

Cochrane corner: Systemic interventions for treatment of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome

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1 | INTRODUCTION

Stevens-Johnson syndrome, toxic epidermal necrolysis and SJS/TEN overlap syndrome form a spectrum of skin disease which, in the most severe form, carries a mortality of up to 40%.¹ Its incidence is low, estimated in the United Kingdom as 5.76 cases per million person-years.² This presents a significant barrier to collecting robust data regarding optimal management. Many different interventions have been proposed, including corticosteroids, etanercept, N-acetylcysteine, thalidomide and IVIG. Conversely, over 200 drugs have been identified as potential triggers of SJS/TEN, with antibiotics, allopurinol and antiepileptics being among the most frequently reported culprits. Although predisposing HLA alleles have been found, the pathogenesis of SJS/TEN is not fully understood. The disease is thought to be driven by T lymphocytes, natural killer cells and natural killer T cells secreting various mediators of apoptosis and cytotoxic peptides such as granulysin.³

[cochranelibrary.com](https://www.cochranelibrary.com) for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Library should be consulted for the most recent version of the review.

2.2 | Background

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome are rare, severe cutaneous adverse reactions usually triggered by medications. In addition to tertiary-level supportive care, various systemic therapies have been used including glucocorticoids, intravenous immunoglobulins (IVIGs), cyclosporin, N-acetylcysteine, thalidomide, infliximab, etanercept and plasmapheresis. There is an unmet need to understand the efficacy of these interventions.

2 | COCHRANE ABSTRACT

Jacobsen A, Olabi B, Langley A, et al. Systemic interventions for the treatment of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome. *Cochrane Database of Syst Rev* 2022, Issue 3: CD013130.

2.1 | Disclaimer

This is an abstract of the above Cochrane review published in the Cochrane Database of Systematic Reviews 2022, Issue 3 (see www.cochrane.org).

2.3 | Objectives

To assess the effects of systemic therapies (medicines delivered orally, intramuscularly, or intravenously) for the treatment of SJS, TEN and SJS/TEN overlap syndrome.

2.4 | Search methods

We searched the following databases up to March 2021: the Cochrane Skin Specialised Register, CENTRAL, MEDLINE and Embase. We also searched five clinical trial registers, the reference

lists of all included studies and of key review articles and a number of drug manufacturer websites. We searched for errata or retractions of included studies.

2.5 | Selection criteria

We included only randomized controlled trials (RCTs) and prospective observational comparative studies of participants of any age with a clinical diagnosis of SJS, TEN or SJS/TEN overlap syndrome. We included all systemic therapies studied to date and permitted comparisons between each therapy, as well as between therapy and placebo.

2.6 | Data collections and analysis

We used standard methodological procedures as specified by Cochrane. Our primary outcomes were SJS/TEN-specific mortality and adverse effects leading to discontinuation of SJS/TEN therapy. Secondary outcomes included time to complete re-epithelialisation, intensive care unit length of stay, total hospital length of stay, illness sequelae and other adverse effects attributed to systemic therapy. We rated the certainty of the evidence for each outcome using GRADE.

2.7 | Main results

We included nine studies with a total of 308 participants (131 males and 155 females) from seven countries. We included two studies in the quantitative meta-analysis.

We included three RCTs and six prospective, controlled observational studies. Sample sizes ranged from 10 to 91. Most studies did not report study duration or time to follow-up. Two studies reported a mean SCORe of Toxic Epidermal Necrosis (SCORTEN) of 3 and 1.9. Seven studies did not report SCORTEN, although four of these studies reported average or ranges of body surface area (BSA) (means ranging from 44% to 51%). Two studies were set in burns units, two in dermatology wards, one in an intensive care unit, one in a paediatric ward and three in unspecified inpatient units. Seven studies reported a mean age, which ranged from 29 to 56 years. Two studies included paediatric participants (23 children).

We assessed the results from one of three RCTs as low risk of bias in all domains, one as high and one as some concerns. We judged the results from all six prospective observational comparative studies to be at a high risk of bias. We downgraded the certainty of the evidence because of serious risk of bias concerns and for imprecision due to small numbers of participants.

The interventions assessed included systemic corticosteroids, tumour necrosis factor-alpha (TNF-alpha) inhibitors, cyclosporin, thalidomide, N-acetylcysteine, IVIG and supportive care. No data were available for the main comparisons of interest as specified in

Key Messages

- Currently there is no established systemic treatment for SJS/TEN.
- Compared with corticosteroids, etanercept may result in a reduction in mortality.
- There is an unmet need for adequately powered multi-centre studies to determine optimal systemic treatment.

the review protocol: etanercept versus cyclosporin, etanercept versus IVIG, IVIG versus supportive care, IVIG versus cyclosporin and cyclosporin versus corticosteroids.

2.7.1 | Corticosteroids versus no corticosteroids

It is uncertain if there is any difference between corticosteroids (methylprednisolone 4 mg/kg/day for two more days after fever had subsided and no new lesions had developed) and no corticosteroids on disease-specific mortality (risk ratio [RR] 2.55, 95% confidence interval [CI] 0.72–9.03; 2 studies; 56 participants; very low-certainty evidence). Time to complete re-epithelialisation, length of hospital stay and adverse effects leading to discontinuation of therapy were not reported.

2.7.2 | IVIG versus no IVIG

It is uncertain if there is any difference between IVIG (0.2 to 0.5 g/kg cumulative dose over 3 days) and no IVIG in risk of disease-specific mortality (RR 0.33, 95% CI 0.04–2.91); time to complete re-epithelialisation (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). All results in this comparison were based on one study with 36 participants and very low-certainty evidence. Adverse effects leading to discontinuation of therapy were not reported.

2.7.3 | 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 with corticosteroids (intravenous prednisolone 1 to 1.5 mg/kg/day “until skin lesions healed”) (RR 0.51, 95% CI 0.16–1.63; 1 study; 91 participants; low-certainty evidence); however, the CIs were consistent with possible benefit and possible harm. Serious adverse events, such as sepsis and respiratory failure, were reported in 5 of 48 participants with etanercept and 9 of 43 participants with corticosteroids, but it was not clear if they led to discontinuation of therapy. Time to complete re-epithelialisation and length of hospital stay were not reported.

2.7.4 | Cyclosporin versus IVIG

It is uncertain if there is any difference between cyclosporin (3 mg/kg/day or intravenous 1 mg/kg/day until complete re-epithelialisation and then tapered off [10 mg/day reduction every 48h]) 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, 1 study; 22 participants; very low-certainty evidence). Time to complete re-epithelialisation, length of hospital stay and adverse effects leading to discontinuation of therapy were not reported.

No studies measured intensive care unit length of stay.

2.8 | Authors' conclusions

When compared to corticosteroids, etanercept may result in mortality reduction. For the following comparisons, the certainty of the evidence for disease-specific mortality is very low: corticosteroids versus no corticosteroids, IVIG versus no IVIG and cyclosporin versus IVIG. There is a need for more multicentric studies, focussed on the most important clinical comparisons, to provide reliable answers about the best treatments for SJS/TEN.

3 | COMMENTARY

This Cochrane review attempted to assess different systemic treatments used in SJS/TEN, including steroids, IVIG, cyclosporin and TNF-alpha inhibitors such as etanercept.⁴ Remarkably, only nine studies, including a total of 308 patients from seven countries, met the selection criteria. Of these, just three were RCTs. The authors were able to conclude with low certainty, based on a single-centre RCT ($n = 91$), that etanercept may reduce disease-specific mortality versus corticosteroids. It would be interesting to evaluate the impact of etanercept on time to re-epithelialisation and length of hospital stay, which were not reported. For all other treatment comparisons only very low-certainty evidence was found.

Aside from the paucity of high-quality studies on the subject, the authors also identified inconsistent use of validated disease-severity scores such as SCORTEN in published work. Anecdotally this is also a problem in routine clinical practice which should be further elucidated by the 2022 British Association of Dermatologists national clinical audit of SJS/TEN treatment in the United Kingdom. Since SCORTEN predictions of disease mortality can be as low as 3% or as high as 90%,⁵ this has important implications for ensuring a study is adequately powered to detect changes in disease-specific mortality.

Clearly more work is needed in this area. The review does identify one promising study comparing cyclosporin, etanercept and supportive care. The investigators intend to recruit around 267 participants with an estimated completion date of August 2027 (ClinicalTrials.gov identifier: NCT02987257). It is also important to

acknowledge that, by including only RCTs and prospective observational comparative studies, this review does by design miss a significant volume of lower-quality evidence. The authors do mention the large EuroSCAR and RegiSCAR cohorts; these have produced retrospective studies examining a variety of systemic treatments.

Stevens-Johnson syndrome/toxic epidermal necrolysis has a low incidence yet causes significant morbidity and mortality in those affected. There is a pressing need for a collaborative multicentre approach using harmonized outcome measures. None of the studies included in this review report length of stay in an intensive care unit (ICU), but this has substantial financial implications. The treatments considered in this review are dwarfed by the daily cost of an ICU bed. As an example, following the protocol outlined in the etanercept RCT, a week of treatment would cost the NHS £160.88 for a patient weighing <65 kg (£321.75 for 4 pre-filled 25 mg syringes of Erelzi, Sandoz Ltd, BNF May 2022). In contrast, an ICU bed at a leading central London hospital for the same period would cost an estimated £23,471. As such, even a small reduction in length of stay would make the treatment cost-effective. The ongoing study mentioned above comparing cyclosporin, etanercept and supportive care does list hospital length of stay as a secondary outcome measure.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the writing of this article.

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CONFLICT OF INTEREST

Dr Gladman and Dr Kloczko have no conflicts of interest to declare.

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