Chinese hospital [3*].

The most frequently implicated drugs in SJS and TEN are antibiotics (particularly sulfonamides), anticonvulsants, oxicam NSAIDs and allopurinol [1,4]. The association of oxicam NSAIDs with SJS and TEN was confirmed in a large multinational study. The Drug Safety Research Unit in the UK reported that four cases of SJS and none of TEN were reported from 206 830 who received selective cyclooxygenase-2 (COX-2) inhibitors. The four COX-2 inhibitors caused one reaction each [5]. In China and other countries with a large oriental population, traditional Chinese medicines should also be considered as a causative drug for SJS/TEN [3*].

SJS and TEN are characterized by epidermal detachment ranging from mild (0–10% of total body surface area in SJS), moderate (10–30% in SJS/TEN overlap) and severe (>30% in TEN). They are hence considered as a spectrum of drug-induced skin diseases distinct from erythema multiforme and maculopapular rashes [6]. The evolving definitions of SJS and TEN proposed by various authors have been well documented [7].

Both SJS and TEN begin with a prodromal phase of fever, sore throat and stinging eyes for 1–3 days. Mucosal lesions subsequently appear, followed by cutaneous lesions, which begin as erythematous macules with dusky centres that coalesce. As the necrotic epidermis detaches from the underlying dermis, flaccid blisters that tear easily appear. Mucous membranes erosions are present in over 90% of patients with TEN, involving not just the conjunctival, oral and genital mucosa, but also that of the trachea, bronchi and gastrointestinal tract. Bircher considered skin pain, Nikolsky's sign and epidermolysis to be the most important 'danger signs' of an impending severe cutaneous adverse reaction [8]. The mortality of SJS is approximately 5% and that of TEN 30–50% [7].

Pathogenesis

The pathogenesis of SJS/TEN is not fully understood, but there have been many advances that will contribute

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Abbreviations

CLA	cutaneous lymphocyte-associated antigen
IVIg	intravenous immunoglobulin
SJS	Stevens–Johnson syndrome
TEN	toxic epidermal necrolysis
TNF	tumour necrosis factor

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to formulating a pathophysiological model for SJS and TEN.

Genetic susceptibility plays a role in the pathogenesis of TEN/SJS. A recent study [9] in a Han Chinese population showed that HLA-B*1502 is strongly associated with carbamazepine-induced SJS. While all patients with SJS from carbamazepine had the HLA-B*1502 allele, this was observed in only 3% of the tolerant patients. Furthermore, in contrast to SJS/TEN, HLA-B*1502 was not observed in patients with other forms of carbamazepine-induced reactions such as hypersensitivity syndrome or maculopapular eruptions [10]. Importantly, these findings have not been replicated in Caucasian patients [11], although a European study from the RegiSCAR group found that of 12 patients with carbamazepine-induced SJS/TEN, all four who were positive for the HLA-B*1502 allele had Asian ancestry [12]. In another study in Han Chinese, HLA-B*5801 allele was an important genetic risk factor for allopurinol-induced SJS and TEN [13]. HLA-A*0206 was associated with SJS with ocular complications in Japanese patients, though the authors did not list the causative drugs, which are likely to be multiple [14].

The association between specific HLA subtypes and drug reactions is patently different in different populations and more studies must be performed to understand this phenomenon. The knowledge of the HLA association with drug allergy will be useful in primary and secondary prevention. For example, a physician may order HLA typing to estimate the patient's risk of reaction before initiating treatment with a drug commonly associated with allergy. For a patient who is developing a maculopapular rash after drug treatment, genetic testing may predict if the reaction is likely to progress to SJS or TEN. Pharmacoeconomic studies must be carried out before routine genotyping for a particular HLA allele prior to prescription of drugs can be recommended. It had been shown that pretesting for HLA-B*5701 reduced the incidence of abacavir hypersensitivity syndrome in HIV patients [15•].

The T lymphocyte is accepted as the key mediator in most delayed drug reactions [16•,17]. Over the course of the drug reaction, the T cells' expression of cutaneous lymphocyte-associated antigen (CLA) rises and falls in parallel with disease severity, facilitating lymphocytic traffic to the skin. There is also a corresponding increase in the E-selectin expression (the ligand of CLA) on cutaneous endothelial cells. The elevated level of CLA tends to persist in the dermal lymphocytes compared with those in the peripheral blood. Tumour necrosis factor (TNF)- α and IFN γ were also strongly expressed by peripheral blood mononuclear cells early in the course of the reaction [18]. In another report, most of the lymphocytes derived from blister fluid of patients with TEN were found

to be T cell receptor $\alpha\beta$ -positive, CD3-positive and CD8-positive. These cells are activated and most express CD56 as well. They displayed in-vitro cytotoxic activity via the perforin/granzyme-mediated pathway in response to the appropriate drug [19].

The overriding pathological finding in SJS and TEN is dermal cell apoptosis, which can be triggered by at least four pathways: Fas and Fas ligand, TNF- α , TNF- α -related apoptosis-inducing ligand (TRAIL) and granzyme B. Increased serum soluble Fas ligand concentration was demonstrated in patients with TEN and SJS patients compared to patients with drug-induced erythema multiforme and to healthy controls [20]. The peripheral blood mononuclear cells (PBMCs) secreted Fas ligand when stimulated by the appropriate drugs [20]. Furthermore, levels of perforin, granzyme B and Fas ligand have been shown to correspond to disease severity in delayed reactions to drugs [21].

Lesional skin from patients with SJS and TEN overexpress TNF- α , IFN γ , IL-2, IL-5, IL-13, CCR-3, CXCR3, and CXCR4 [22••]. Because both the Th1 and Th2 cytokines are expressed, the authors concluded that there was no skewing of the lymphocytic phenotype. Cutaneous T cell-attracting chemokine (CTACK)-CCR10 mRNA levels were found to be raised in lesional skin of patients with SJS/TEN, returning to baseline after resolution of the disease [23].

The role of the dendritic cell has been assessed in patients with extant maculopapular rashes induced by amoxycillin. The drug-induced changes in the dendritic cells isolated from these patients include increases in cell proliferation and HLA-DR, CD80 and CD86 expression [24].

Validation of SCORTEN

In 2000, Bastuji-Garin *et al.* [25] proposed a TEN-specific severity of illness score based on seven prognostic factors including age, presence of malignancy, surface area involved, heart rate, serum urea, bicarbonate and glucose. The SCORTEN was to be calculated within 24h of admission and accurately predicted the risk of mortality. SCORTEN has since been validated in a US-based patient cohort and has been used as a valuable tool for predicting patient outcome, as well as a basis of comparison for efficacy of treatment [26].

The performance of SCORTEN has recently been assessed over the first 5 days of hospitalization and found to be good on each day, but predicted the mortality rate most accurately on day 3 of hospitalization. Delay to admission did not appear to affect the prognosis [27••].

Treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis

Both SJS and TEN are potentially life-threatening conditions and require prompt recognition and diagnosis, with early withdrawal of the potential causative drugs. An observational study [28] showed that mortality rates decreased from 26 to 5% when causative drugs with short half-lives were withdrawn once blisters or erosions appeared. There was no difference for drugs with long half-lives. Overall, the earlier the causative drug was withdrawn, the better the prognosis (odds ratio 0.69 for each day). In one instance, continued use of allopurinol 10 days beyond the onset of TEN was associated with delayed re-epithelialization [29].

Priority should also be given to transferring patients with TEN to a specialized intensive care unit or burns unit. Principles of supportive therapy for patients with TEN are similar to those with major burns and include maintenance of fluid and electrolyte balance, nutritional support, control of environmental temperature, use of appropriate nonadhesive dressing and analgesia. The ophthalmologist should be consulted early [30]. It has been argued that, unlike burns, beyond the initial insult to the skin, there is ongoing immunological attack, so it is worthwhile suppressing the immune response.

Immunosuppression

A Cochrane review on interventions in TEN in 2002 bleakly concluded that there was 'no reliable evidence on which to base treatment for TEN'. Throughout the literature, there has only been one randomized controlled trial using thalidomide in the treatment of TEN, but it was terminated early due to excessive mortality in the study arm. Since then, although there have been many more studies published, the literature is still dominated by uncontrolled trials, retrospective studies, case series and anecdotal reports.

Systemic corticosteroids

The use of corticosteroids in the management of TEN remains controversial. The use of corticosteroids as an anti-inflammatory agent must be tempered with the risk of increasing the already high risk of septic complications. Current available data do not allow for the recommendation of corticosteroids as a therapy for TEN, particularly if major skin loss has already occurred. High-dose corticosteroid, however, may have a place for use in patients who present with early TEN during the erythrodermic stage before skin loss occurs. Even so, the use should be limited to the first 48 h to avoid serious complications [31–33].

Unlike in TEN, the potential benefit of corticosteroids is less controversial for SJS. A prospective analysis of 67 consecutive patients with SJS treated with cortico-

steroids concluded that prompt treatment with systemic steroids reduces morbidity and improves outcomes of SJS patients [34].

Intravenous immunoglobulin

In a landmark paper in 1998, Viard *et al.* [35] reported that commercial preparations of intravenous immunoglobulin (IVIg) contained natural antibodies to Fas (CD95) that were able to block the binding of FasL to Fas. *In vitro*, this potentially inhibited cell death mediated by recombinant FasL. IVIg may affect the lymphocytes as well because in a child with TEN due to lamotrigine, it was shown that the high levels of CD8, CLA and CD69 in blister-fluid lymphocytes decreased 24 h after IVIg infusion [36].

There are many case reports and nine studies with 10 or more patients with TEN treated with IVIg, the largest of which is a retrospective multicentre study of 48 patients [37]. Seven of these nine studies showed a trend towards a benefit on the mortality rate of TEN with high-dose IVIg [38*,39*].

Of the three studies that did not show any benefit on mortality [40–42], two were retrospective and only one was a prospective noncomparative evaluation of IVIg therapy at 2 g/kg in 34 patients with SJS and TEN from a single center [40]. Progression of disease and mortality rates were not significantly different from that predicted by SCORTEN (11 deaths, 32% versus 8 deaths, 24%). The mean interval between onset and IVIg administration was 4 days. The mean age of the survivors was 37.6 years compared to 66.4 years in those who perished. Significantly, two out of 12 patients with HIV died.

Patients who received IVIg within the first 4 days of onset of eruption appear to have a shorter time to cessation of progression and to complete re-epithelialization compared to those who received it later. Statistical significance was not reached probably due to the small sample size of 16 patients. The authors concluded that most benefit would be derived from IVIg if it was given within 4 days of onset of symptoms [43].

The use of IVIg in children with SJS/TEN has been uniformly favourable [44]. TEN in children, however, has been reported to have a better spontaneous prognosis than in adults, with more rapid re-epithelialization and lower mortality [45].

There have been a few cases of SJS/TEN who were treated with both corticosteroids and IVIg, both in the paediatric as well as adult populations. The experience suggests that these patients take a longer time to respond than those who have not received corticosteroids [37,44].

In addition to lack of controlled studies, it is difficult to compare the existing ones because of variation in patient characteristics, treatment protocols, IVIg dosages, commercial IVIg brands and intervals between TEN onset and initiation of treatment. Despite the lack of randomized controlled trials, the majority of trials point towards a beneficial effect of IVIg on TEN, especially when it is administered early in the disease course and in sufficiently high total dose (beyond 2 g per kg bodyweight). Based on this, we support the use of IVIg in TEN, while acknowledging that further work needs to be done in the form of randomized controlled trials [38[•]].

Anti-tumour necrosis factor agents

Thalidomide was tested in a double-blind placebo controlled trial with the rationale of inhibiting TNF- α production. It was discontinued early, however, due to unexpectedly high mortality in the thalidomide group. The increased mortality could be attributed to a paradoxical increase in TNF- α production as thalidomide also acts as a costimulator of CD8⁺ cytotoxic T cells *in vitro*, or alternatively because TNF could be antiapoptotic in TEN [46].

The use of anti-TNF monoclonal antibody in the treatment of TEN was first reported from Germany in a 56-year-old woman treated with cotrimoxazole. One dose of intravenous infliximab 5 mg/kg body weight, administered 4 days after the onset of symptoms, resulted in the halting of disease progression within a few hours [47]. In a more recent case report, a 69-year-old woman received a single dose of infliximab 5 mg/kg within 3 days of onset of symptoms, with cessation of epidermal detachment in 24 h and complete re-epithelialization after 5 days [48]. In patients with TEN, TNF- α is strongly expressed in keratinocytes and macrophages of lesional skin, and higher concentrations are found in cutaneous blister fluid. In this case, expression of TNF- α in the skin was examined before and 24 h after anti-TNF- α therapy, demonstrating that TNF- α protein and mRNA expressions by inflammatory cells in the dermis was markedly reduced after infusion, reaching levels lower than normal. This promising new treatment of TEN has to be evaluated in larger groups of patients.

Other agents

Ciclosporin is an immunosuppressant that has antiapoptotic properties. There have been several case reports and one case series of 11 patients documenting treatment of TEN with ciclosporin [49]. All the patients had severe TEN, and ciclosporin was administered at 3–5 mg/kg/day until the patient had re-epithelialized, except in the case series where it was given for 4 weeks. There appeared to be a shorter time to arrest of disease progression with no greater risk of septic complications. The patients in the case series, however, were compared to historical controls

who received cyclophosphamide and prednisolone, keeping in mind that steroids are no longer recommended for TEN. Since then, there have been no further studies on ciclosporin.

Redondo *et al.* [50] described the use of intravenous N-acetylcysteine in the treatment of two patients with hypersensitivity syndrome and TEN from anticonvulsants. They postulated that N-acetylcysteine could be beneficial as it is a known precursor of glutathione, a molecule involved in the detoxification pathway of several drugs including anticonvulsants. N-acetylcysteine also inhibits the production of TNF- α and IL-1 β *in vitro*. Following this, two more patients with TEN were treated with intravenous N-acetylcysteine 300 mg/kg/day with complete re-epithelialization in 7 days [51]. More recently, N-acetylcysteine was used together with IVIg with rapid recovery in a HIV positive patient with TEN and toxic hepatitis from the antiretroviral drug nevirapine [52].

Although the authors of both papers suggested that N-acetylcysteine was safe to use aside from the possibility of increased clearance of other drugs other than the culprit drug, a surprisingly high incidence of angioedema (75%) was found in a small series of patients with anticonvulsant hypersensitivity syndrome treated with intravenous N-acetylcysteine 2 g at 6-hourly intervals [53]. Also, a randomized trial showed lack of effectiveness of N-acetylcysteine in prevention of hypersensitivity reactions to trimethoprim-sulfamethoxazole in patients with HIV infection [54].

Ocular manifestations and management

The majority (60 to 88%) of patients with SJS and TEN have ocular involvement [55]. This may range from mild (lid oedema, conjunctival injection or chemosis) to moderate (conjunctival membrane/pseudomembrane, corneal erosion or epithelial defect) to severe manifestations that are vision threatening (conjunctival fornix fore-shortening, symblepharon, corneal infiltrate or ulceration) [56]. Although the majority of patients have mild manifestations, long-term sequelae occur in almost half of all patients, the most common being dry eyes, conjunctival or corneal scarring and symblepharon [57].

Early ophthalmological consultation should be sought for all patients to ensure best outcome, with judicious use of topical lubricants, steroids and antibiotics. Patients with ocular adhesions require daily lysis and sweeping of the fornix. Therapeutic gas permeable contact lenses may be used for patients with corneal epithelial defects.

As with systemic treatment, the efficacy of topical treatments has not been evaluated in any randomized controlled prospective study. According to current knowledge, the use of systemic or topical steroids apparently fails to

prevent long-term complications [56]. Cases of corneal opacification would benefit from corneal transplant with or without limbal stem cell transplantation. A recent paper [58] suggested that cultivated limbal stem cell transplant for SJS resulted in better clinical results and vision than conventional limbal stem cell transplant.

Treatment of Stevens–Johnson syndrome and toxic epidermal necrolysis in patients with HIV/AIDS

The advent of HIV/AIDS brings new challenges to the allergist. These patients are treated with multiple agents that can lead to the development of SJS/TENS, including antituberculosis drugs, antiretroviral therapy (especially nevirapine and abacavir) and sulfonamides (trimethoprim-sulfamethoxazole and dapsone). HIV positivity is itself a risk factor for serious cutaneous reactions due to antituberculosis therapy, increasing the odds by 3.8 times [59]. It is possible that HIV-positive patients with SJS or TEN may have a poorer outcome [40].

Drug challenge after treatment of Stevens–Johnson syndrome or toxic epidermal necrolysis

Classical teaching holds that drug challenge must be avoided if a patient has developed severe reaction to the implicated drug. This position is supported by the European Network for Drug Allergy, which lists SJS and TEN among the contraindications for drug provocation testing [60]. This doctrine has been questioned on occasion, especially when the reaction had been SJS and not TEN, which has a lower mortality than TEN, and when there are no reasonable alternative drugs. A 60-year-old woman with chronic myeloid leukaemia developed SJS 12 days into treatment with imatinib 400 mg daily. Twenty-two days after imatinib was discontinued and after all the lesions have healed, the drug was reintroduced. Oral lesions started the next day, and the drug was again discontinued. The doctors waited 1 month before using imatinib 100 mg daily together with prednisolone. The patient could subsequently tolerate the medication [61]. It has been reported that skin patch test may predict a positive provocation test for patients with tetrazepam allergy. The authors did not re-challenge a patient with a history of SJS and strongly positive patch test [62]. We have also challenged patients with individual antituberculous drugs after they have developed SJS while receiving combination chemotherapy. Drug challenge after TEN is still taboo.

Conclusion

SJS and TEN are rare but serious conditions with significant mortality rates, reflecting the inadequacy of current available treatment. Early withdrawal of causative drugs and meticulous supportive therapy still form the cornerstone of treatment. The use of IVIg is supported by most

studies, albeit uncontrolled ones. The use of anti-TNF monoclonal antibodies appears promising with dramatic success in two cases so far. Recent understanding of pathogenic mechanisms may lead to therapies that target other mediators of apoptosis. Multicentre studies and collaborations such as the RegiSCAR project are needed to establish effective treatment protocols for these uncommon conditions.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 360–361).

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