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Drug-induced Stevens Johnson syndrome and toxic epidermal necrolysis: Interpreting the systematic reviews on immunomodulatory therapies

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ABSTRACT

Drug-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are non-immunoglobulin E-mediated severe cutaneous adverse reactions with a high risk of morbidity, mortality, and physical and mental health impact. These are associated with certain high-risk drugs, human leukocyte antigen (HLA)-specific genotypes and ethnicities. HLA class I–restricted oligoclonal CD8 cytotoxic T-cell responses occur at the tissue level in SJS/TEN. Cytotoxic T cells are the T effector cells that result in keratinocyte apoptosis (cell death) mediated by T effector molecules granzyme B, perforin, granulysin, gamma interferon, tumor necrosis factor-alpha, and lipocalin-2. The clinical hallmarks of SJS/TEN include fever, ≥2 mucosal involvements (ocular, oral, and genital), and positive Nikolsky sign with epidermal detachment. Systematic reviews on immunomodulatory treatments remain limited by the paucity of randomized controlled trials, heterogeneity of studies, and non-standardization of outcome measures. Preventive HLA genotype screening before the prescription of carbamazepine and allopurinol may further reduce the incidence of SJS/TEN. The role of immunomodulatory treatments in SJS/TEN is at present not supported by robust evidence from systematic reviews given the lack of randomized controlled trials. The evidence for improved survival with off-label use of corticosteroids plus intravenous immunoglobulins, ciclosporin plus intravenous immunoglobulins, and ciclosporin alone has not been demonstrated by network meta-analyses and meta-regression. In the real-world clinical setting, systemic corticosteroids (in SJS and overlap SJS/TEN), ciclosporin, and etanercept (in TEN) appear to be the off-label treatments currently most widely used.

Keywords: Drug hypersensitivity; immunomodulation; pharmacogenetics

1. Introduction

Severe cutaneous adverse reactions comprise 3 main phenotypes of serious non-immunoglobulin E mediated immune-mediated drug hypersensitivity reactions: acute generalized exanthematous pustolosis, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). These 3 phenotypes differ in their clinical presentation, T-effector cell and molecules involved, and T-effector outcomes [1] although there may sometimes be overlap features [2]. SJS/TEN are associated with a high risk of morbidity, mortality, and potential physical and mental health impact [3].

2. Clinical features

The clinical hallmarks of SJS/TEN include fever, ≥2 mucosal involvement (ocular, oral, and genital), and positive Nikolsky sign with epidermal detachment. Patients often present with a prodrome of fever, malaise, upper respiratory symptoms, difficulty swallowing, and pain or burning sensation affecting the skin and mucous membranes. These may precede the cutaneous manifestations by up to 3 days. Epidermal detachment usually begins on the trunk and then progresses to involve the extremities, head, and neck. Over 90% of patients have involvement of oral, ocular, or genital mucosa that is, with overlap features of SJS. The time to onset from initiation of the drug is usually a median of 2 weeks, and may range from 4 days to 8 weeks. There may still be a lag time from cessation of the suspected drug to improvement/resolution of SJS/TEN.

3. Immunopathogenesis

Human leukocyte antigen (HLA) class I–restricted oligoclonal CD8 cytotoxic T-cell responses occur at the tissue level in SJS/TEN [1]. Cytotoxic T cells are the T effector cells in SJS/TEN which result in keratinocyte apoptosis (cell death) mediated by the T effector molecules granzyme B, perforin, granulysin, gamma interferon, tumor necrosis factor-alpha (TNF-α) and lipocalin-2. The correlations between immunopathogenesis and the hypothesized role of immunomodulatory therapies are as follows:

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(1) Dysregulation of Fas-mediated apoptosis mitigated through autoantibodies against Fas present in intravenous immunoglobulins (IVIG) [4]
(2) Effects of activated T-lymphocytes, cytokines, and granulysin at the cellular level, cytotoxicity, and apoptosis of skin and mucosal surfaces [5]; potentially mitigated through the use of TNF-α inhibitors such as etanercept or infliximab [6]. Thalidomide which reduces TNF-α production, was associated with excessive deaths in the treatment arm of a randomized controlled trial and thus no longer considered [7]. Cyclosporin inhibits interleukin-15 (IL-15) and interleukin-17 which are the main drivers of TNF-α [8]
(3) Cell apoptosis mitigated through DNA alkylation and T-cell inhibition by cyclophosphamide used in an early case series [9]
(4) Removal of pathogenic particles from the blood through plasmapheresis [10] or haemoperfusion
(5) Enhanced bioregeneration of skin tissue through accelerated re-epithelialization with granulocyte colony-stimulating factor [11] and downregulation of nuclear factor kappa light chain enhancer of activated B cells with cyclosporin and N-acetylcysteine [12, 13].

4. Epidemiology

The most common causes of drug-induced SJS/TEN from electronic medical records [14], registry databases [15, 16], and systematic reviews of case reports [17] comprise the drug classes antibiotics (sulfonamides, penicillins, cephalosporins, and quinolones) [18], anticonvulsants (carbamazepine, phenytoin, and lamotrigine), analgesics/anesthetics (non-steroidal anti-inflammatory drugs), and antineoplastics (imatinib, methotrexate, lenalidomide, and nivolumab). In terms of individual drugs, phenytoin, trimethoprim-sulfamethoxazole, carbamazepine, lamotrigine, allopurinol, acetaminophen, amoxicillin, ibuprofen, phenobarbital, and vancomycin were the most reported drugs, each associated with over twenty SJS/TEN cases. [17] The most commonly associated immunocompromising conditions were cancer, autoimmune diseases, and human immunodeficiency virus infection. There is emerging evidence that immune checkpoint inhibitors used in cancer treatment appear to be increasingly associated with SJS/TEN [19].

5. International management guidelines

Most international guidelines on the management of SJS/TEN in pediatric and adult patients recommend the importance of prompt discontinuation of the offending drug and the need for supportive care [20]. Expert dermatologists and working groups from North America [21], the United Kingdom [22, 23], France [24], and India [25] concur that supportive care remains key to the management of SJS/TEN although there are regional differences in the expectation of best supportive care. Supportive care includes early access and admission to an intensive care unit or burns unit for monitoring and wound care; involvement of a multidisciplinary team including dermatology, ophthalmology, gynecology, urology, gastroenterology, otolaryngology, pulmonology, intensive care specialists, wound care; careful control of fluid and electrolyte status, temperature regulation, prevention of infection and nutritional services as needed. SCORe of toxic epidermal necrosis (SCORTEN) [26], a prognostic scoring system used in SJS/TEN takes into account the patient's age, presence of underlying malignancy, heart rate, body surface area with epidermal detachment at presentation, serum urea levels, serum bicarbonate levels, and serum glucose levels. The presence of each factor scores 1 point, where total SCORTEN ≥5 is associated with 90% mortality.

6. Systematic reviews on immunomodulatory therapies

Evidence on the use of immunomodulatory therapies from recent systematic reviews [27–30] remains limited in view of SJS/TEN being a rare disease, paucity of randomized controlled trials (RCTs), heterogeneity of studies, wide range of causative drugs, and nonstandardization of outcome measures used in the various studies. Immunomodulatory drugs commonly described in SJS/TEN literature include corticosteroids, ciclosporin, infliximab, etanercept, IVIG, combination of corticosteroids with IVIG, and plasmapheresis.

Preventive prescreening of HLA genotypes [31–33] and genetic variants before prescription of high-risk drugs for SJS/TEN for example HLA-B*1502 for carbamazepine and HLA-B*5801 for allopurinol has over time reduced the incidence of SJS/TEN to these drugs in countries where prescreening has been made mandatory or highly recommended. Prescreening strategies which may be cost-effective in one country within the Asia Pacific region [34–37] may not be cost-effective in another country [38–40] because of different healthcare financing systems, cost of HLA testing, availability of alternative drugs, and different methods of modeling or health technology assessment used in each country.

In a systematic review and network meta-analysis (NMA) evaluating the effects of systemic immunomodulating therapies on mortality for SJS/TEN overlap and TEN [28], a frequentist random-effects model was used to evaluate the impact of these therapies on SCORTEN-based standardized mortality ratio (SMR). Comprising 67 studies involving 2,079 patients, an NMA of 10 treatments showed that none was superior to supportive care in reducing mortality rates. Thalidomide was associated with a significantly higher mortality rate (odds ratio, 11.67; 95% confidence interval [CI], 1.42–95.96). For SMR, an NMA of 11 treatment arms showed that a combination of corticosteroids and IVIG was the only treatment with significant survival benefits (SMR, 0.53; 95% CI, 0.31–0.93). Although ciclosporin and etanercept appeared to be promising therapies, there were insufficient studies to inform the evidence.

In another systematic review where SCORTEN-score based effectiveness of immunomodulatory therapies on SJS/TEN was studied [29], 6 meta-analyses were carried out on patients with SJS/TEN who received supportive care only or in combination with immunomodulating drugs: corticosteroids, ciclosporin, etanercept, IVIG or a combination of corticosteroids plus IVIG. Multivariate meta-regression and NMA performed on 38 pooled studies (1,827 patients) showed log(SMR) of –0.13 (95% CI, –0.42 to 0.16) for corticosteroids, –0.39 (95% CI, –0.87 to 0.09) for IVIG, –0.88 (95% CI, –1.47 to –0.29) for cyclosporin, –0.95 (95% CI, –1.82, to –0.07) for etanercept and –0.56 (95% CI, –0.94, to 0.19) for corticosteroids plus IVIG; compared to 0.13 (95% CI, –0.15 to 0.40) for supportive treatment. The meta-regression analysis confirmed that ciclosporin and corticosteroids plus IVIG were associated with less deaths than predicted by SCORTEN. However, the NMA showed that no treatment achieved a significant reduction in the SMR.

A recent Cochrane systematic review published in 2022 [30] assessed the effects of systemic therapies for the treatment of SJS,

TEN, and SJS/TEN overlap syndrome. Inclusion criteria included only RCTs and prospective observational comparative studies of participants of any age with a clinical diagnosis of SJS, TEN, or SJS/TEN overlap syndrome. All systemic therapies studied to date, permitted comparisons between each therapy, as well as between therapy and placebo were included. The primary outcomes were SJS/TEN-specific mortality and adverse effects leading to discontinuation of SJS/TEN therapy; secondary outcomes included time to complete re-epithelialization, intensive care unit length of stay, total hospital length of stay, illness sequelae, and other adverse effects attributed to systemic therapy. The systematic review was carried out using the Grading of Recommendations, Assessment, Development, and Evaluations methodology—a transparent framework for developing and presenting summaries of evidence and providing a systematic approach for making clinical practice recommendations [41]. Nine studies (3 RCTs and 6 prospective, controlled observational studies; sample sizes ranging from 10 to 91; a total of 308 participants from 7 countries) were included. Most studies did not report study duration or time to follow-up. Two studies reported a mean SCORTEN of 3 and 1.9. Seven studies did not report SCORTEN, although 4 of these studies reported average or ranges of body surface area (means ranging from 44% to 51%). The interventions assessed included systemic corticosteroids, TNF-α inhibitors, ciclosporin, thalidomide, *N*-acetylcysteine, IVIG, and supportive care. No data were available for the main comparisons of interest as specified in the review protocol: etanercept versus cyclosporin, etanercept versus IVIG, IVIG versus supportive care, IVIG versus cyclosporin, and cyclosporin versus corticosteroids. The following conclusions, predominantly from low/very low levels of evidence, were drawn:

(1) Etanercept (TNF-alpha inhibitor) versus corticosteroids: Etanercept (25 mg (50 mg if weight >65 kg) twice weekly "until skin lesions healed") may reduce disease-specific mortality compared to corticosteroids (intravenous prednisolone 1–1.5 mg/kg/day "until skin lesions healed")
(2) Corticosteroids versus no corticosteroids: uncertain if there is any difference between corticosteroids (methylprednisolone 4 mg/kg/day for 2 more days after the fever had subsided and no new lesions had developed) and no corticosteroids on disease-specific mortality
(3) IVIG versus no IVIG: uncertain if there is any difference between IVIG (0.2–0.5 g/kg cumulative dose over three days) and no IVIG in risk of disease-specific mortality (RR, 0.33; 95% CI, 0.04–2.91); time to complete re-epithelialization (mean difference [MD] –2.93 days, 95% CI, –4.4 to –1.46); or length of hospital stay (MD, –2.00 days; 95% CI, –5.81 to 1.81).
(4) Ciclosporin versus IVIG: uncertain if there is any difference between cyclosporin (3 mg/kg/day or intravenous 1 mg/kg/day until complete re-epithelialization, then tapered off [10 mg/day reduction every 48 hours]) and IVIG (continuous infusion 0.75 g/kg/day for 4 days [total dose 3 g/kg] in participants with normal renal function) in risk of disease-specific mortality (RR. 0.13; 95% CI, 0.02–0.98).

In summary, the Cochrane review concluded that when compared with corticosteroids, etanercept may result in mortality reduction. For the following comparisons, the certainty of the evidence for disease-specific mortality is also very low:

(1) corticosteroids versus no corticosteroids
(2) IVIG versus no IVIG
(3) cyclosporin versus IVIG.

In contrast, the earlier systematic review [28] appeared to demonstrate improved survival with combination therapy of corticosteroids and IVIG, and a later meta-regression analysis [29] showed that ciclosporin and corticosteroids plus IVIG were associated with less deaths than predicted by SCORTEN. However, the NMA showed that no treatment achieved a significant reduction in the SMR.

7. Conclusion

SJS/TEN is a rare disorder. The role of immunomodulatory treatments in SJS/TEN is at present not supported by robust evidence from systematic reviews given the lack of RCTs. The evidence for improved survival with off-label use of corticosteroids plus IVIG, ciclosporin plus IVIG, and ciclosporin alone has not been demonstrated by NMA and meta-regression. The Optimal Management and Mechanisms of SJS/TEN (NATIENS) study from the United States is a phase III randomized study to examine the optimal treatment and mechanisms of each of 2 treatments (ciclosporin 5 mg/kg bid for 14 days versus etanercept 50 mg subcutaneously at day 0 and day 3) versus the current standard of care which is harmonized supportive care for the treatment of SJS/TEN. This opened in March 2023 and is currently enrolling (https://clinicaltrials.gov/ct2/show/record/NCT02987257). Hopefully, this study will be able to demonstrate the efficacy of specific targeted immunomodulatory treatments in SJS/TEN.

In the real-world clinical setting, systemic corticosteroids (in SJS and overlap SJS/TEN), ciclosporin [42], and etanercept [43] (in TEN) appear to be the off-label treatments currently most widely used.

Conflicts of interest

The authors have no financial conflicts of interest.

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