# Treating toxic epidermal necrolysis with systemic immunomodulating therapies: A systematic review and network meta-analysis

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***Background:*** Various systemic immunomodulating therapies have been used to treat toxic epidermal necrolysis (TEN), but their efficacy remains unclear.

***Objective:*** To perform a systematic review and network meta-analysis (NMA) evaluating the effects of systemic immunomodulating therapies on mortality for Stevens-Johnson syndrome (SJS)/TEN overlap and TEN.

***Methods:*** A literature search was performed in online databases (from inception to October 31, 2019). Outcomes were mortality rates and Score of Toxic Epidermal Necrolysis (SCORTEN)—based standardized mortality ratio (SMR). A frequentist random-effects model was adopted.

***Results:*** Sixty-seven studies involving 2079 patients were included. An NMA of 10 treatments showed that none was superior to supportive care in reducing mortality rates and that 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 corticosteroids and intravenous immunoglobulin combination therapy was the only treatment with significant survival benefits (SMR, 0.53; 95% CI, 0.31-0.93).

***Limitations:*** Heterogeneity and a paucity of eligible randomized controlled trials.

***Conclusions:*** Combination therapy with corticosteroids and IVIg may reduce mortality risks in patients with SJS/TEN overlap and TEN. Cyclosporine and etanercept are promising therapies, but more studies are required to provide clearer evidence. (J Am Acad Dermatol 2021;84:390-7.)

***Key words:*** corticosteroids; intravenous immunoglobulin; network meta-analysis; SCORTEN; Stevens-Johnson syndrome; toxic epidermal necrolysis.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous adverse reactions characterized by epidermal necrosis and high mortality.[1] SJS and TEN are considered to be a continuum of the same disease involving skin detachments of less than 10% and of greater than 30% of the body surface area (BSA), respectively; the involvement of skin detachment of 10% to 30% of the BSA is considered SJS/TEN overlap.[2]

Epidermal necrosis is mediated by cytotoxic T cells and natural killer cells, which induce various cytokines and cytotoxic proteins.[1,3,4] In light of the immune-mediated pathogenesis, various systemic immunomodulating therapies (SITs) have been proposed, such as corticosteroids, intravenous immune globulin (IVIg), cyclosporine, etanercept (ETN), infliximab, *N*-acetylcysteine (NAC), thalidomide, cyclophosphamide, plasmapheresis, and combination of these therapies.[5-9] Unfortunately, beyond supportive care, the efficacy of these SITs remains unclear. Because the disease is rare, most of the existing studies are retrospective observational studies.[6,10] There are only few randomized controlled trials (RCTs) and prospective studies that have been conducted.[7,11] Several traditional pairwise meta-analyses of mostly observational studies have been conducted to evaluate the efficacy of various SITs.[6,12,13] However, they are limited by the sole dependence on direct evidence and comparison of 2 treatments at a time. In contrast, a network meta-analysis (NMA) synthesizes both direct and indirect evidence and simultaneously compares multiple treatments, yielding greater statistical power. NMA is particularly valuable when there is limited direct evidence. Unfortunately, an NMA that compares the efficacy of various SITs has yet to be conducted. Additionally, very few previous pairwise meta-analyses examined the efficacy of combined therapies with potential synergistic effects. Another limitation of previous pairwise meta-analyses is that the disease at different degrees of severity (SJS, SJS/TEN overlap, and TEN) was pooled together. Compared to SJS/TEN overlap and TEN, the mortality of SJS is relatively low. Thus, when mortality is chosen as the outcome, pooling patients with all 3 forms as a group may undermine the clinical relevance of the results.

**CAPSULE SUMMARY**

- This network meta-analysis showed that among various systemic immunomodulating therapies for toxic epidermal necrolysis, corticosteroids combined with intravenous immune globulin could significantly reduce observed mortality rates.
- Combination therapy with corticosteroids and intravenous immune globulin should be considered by clinicians to treat toxic epidermal necrolysis.

We therefore conducted a systematic review and NMA that evaluated the efficacy of various SITs, used either alone or in combination, in treating specifically patients associated with greater severity, namely, SJS/TEN overlap syndrome and TEN.

## METHODS

This NMA was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension guidelines (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).[14]

### Data source and search strategy

We identified studies published in PubMed, Embase, and Cochrane Library (from January 1, 1990, to October 31, 2019) and Web of Science (from January 1, 1992 to October 31, 2019). Articles published before 1990 were excluded because the internationally accepted consensus definition for diagnosing SJS/TEN was developed in 1990.[2] The search terms and strings are shown in Supplemental Method 1 (available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). All articles included in the present study were clinical human studies. No language restriction was applied. References within searched articles were also reviewed to identify potentially missed studies.

### Eligibility criteria and study selection

The eligibility criteria included (1) patients with SJS/TEN overlap or TEN with diagnostic accuracy, (2) sufficient treatment information, (3) studies with at least 2 arms of therapy that provide information on mortality rates (MRs) or at least 1 arm of therapy that provide Score of Toxic Epidermal Necrolysis (SCORTEN)—based standardized mortality ratio (SMR) data, and (4) at least 5 patients in 1 arm of therapy. Review articles, guidelines, and case reports were excluded. The titles and abstracts of identified articles were independently screened by 2 authors (TYT and IHH).

### Outcomes

The outcomes of the present study were crude MRs and SCORTEN-based SMR (Supplemental Method 2; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).

*Abbreviations used:*

| | |
|---|---|
| BSA: | body surface area |
| CI: | confidence interval |
| ETN: | etanercept |
| IPD: | individual patient data |
| IVIg: | intravenous immunoglobulin |
| MR: | mortality rate |
| NAC: | *N*-acetylcysteine |
| NMA: | network meta-analysis |
| RCT: | randomized controlled trial |
| SCORTEN: | Score of Toxic Epidermal Necrolysis |
| SIT: | systemic immunomodulatory therapy |
| SJS: | Stevens-Johnson syndrome |
| SMR: | standardized mortality ratio |
| SUCRA: | surface under the cumulative ranking curve |
| TBSA: | total body surface area |
| TEN: | toxic epidermal necrolysis |

### Quality assessment

An instrument proposed by MacLehose et al[15] and modified by Zimmermann et al[6] was applied for the quality assessment of the included studies (Supplemental Method 3; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). Quality assessment was performed independently by 2 authors (CYC and YCH).

### Data extraction

Data were independently extracted by 2 authors (CYC and IHH); any disagreement was resolved by consensus. For studies including both patients with SJS and those with TEN, we extracted only the data related to patients with SJS/TEN overlap or TEN only. If there was no apparent classification in the original study, patients were categorized based on raw data, according to the classification described by Roujeau and Stern[16] as follows: SJS/TEN overlap, 10% to 30% skin detachment of total body surface area (TBSA), and TEN, greater than 30% skin detachment of TBSA.

Data on the following measures were extracted: study design, study period and country, sample size and clinical entity, and treatment regimen. Ages, TBSAs, observed deaths, and MRs were also extracted. Predicted death and SMR with 95% confidence intervals (CIs) were calculated in studies providing the SCORTEN of patients. Where mortality data were not reported in the original publication, corresponding authors were contacted to obtain the raw data.

### Data analysis

For categorical data, we estimated summary odds ratios with 95% CIs. For studies providing SCORTEN, the SMRs of the patients with TEN were calculated as stated, with an accompanying 95% CI calculated by the method described by Rothman and Greenland.[17] An imaginary control arm, adopted from the study of Bastuji-Garin et al,[18] who initially developed the SCORTEN for studies that provided SMR information of other therapeutic arms, was added; the SMR of the control arm was 1. We estimated the pooled ratio of SMR with 95% CI for these studies. In cases with zero mortality, we added 0.01 to the value in each cell to calculate the MR and SMR. Sensitivity analyses were performed by eliminating the studies with zero mortality in any 1 of the therapeutic arms.

Frequentist random-effects models of the NMA were adopted to compare the effect sizes between studies with the same interventions due to the presumed heterogeneity among the included studies. Egger tests were used to examine potential publication biases. Potential local inconsistency between the direct and indirect evidence within the network was analyzed by using the loop-specific approach and the side-splitting models. Additionally, we used the design-by-treatment model to evaluate global inconsistency within the whole NMA.

We calculated the relative ranking probabilities between all treatments using the surface under the cumulative ranking curve (SUCRA), defined as the percentage of the mean rank of each medication relative to an imaginary intervention that is always the best without uncertainty. The described analyses were all performed by using Stata, version 14.0 (Stata Corp, College Station, TX).[19]

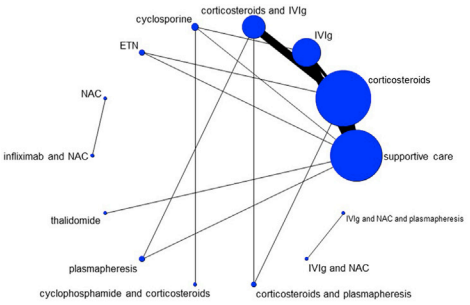
## RESULTS

### Search results and trial characteristics

Sixty-seven studies involving 2079 patients with SJS/TEN overlap and TEN met the inclusion criteria (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). A summary of the trial characteristics is presented in Supplemental Table II, *A* and *B* (available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). Two of the 67 studies showed partially duplicated data; therefore, only 66 studies were included for NMA. Most of the included studies were retrospective comparative studies or case series. Only 3 RCTs and 6 prospective comparative studies were included. The results of the quality assessment are shown in Supplemental Table III (available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).

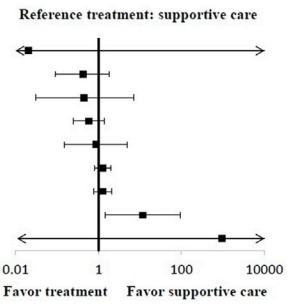
### Characterization of patients with TEN and treatment regimen

Clinical data for patients with SJS/TEN overlap and TEN are summarized in Supplemental Table II, *A* and *B*. In total, 18 treatment arms, including the imaginary control arm, were included.

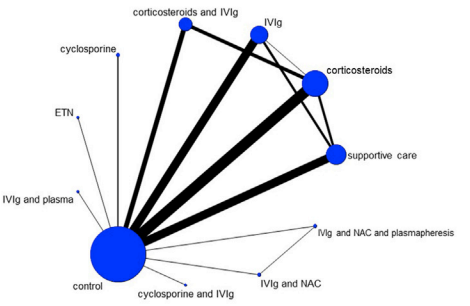



A

| Treatment | Odds ratio (95% CI) |
|---|---|
| Plasmapheresis | 0.02 (0.00,>1000) |
| ETN | 0.42 (0.10,1.83) |
| Corticosteroids + plasmapheresis | 0.44 (0.03,7.10) |
| Corticosteroids + IVIg | 0.59 (0.25,1.39) |
| Cyclosporine | 0.85 (0.15,4.92) |
| IVIg | 1.25 (0.80,1.97) |
| Corticosteroids | 1.27 (0.78,2.07) |
| Thalidomide | 11.67 (1.42, 95.96) |
| Cyclophosphamide + corticosteroids | 936.98 (0, >1000) |

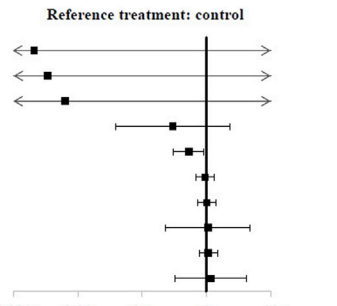



B




C

| Treatment | Ratio of SMR (95% CI) |
|---|---|
| Cyclosporine + IVIg | 0.00 (0.00, 1111443.3) |
| ETN | 0.00 (0.00, 695857.38) |
| Cyclosporine | 0.01 (0.00, 6727.1) |
| IVIg + plasmapheresis | 0.30 (0.04, 2.34) |
| Corticosteroids + IVIg | 0.53 (0.31, 0.93) |
| Supportive care | 0.96 (0.68, 1.34) |
| IVIg | 1.02 (0.73, 1.42) |
| IVIg+NAC+plasmapheresis | 1.06 (0.23, 4.81) |
| Corticosteroids | 1.07 (0.77, 1.49) |
| IVIg + NAC | 1.18 (0.33, 4.25) |




D

**Fig 1.** **A**, Network plot of treatments for SJS/TEN overlap and TEN: analysis based on mortality rate. **B**, Forest plot of network meta-analysis of treatments for SJS/TEN overlap and TEN: analysis based on mortality rate. None of the treatments was significantly superior to supportive care in reducing mortality rates. Thalidomide was associated with a significantly higher mortality rate than supportive care. **C**, Network plot of treatments for SJS/TEN overlap and TEN: analysis based on standardized mortality ratio. **D**, Forest plot of network meta-analysis of treatments for SJS/TEN overlap and TEN: analysis based on standardized mortality ratio. Patients receiving combination therapy with corticosteroids and IVIg had a significantly superior standardized mortality ratio than control individuals. *CI*, Confidence interval; *ETN*, etanercept; *IVIg*, intravenous immunoglobulin; *NAC*, *N*-acetylcysteine; *SJS*, Stevens-Johnson syndrome; *SMR*, standardized mortality ratio; *TEN*, toxic epidermal necrolysis.

## Mortality

Forty included articles stated the mortality of TEN, totaling 14 treatment arms, including supportive care, corticosteroids, IVIg, cyclosporine, ETN, NAC, thalidomide, plasmapheresis, combination of corticosteroids and IVIg, combination of plasmapheresis and corticosteroids, combination of cyclophosphamide and corticosteroids, combination of NAC and infliximab, combination of NAC and IVIg, and combination of NAC/IVIg and plasmapheresis. However, 4 of the treatments did not have a connection to other therapies (Fig 1, *A*).

In the NMA of 10 treatments, no treatment was significantly superior to supportive care concerning the MR. However, thalidomide showed a significantly higher MR than those of supportive care (odds ratio, 11.67; 95% CI, 1.42-95.96) (Table I and Fig 1, *B*). According to the SUCRA for MR, ETN was ranked the best among the 10 treatments, followed by a combination of corticosteroids and IVIg (Supplemental Table IV, *A*; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).

We excluded plasmapheresis and a combination of corticosteroids and cyclophosphamide when performing sensitivity analysis due to their zero mortality (Supplemental Fig 2, *A*; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). The results of the NMA were unchanged (Supplemental Table IV, *B* and Supplemental Fig 2, *B*); ETN and the combination of corticosteroids and IVIg remained the first 2 ranked therapies among the 8 treatments according to the SUCRA (Supplemental Table IV, *C*).

## Standardized mortality ratio

Forty articles, totaling 11 treatment arms, reported SMR information of TEN, including imaginary control, supportive care, corticosteroids, IVIg, cyclosporine, ETN, corticosteroids and IVIg combination, cyclosporine and IVIg combination, plasmapheresis

**Table I.** League table of treatment response with analysis based on mortality rate

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Supportive care** | 1.27 (0.78-2.07) | 1.25 (0.80-1.97) | 0.59 (0.25-1.39) | 0.85 (0.15-4.92) | 0.42 (0.10-1.83) | 11.67 (1.42-95.96) | 0.02 (0.00-186,851.98) | 936.98 (0.00-3.57e+11) | 0.44 (0.03-7.10) |
| 0.79 (0.48-1.28) | **Corticosteroids** | 0.99 (0.55-1.76) | 0.46 (0.23-0.94) | 0.67 (0.11-4.09) | 0.33 (0.08-1.43) | 9.18 (1.06-79.84) | 0.02 (0.00-147,391.34) | 737.30 (0.00-2.82e+11) | 0.35 (0.02-5.35) |
| 0.80 (0.51-1.26) | 1.01 (0.57-1.81) | **IVIg** | 0.47 (0.19-1.17) | 0.68 (0.12-3.99) | 0.34 (0.07-1.53) | 9.31 (1.08-80.38) | 0.02 (0.00-149,890.56) | 747.66 (0.00-2.85e+11) | 0.35 (0.02-5.76) |
| 1.70 (0.72-3.98) | 2.15 (1.07-4.34) | 2.12 (0.86-5.27) | **Corticosteroids and IVIg** | 1.44 (0.21-10.04) | 0.72 (0.14-3.62) | 19.78 (2.04-192.19) | 0.03 (0.00-319,220.81) | 1588.76 (0.00-6.16e+11) | 0.75 (0.05-10.53) |
| 1.17 (0.20-6.78) | 1.49 (0.24-9.10) | 1.47 (0.25-8.65) | 0.69 (0.10-4.81) | **Cyclosporine** | 0.50 (0.05-4.86) | 13.70 (0.88-212.37) | 0.02 (0.00-241,265.88) | 1100.15 (0.00-3.88e+11) | 0.52 (0.02-13.74) |
| 2.36 (0.55-10.17) | 2.99 (0.70-12.86) | 2.95 (0.65-13.38) | 1.39 (0.28-7.00) | 2.01 (0.21-19.58) | **ETN** | 27.49 (2.12-357.33) | 0.05 (0.00-469,379.50) | 2208.17 (0.00-8.87e+11) | 1.04 (0.05-23.05) |
| 0.09 (0.01-0.71) | 0.11 (0.01-0.95) | 0.11 (0.01-0.93) | 0.05 (0.01-0.49) | 0.07 (0.00-1.13) | 0.04 (0.00-0.47) | **Thalidomide** | 0.00 (0.00-18,381.80) | 80.31 (0.00-3.42e+10) | 0.04 (0.00-1.24) |
| 49.75 (0.00-4.63e+08) | 63.23 (0.00-5.89e+08) | 62.35 (0.00-5.83e+08) | 29.34 (0.00-2.75e+08) | 42.37 (0.00-4.33e+08) | 21.11 (0.00-2.09e+08) | 580.46 (0.00-6.19e+09) | **Plasmapheresis** | 46,617.93 (0.00-5.28e+15) | 21.97 (0.00-2.55e+08) |
| 0.00 (0.00-406,494.28) | 0.00 (0.00-519,157.03) | 0.00 (0.00-510,240.38) | 0.00 (0.00-243,938.08) | 0.00 (0.00-320,260.31) | 0.00 (0.00-181,955.42) | 0.01 (0.00-5.30e+06) | 0.00 (0.00-2.43e+06) | **Cyclophosphamide and corticosteroids** | 0.00 (0.00-217,753.02) |
| 2.26 (0.14-36.38) | 2.88 (0.19-44.27) | 2.84 (0.17-46.41) | 1.34 (0.10-18.77) | 1.93 (0.07-51.12) | 0.96 (0.04-21.28) | 26.42 (0.81-862.53) | 0.05 (0.00-529,113.88) | 2121.74 (0.00-9.80e+11) | **Corticosteroids and plasmapheresis** |

*ETN*, Etanercept; *IVIg*, intravenous immunoglobulin.

and IVIg combination, NAC and IVIg combination, and NAC/IVIg and plasmapheresis combination (Fig 1, *C*).

In the NMA of 11 treatments, only a combination of corticosteroids and IVIg showed a significantly superior SMR than that of the control (SMR, 0.53; 95% CI, 0.31-0.93) (Table II and Fig 1, *D*). According to the SUCRA for MR, the cyclosporine and IVIg combination was the best ranked among the 11 treatments, followed by the corticosteroids and IVIg combination (Supplemental Table V, *A*; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).

In the sensitivity analysis, cyclosporine, ETN, and the cyclosporine and IVIg combination were excluded because of their zero mortality (Supplemental Fig 3, *A*; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1). The corticosteroids and IVIg combination still showed a significantly superior SMR than that of the control (SMR, 0.54; 95% CI, 0.31-0.93) (Supplemental Table V, *B* and Supplemental Fig 3, *B*). However, the plasmapheresis and IVIg combination was the best-ranked therapy among the 8 treatments based on the SUCRA, followed by the corticosteroids and IVIg combination (Supplemental Table V, *C*).

### Publication of bias and inconsistency

Funnel plots of the included studies showed symmetry, and the results of the Egger test showed no significant publication bias (Supplemental Fig 4, *A-H*; available via Mendeley at https://doi.org/10.17632/4b3cd3d53x.1).

The NMAs showed neither local inconsistency (loop-specific approach and the side-splitting method) nor global inconsistency (design by treatment interaction method) for all analyses.

## DISCUSSION

This NMA showed that none of the included SITs reduced MRs in patients with SJS/TEN overlap and TEN. However, in the analysis based on SMR, combination therapy with corticosteroids and IVIg significantly reduced the observed mortality risks. Because the range of predicted mortality of patients with SJS, SJS/TEN overlap, and TEN is extremely wide (from 3.2% to 90%), analysis using SMR can account for the baseline severity of the disease, thus reflecting a more accurate treatment response. Although several therapies (such as cyclosporine and ETN) have a slightly larger SUCRA and are ranked higher than combination therapy with corticosteroids and IVIg in the analysis based on SMR, their effect estimates were not statistically significant. These effect estimates had extremely wide CIs

**Table II.** League table of treatment response with analysis based on standardized mortality ratio

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Supportive care** | 1.12 (0.70-1.77) | 1.06 (0.69-1.63) | 0.56 (0.29-1.06) | 0.01 (0.00-7054.85) | 0.00 (0.00-728,886.50) | 0.31 (0.04-2.51) | 1.04 (0.75-1.46) | 0.00 (0.00-1.16e+06) | 1.23 (0.33-4.64) | 1.11 (0.24-5.22) | | |
| 0.89 (0.56-1.42) | **Corticosteroids** | 0.95 (0.60-1.51) | 0.50 (0.27-0.92) | 0.01 (0.00-6311.89) | 0.00 (0.00-652,170.00) | 0.28 (0.04-2.24) | 0.93 (0.67-1.30) | 0.00 (0.00-1.04e+06) | 1.10 (0.29-4.14) | 0.99 (0.21-4.66) | | |
| 0.94 (0.61-1.45) | 1.05 (0.66-1.67) | **IVIg** | 0.53 (0.28-1.00) | 0.01 (0.00-6651.61) | 0.00 (0.00-687,249.44) | 0.30 (0.04-2.37) | 0.98 (0.71-1.37) | 0.00 (0.00-1.10e+06) | 1.16 (0.31-4.37) | 1.05 (0.22-4.91) | | |
| 1.79 (0.95-3.40) | 2.00 (1.09-3.69) | 1.90 (1.00-3.60) | **Corticosteroids and IVIg** | 0.01 (0.00-12,744.85) | 0.00 (0.00-1.31e+06) | 0.56 (0.07-4.72) | 1.87 (1.08-3.26) | 0.01 (0.00-2.10e+06) | 2.21 (0.55-8.93) | 1.99 (0.40-9.95) | | |
| 149.63 (0.00-1.58e+08) | 167.20 (0.00-1.76e+08) | 158.68 (0.00-1.67e+08) | 83.40 (0.00-8.87e+07) | **Cyclosporine** | 0.33 (0.00-8.92e+09) | 47.09 (0.00-5.76e+07) | 156.28 (0.00-1.64e+08) | 0.53 (0.00-1.42e+10) | 184.58 (0.00-2.06e+08) | 166.08 (0.00-1.90e+08) | | |
| 451.45 (0.00-1.49e+11) | 504.47 (0.00-1.66e+11) | 478.76 (0.00-1.58e+11) | 251.64 (0.00-8.32e+10) | 3.02 (0.00-8.12e+10) | **ETN** | 142.06 (0.00-5.19e+10) | 471.50 (0.00-1.55e+11) | 1.60 (0.00-1.77e+12) | 556.89 (0.00-1.91e+11) | 501.06 (0.00-1.74e+11) | | |
| 3.18 (0.40-25.37) | 3.55 (0.45-28.31) | 3.37 (0.42-26.88) | 1.77 (0.21-14.80) | 0.02 (0.00-25,958.47) | 0.01 (0.00-2.57e+06) | **IVIg and plasmapheresis** | 3.32 (0.43-25.78) | 0.01 (0.00-4.10e+06) | 3.92 (0.35-43.95) | 3.53 (0.28-44.99) | | |
| 0.96 (0.68-1.34) | 1.07 (0.77-1.49) | 1.02 (0.73-1.42) | 0.53 (0.31-0.93) | 0.01 (0.00-6727.10) | 0.00 (0.00-695,860.00) | 0.30 (0.04-2.34) | **Control** | 0.00 (0.00-1.11e+06) | 1.18 (0.33-4.25) | 1.06 (0.23-4.81) | | |
| 282.64 (0.00-9.30e+10) | 315.84 (0.00-1.04e+11) | 299.74 (0.00-9.86e+10) | 157.55 (0.00-5.21e+10) | 1.89 (0.00-5.08e+10) | 0.63 (0.00-6.92e+11) | 88.94 (0.00-3.25e+10) | 295.20 (0.00-9.69e+10) | **Cyclosporine and IVIg** | 348.66 (0.00-1.19e+11) | 313.71 (0.00-1.09e+11) | | |
| 0.81 (0.22-3.05) | 0.91 (0.24-3.40) | 0.86 (0.23-3.23) | 0.45 (0.11-1.82) | 0.01 (0.00-6041.96) | 0.00 (0.00-614,304.00) | 0.26 (0.02-2.86) | 0.85 (0.24-3.05) | 0.00 (0.00-981,179.56) | **IVIg and NAC** | 0.90 (0.14-5.80) | | |
| 0.90 (0.19-4.23) | 1.01 (0.21-4.72) | 0.96 (0.20-4.49) | 0.50 (0.10-2.51) | 0.01 (0.00-6871.18) | 0.00 (0.00-693,955.38) | 0.28 (0.02-3.62) | 0.94 (0.21-4.26) | 0.00 (0.00-1.11e+06) | 1.11 (0.17-7.17) | **IVIg and NAC and plasmapheresis** | | |

*ETN*, Etanercept; *IVIg*, intravenous immunoglobulin; *NAC*, *N*-acetylcysteine.

(indicating relatively small sample sizes), and more studies on these promising therapies are therefore needed to provide clearer evidence.

Several pairwise meta-analyses were published in the past to examine the efficacy of various SITs on patients with SJS and TEN. For example, Zimmermann et al[6] showed that corticosteroids were associated with a decreased risk of death only in the unstratified model using individual patient data (IPD), but not in the stratified model with IPD or in the analysis at the study level, and that cyclosporine was associated with a significant survival benefit in the unstratified model using IPD.[6] Notably, the outcome adopted in their study was MR, but not SMR, which failed to account for the baseline severity of the patients.[6] Moreover, unlike our study, which included only patients with SJS/TEN and TEN, their study included patients with SJS, SJS/TEN, and TEN.[6] Problems with this approach are 2-fold: first, patients with SJS have relatively low mortality, and thus, the number of deaths in many of the included studies was zero; second, the severity and predicted mortality of these different patient subtypes greatly vary, and therefore, pooling them all may lead to significant heterogeneity. In all of our analyses, corticosteroids were not associated with a significant survival benefit. A RegiSCAR (International Registry of Severe Cutaneous Adverse Reactions to drugs) study also failed to show any survival benefit for patients treated with corticosteroids compared to those treated with supportive care only.[20]

Increasing evidence has suggested a survival advantage in patients with SJS/TEN receiving cyclosporine. Pairwise meta-analyses showed approximately 60% to 70% reduction in the mortality risk of patients with SJS/TEN.[13,21] In the current NMA, cyclosporine ranked high in most analyses, but the effect estimates were all nonsignificant. This can be attributed to the fact that the pairwise meta-analyses included the entire continuum of SJS/TEN, whereas the current NMA included only patients with SJS/TEN and TEN. Additionally, only 1 and 2 studies, respectively, were included in the analysis of the SMR and MR in the current study. The existing evidence was too limited for us to draw any firm conclusions for the therapeutic effects of cyclosporine in treating specifically patients in the subset of SJS/TEN overlap and TEN.

In line with previous pairwise meta-analyses, we did not find survival advantages for patients treated with IVIg in any of our analyses.[12,22] However, IVIg administered in combination with corticosteroids showed a significantly reduced SMR in patients with TEN. Ye et al also suggested the beneficial role of IVIg combined with corticosteroids using a

different outcome, namely, recovery time, in a meta-analysis, showing that patients treated with IVIg combined with corticosteroids had significantly shorter recovery time than those treated with corticosteroids alone.[23] However, a comparison between IVIg combined with corticosteroids and supportive care was not performed in their study.[23] The efficacy of combination therapies was rarely evaluated in previous pairwise meta-analyses. Even if it is evaluated, the efficacy of combination therapies is compared with another SIT, but not supportive care, as in the case of Ye et al.[23] Contrary to pairwise meta-analyses, the NMA approach enabled us to incorporate both direct and indirect evidence, compare all the various treatments simultaneously, and to produce effect estimates with higher statistical power. IVIg inhibits keratinocyte apoptosis by antagonizing the Fas receptor, reduces the number of natural killer cells in peripheral blood, and suppresses the release of granzyme B.[24,25] Additionally, IVIg can protect against infection, a common major complication in patients with SJS/TEN.[26] Corticosteroids, on the other hand, suppress cytotoxic T lymphocytes.[27] IVIg or corticosteroid treatment alone was not associated with survival benefits in the current study. However, combining IVIg with corticosteroids may synergistically create beneficial treatment effects by simultaneously targeting different pathways.

The interpretation of the results was hampered by several limitations. First, the heterogeneity of the included studies was significant, possibly because of variations in study designs, treatment regimens, protocols of supportive care measures, the timing of the administration of SITs, and the withdrawal of offending drugs. The different study designs (case series, RCT, retrospective and prospective comparative studies) included in our analysis may be a major source of heterogeneity. However, because TEN is a rare disease, it is inevitable to include studies of different designs to include more patients and more treatments into statistical analyses, thereby leading to a greater level of heterogeneity. Unfortunately, subgroup analyses by study designs could not be performed because of insufficient data. Although neither local nor global inconsistency was detected in our NMA, our results should still be interpreted with some caution. Second, the differences in patient ages in the included studies may affect the treatment comparisons, and some treatments may be more often used in pediatric patients than others. Nevertheless, no inconsistency was detected in our NMA, suggesting robust results. Third, some treatments have small trial numbers and patient sample sizes, which could lead to wide CIs and unreliably high rankings. Fourth, the MRs of some treatments in some studies were 0, requiring statistical adjustments. Two methods of adjustments were therefore performed, and the results were broadly consistent. Finally, the rarity of the disease precluded the possibility of including a large number of RCTs and high-quality studies.

## CONCLUSIONS

In conclusion, this NMA showed that combination therapy with corticosteroids and IVIg may lower mortality risks in patients with SJS/TEN and TEN. Some other treatments (cyclosporine, cyclosporine combined with IVIg, IVIg combined with plasmapheresis, and ETN) are potential effective treatment options but require more evidence. Further studies, such as RCTs, are required to fill the gap in scientific evidence in treating this life-threatening adverse drug reaction.

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