Comparison of effectiveness of interventions in reducing mortality in patients of toxic epidermal necrolysis: A network meta-analysis

Tejas K. Patel, Parvati B. Patel[1], Sejal Thakkar[2]

Department of Pharmacology, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, [1]Department of Pharmacology, GMERS Medical College, Gotri [2]Department of Dermatology, GMERS Medical College and Hospital, Gotri, Vadodara, Gujarat, India

Abstract

Background: Limited evidence is available about effectiveness and choice of immunomodulating treatment modalities for toxic epidermal necrolysis (TEN).

Aims: To compare the effectiveness of interventions to reduce mortality in patients of toxic epidermal necrolysis through network meta-analysis.

Methods: Studies were retrieved using PubMed, Google Scholar and Cochrane Database of Systematic Reviews from inception to September 18, 2018. Only English language articles were considered. Observational and randomized controlled studies having ≥ 5 TEN patients in each intervention arm were included. Two investigators independently extracted study characteristics, intervention details and mortality data. Bayesian network meta-analysis was performed using the Markov chain Monte Carlo (MCMC) approach through the random effect model. The ranking analysis was done to provide a hierarchy of interventions. The consistency between direct and indirect evidence was assessed through node spit analysis. The primary outcome was to compare the mortality [Odds ratio OR (95% credibility interval CrI)] among all treatment modalities of TEN.

Results: Twenty-four studies satisfying the selection criteria were included. The network analysis showed improved survival with cyclosporine as compared to supportive care [OR- 0.19 (95% CrI: 0.05, 0.59)] and intravenous immunoglobulin [OR- 0.21 (95% CrI: 0.05, 0.76)]. The hierarchy of treatments based on "surface under the cumulative ranking curves" (SUCRA) value were cyclosporine (0.93), steroid+intravenous immunoglobulin (0.76), etanercept (0.59), steroids (0.46), intravenous immunoglobulin (0.40), supportive care (0.34) and thalidomide (0.02). No inconsistencies between direct and indirect estimates were observed for any of the treatment pairs.

Limitations: Evidence is mainly based on retrospective studies.

Conclusion: The use of cyclosporine can reduce mortality in TEN patients. Other promising immunomodulators could be steroid+intravenous immunoglobulin combination and etanercept.

Key words: Cyclosporine, immunologic factors, mortality, Stevens–Johnson syndrome

Plain language summary

Toxic epidermal necrolysis is a type of severe skin reaction most commonly caused by drugs. It affects almost 1 to 2 million people per year. It is considered an emergency and causes death in 15%–30% of the affected patients. There are no proven effective medications against it. The patients are managed symptomatically in intensive care units. The authors have conducted "network meta-analysis" to find out which is the most effective medication against this skin reaction.

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Corresponding author: Dr. Tejas K. Patel, Department of Pharmacology, All India Institute of Medical Sciences, Gorakhpur 273 008, Uttar Pradesh, India. dr.tkp2006@yahoo.co.in

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The "network meta-analysis" is a statistical tool to compare data of multiple medications simultaneously from the already published literature. It also provides hierarchies among the medications and identifies the best possible medications against the disease or condition being studied. A total of 24 published studies were analyzed and five medications were compared with each other. The medications were corticosteroid, intravenous immunoglobulin, combination of steroid+intravenous immunoglobulin, etanercept and cyclosporine. The authors found that use of cyclosporine can reduce death due to toxic epidermal necrolysis. The other effective medications could be combination of steroid+intravenous immunoglobulin and etanercept.

Introduction

Stevens–Johnson syndrome (SJS) is considered to be a rare and serious cutaneous reaction. The main causative factor is drugs. It is classified into three categories based on the percentage of body surface area involvement: SJS (<10%), toxic epidermal necrolysis – TEN (>30%) and SJS-TEN overlap (10%–30%).[1] They are associated with high morbidity and mortality. An earlier systematic review suggests that TEN is associated with significantly higher mortality than SJS [odd ratio- OR: 7.2 (95% CI: 1.6–31.9)].[2] The reported mortality rate of SJS, SJS-TEN overlap and TEN varies from 1.9 to 4.8, 5.3 to 19.4 and 14.3 to 28.2, respectively.[2-4]

Earlier systematic reviews did not suggest significant survival benefit of steroids,[5,6] intravenous immunoglobulin[5,7,8] and combination of steroid+intravenous immunoglobulin in SJS/TEN patients.[9] A recent individual patient-level meta-analysis suggests steroids and cyclosporine are two most promising immunomodulating treatment options for SJS/TEN patients.[10] Two more recent meta-analyses observed cyclosporine therapy can reduce the risk of mortality in SJS/TEN patients.[11,12] All these earlier meta-analyses had limited direct head to head comparison of treatment modalities.

Unlike traditional meta-analyses, network meta-analysis provides a comparative treatment effectiveness through analysis of both direct and indirect evidence. It also provides hierarchies among the treatment modalities and offers a comprehensive framework for decision-making.[13]

In this study, we focused on TEN cases with body surface area > 10%. SJS usually have lower mortality than TEN.[1-4] We anticipated the inclusion of observational studies. The differences in the number of patients of SJS or TEN in different treatment arms could have affected direct/indirect comparisons and ranking analysis. We conducted the network meta-analysis to compare the effectiveness of interventions to reduce mortality in patients of TEN.

Methods

Information sources and search strategy

Two investigators (TKP and PBP) independently searched the PubMed, Google Scholar and Cochrane Database of Systematic Reviews. We also searched the bibliographies of relevant articles and systematic reviews. There was no restriction on time period to be considered. The search strategy of PubMed and Google Scholar were: (Stevens-Johnson syndrome OR Toxic epidermal necrolysis OR Lyell's syndrome) AND (Treatment OR Management OR Supportive care OR Palliative care OR Corticosteroid OR Immunoglobulin OR Cyclosporine). We included English language articles only. The last search was carried out on September 9, 2018 on PubMed and September 18, 2018 on Google Scholar. The study protocol was prospectively registered on PROSPERO register (CRD42018092567).

Case definition of TEN

SJS/TEN overlap and TEN were considered as TEN as defined by Bastuji-Garin *et al*. (body surface area involvement – body surface area >10%).[1] In case of absence of apparent classification in the study, raw data of body surface area was used to categorize patients into TEN.

Selection criteria

Inclusion criteria

- Observational and randomized controlled studies of any age group assessing the effectiveness of two interventions for reducing mortality in TEN patients. The intervention can be supportive care or any treatment modality
- Studies should have ≥ 5 TEN patients in each intervention arm.

Exclusion criteria

- Studies not differentiating SJS from TEN or not providing the raw data of body surface area involvement to categorize TEN
- SJS/TEN studies not focusing on mortality as an outcome
- Non-comparative studies
- Duplicate studies (In case of duplicate reports, studies with most comprehensive, up-to-date and largest dataset was included)
- Review articles, editorials, non-research letters, discussion papers.

Study screening and selection strategy

Two investigators (TKP and PBP) independently initially assessed title, abstract and then, if potentially relevant, retrieved full text as per selection criteria. All full-text articles were initially screened for differentiation between

SJS and TEN based on body surface area, treatment arms, number of included patients in each arm and mortality data. A predefined Excel sheet was used to record the reason of each excluded study. The disagreements in study selection were resolved through discussion, consensus and consultation with third investigator (ST).

Data extraction process

The following data were collected from the included studies in a predefined Excel sheet:

- General study characteristics: first author, publication year, types of publication, country, data collection period, study duration, study design, age group studied, admission ward, diagnosis of TEN
- Intervention characteristics: Dose, route, duration of each treatment modality studied; basis of assigning treatment; mean or median age, body surface area and SCORTEN score involvement and delay of stating treatment in each treatment arms; observed and expected mortality
- Mortality data: treatment sample size and number of patients died in each treatment arm.

All extracted data were cross-checked to ensure accuracy.

Risk of bias (quality) assessment

The risk of bias was assessed using scoring tool designed by Zimmermann *et al*. for the SJS/TEN studies.[10] It scores each study based on clear description of hypothesis, main outcomes, selection criteria, ineligible and those refuse to participate in the study, participants completing the treatment, distributions of the principal confounders (age, severity, country, year) and use of 95%-confidence interval (CI) and/or actual probability values to report mortality. The range of total score is 0 to 13.17. The score below 5 was used as a cut off point to define high-risk studies.

Statistical analysis

The primary outcome was to compare the mortality among the all treatment modalities of TEN.

Initially, proportions of deaths were analyzed and expressed as Odds ratio (OR) and its 95% CI for each study. The direct pairwise meta-analysis of all interventions was performed using Mantel-Haenszel's method with random-effect models to evaluate statistical heterogeneity within each comparison. An I^2 test was used to evaluate the heterogeneity. An I^2 value of 25%, 50% and 75% was considered as low, medium and high heterogeneity, respectively.[14]

On completion of pairwise meta-analysis, Bayesian network meta-analysis was performed using the Markov chain Monte Carlo (MCMC) approach.[15,16] The vague prior distribution was used to obtain the closest findings with frequentist method.[17] The pooled OR and its corresponding 95% credibility interval (CrI) was obtained through random effect model for each treatment pair comparison. The treatment modality was considered effective in reducing mortality, when the upper and lower 95% CrI for OR were less than 0 (equivalent to $P < 0.05$). Network diagram was plotted to depict the treatment modalities that directly compared with each other.

Ranking analysis was done to rank all interventions. Surface under the cumulative ranking curves (SUCRA), a numerical summary of the probabilities, was used to provide a hierarchy of interventions. SUCRA value 100% indicates a treatment is certain to be the best and 0% value suggests a treatment is certain to be the worst.[18] Based on SUCRA, the league table was arranged to present the network meta-analysis summary estimates. The treatments were ranked in order of better to worst outcome from left to right in a league table.

The sensitivity analysis of network meta-analysis was performed by risk of bias assessment (excluding the high-risk studies), study design and study region (developed/developing countries). A comparison-adjusted funnel plot was used to assess publication bias.

Assessment of inconsistency

Node splitting was used to assess consistency between direct and indirect evidence. The mean treatment effect estimates were calculated based on the direct and indirect evidence. The consistency of the estimates of treatment effects was examined to evaluate the discrepancy between direct and indirect comparisons.[19]

Statistical packages used

The direct pairwise meta-analysis was done through "Review manager software version 5.3." The network meta-analysis was performed using the Microsoft-Excel-based Network Meta-analysis tool - NetMetaXL version 1.6.1 (Cornerstone research group, Canada) and WinBUGS 1.4.3. software (MRC Biostatistics Unit, Cambridge Institute of Public Health, United Kingdom). The node split analysis was done through MetaInsight (binary) software version 1.1 (Complex review support unit, University of Glasgow, United Kingdom).

Results

Literature search

We assessed 273 full texts and included 24 articles fulfilling the selection criteria from the literature search [Figure 1].

Characteristics of the included studies

The detailed characteristics of all included studies are presented in Table 1.[20-43] The study designs of included studies were retrospective (18), prospective (3), randomized controlled trial (2) and prospective-retrospective (1). Ten, twenty and thirty percent body surface area involvement was considered as TEN in 14, 2 and 8 studies, respectively. Twelve studies included all age group and 8 studies adults and elderly age group patients, while four studies did not

Table 1: General characteristics of all included studies

Study	Country	Data collection period	Study design	Study specific department	TEN definition - Percentage of BSA involvement	Diagnosis of TEN	Study age group	Study population			Total TEN sample
								Age to range, mean ± SD* (years)	BSA to range, mean ± SD*, mean (95% CI)**, median (IQR)*** %	SCORTEN score to mean ± SD*, mean (95% CI)**	
Brand and Rohr, 2000[20]	Australia	1978–1998	Retrospective	ICU	>30	Clinical	Adults and elderly	23–73	NM	NM	12
Brown *et al.*, 2004[21]	USA	1997–2002	Retrospective	BU	>10	Clinical, biopsy	NM	45 ± 25*	45.6 ± 25*	NM	45
Chantaphakul *et al.*, 2015[22]	Thailand	2009–2014	Retrospective	NM	>10	Clinical	Adults and elderly	20–85	NM	NM	19
Chen *et al.*, 2010[23]	China	1994–2009	Retrospective	NM	>30	Clinical, biopsy	All age	11–81	30.2*	NM	30
González-Herrada *et al.*, 2017[24]	Spain	2001–2015	Prospective-retrospective	BU	>10	Clinical, biopsy	Adults and elderly	NM	NM	NM	32
Gravante *et al.*, 2007[25]	Italy	1995–2005	Retrospective	BU	>10	Clinical, biopsy	All age	4–94	62.8 ± 32.8*	NM	31
Hirapara *et al.*, 2017[26]	India	2009–2012	Retrospective	NM	>10	Clinical	All age	6–78	38.4 (32.2–44.4)**	1.8 (1.5–2.0)**	36
Ioannides *et al.*, 1994[27]	Greece	1972–1990	Retrospective	NM	>20	Clinical, biopsy	All age	2–84	42.1 ± 16.1*	NM	19
Jagadeesan *et al.*, 2013[28]	India	2008–2012	Prospective	DW	>30	Clinical ± biopsy	All age	6–68	51.6*	NM	36
Kaur *et al.*, 1990[29]	India	1982–1989	Prospective	DW	>20	Clinical, biopsy	All age	0.4–60	23*	NM	30
Kim *et al.*, 2005[30]	South Korea	1990–2003	Retrospective	NM	>30	Clinical, biopsy	All age	2–80	48.7 ± 17.1*	NM	38
Lalosevic *et al.*, 2015[31]	Serbia	1993–2012	Retrospective	NM	>30	Clinical, biopsy	All age	1–94	74.0 ± 20.8*	NM	17
Lee *et al.*, 2017[32]	Singapore	2011–2014	Retrospective	BU	>10	Clinical, biopsy	Adults and elderly	57 ± 20*	29 ± 25*	NM	28
Mohanty *et al.*, 2017[33]	India	2014–2015	Retrospective	DW	>10	Clinical	All age	38.4 ± 8.8*	34.9 ± 19.9	2.57 ± 1.1	22
Paquet *et al.*, 2006[34]	Belgium	NM	Prospective	NM	>30	Clinical, biopsy	Adults and elderly	18–78	59.0 ± 15.9	NM	11
Poizeau *et al.*, 2018[35]	France	2005–2016	Retrospective	BU	>10	Clinical	NM	NM	NM	NM	174
Schneck *et al.*, 2008[36]	Germany, France	1997–2001	Retrospective	NM	>10	Clinical ± biopsy	NM	47 ± 25*	NM	NM	171
Shortt *et al.*, 2004[37]	Canada	1995–2002	Retrospective	BU	>10	Clinical ± biopsy	NM	NM	NM	NM	32
Stella *et al.*, 2007[38]	Italy	1993–2005	Retrospective	BU	>10	Clinical, biopsy	Adults and elderly	27–81	33.3 ± 26.3*	NM	27
Wang *et al.*, 2018[39]	Taiwan	2009–2015	RCT Open labeled	NM	>10	Clinical ± biopsy	All age	6–87	44.6 ± 23.1*	NM	35
Wolkenstein *et al.*, 1998[40]	France	1995–1996	RCT Double blind	BU, ICU	>10	Clinical, biopsy	Adults and elderly	23–81	NM	NM	22
Yang *et al.*, 2009[41]	China	1993–2007	Retrospective	ICU	>10	Clinical, biopsy	All age	6–86	41.0 ± 12.5*	2.3 ± 1.0	47
Yeong *et al.*, 2011[42]	Taiwan	2000–2006	Retrospective	BU	>30	Clinical, biopsy	All age	11–89	66.2 ± 28.6	3.2 ± 1.4	16
Zhu *et al.*, 2012[43]	China	2000–2010	Retrospective	ICU	>30	Clinical, biopsy	Adults and elderly	18–91	90.3 ± 12.1	2.3 ± 1.2	55

ICU: Intensive care unit, BU: Burn unit, DW: Dermatology ward, RCT: Randomized controlled trial, NM: Not mentioned, IQR: Interquartile range, TEN: Toxic epidermal necrolysis, SCORTEN: Score of TEN, SD: Standard deviation

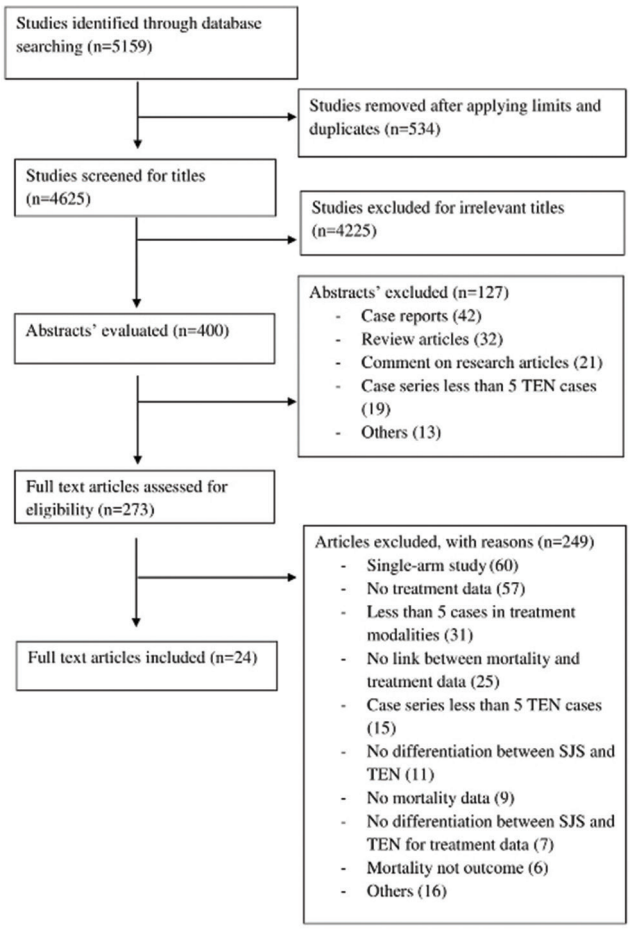

Figure 1: PRISMA flow diagram showing study selection process

have a clear description of age group studied. Total sample size of included TEN patients varied from 11 to 174.

Intervention group characteristics

Total of 979 patients with TEN from 24 studies were assigned to 7 intervention groups. Total of 223 deaths were observed. The interventions used in included studies were supportive care (15), steroids (14), intravenous immunoglobulin (8), Steroid+intravenous immunoglobulin (7), Cyclosporine (4), Etanercept (1) and Thalidomide (1). Number of two-arm intervention studies were 23. One study assessed multi-arm interventions.[36] Basis of allocation of the treatment was clearly described in 14 studies. Only 5 studies described the delay in start of treatment.[21,25,32,35,36] In case of Shortt *et al*., intravenous immunoglobulin group of patients were admitted significantly earlier than those who received supportive care only.[37] The studies that described or provided sufficient data to calculate the age group, body surface area and SCORTEN score distribution of intervention groups were 20, 19 and 9, respectively. In case of Hirapara *et al*.[26] and Lee *et al*.[32] age group data were not comparable among the intervention groups. In case of Stella *et al*., patients in corticosteroid group had significantly higher body surface area involvement than steroid+intravenous immunoglobulin group patients. In case of Mohanty *et al*., patients in supportive care group had higher SCORTEN score than cyclosporine group patients.[33] Five included studies did not differentiate the mortality data between SJS and TEN patients. The corresponding authors provided the mortality data on request through mail.[24,32,33,35,36] Detailed characteristics of intervention groups are presented in Table 2.

Risk of bias assessment

Total 16 studies scored ≥5 in risk of bias assessment. As shown in risk of bias summary [Figure 2], most of the studies did not clearly describe the details of ineligible participants, eligible subjects refused to participate, patients completed the allocated treatment regimen and years of treatment for each group of patients. The details of risk of bias assessment in individual studies are described in Table 3.

Direct pairwise meta-analysis

There were total 10 direct pairwise comparisons [Figure 3]. Cyclosporine was associated with significantly reduced risk of mortality as compared with supportive care [OR- 0.32 (95% CI: 0.13, 0.82)] and intravenous immunoglobulin [OR- 0.08 (95% CI: 0.01, 0.54)]. Steroid+intravenous immunoglobulin combination also showed significantly reduced mortality as compared to intravenous immunoglobulin alone [OR- 0.16 (95% CI: 0.04, 0.61)]. Thalidomide was associated with a significantly higher risk of mortality as compared with supportive care [OR- 11.67 (95% CI: 1.53, 89.12)]. Other pairwise comparisons did not show a statistically significant difference. There was no significant heterogeneity in a pairwise comparison with an exception of comparison between intravenous immunoglobulin and steroids (I^2=72%).

Network meta-analysis

The network of direct treatment comparisons is presented in Figure 4. The size of each node corresponds to the number of participants and thickness of line between the nodes indicate number of comparisons. In line with direct meta-analysis, network analysis showed that risk of death was reduced in cyclosporine arm as compared with supportive care [OR- 0.19 (95% CrI: 0.05, 0.59)] and intravenous immunoglobulin [OR- 0.21 (95% CrI: 0.05, 0.76)]. Interventions which showed reduced risk of death as compared to thalidomide were cyclosporine [OR- 0.01 (95% CrI: 0.00 – 0.31)], steroid+intravenous immunoglobulin [OR- 0.03 (95% CrI: 0.00 – 0.51)], steroids [OR- 0.06 (95% CrI: 0.00 – 0.90)] and supportive care [OR- 0.08 (95% CrI: 0.00 – 0.95)]. Unlike direct comparison, Steroid+intravenous immunoglobulin combination did not show significantly reduced mortality as compared to intravenous immunoglobulin alone [OR- 0.45 (95% CrI: 0.13, 1.60)]. Other pairwise comparisons did not show statistically significant difference [Figures 5a and b]. As shown in Table 4, the hierarchy of treatments based on SUCRA value were cyclosporine (0.93), steroid+intravenous immunoglobulin (0.76), etanercept (0.59), steroids (0.46),

Table 2: Characteristics of intervention groups

Study	Intervention	Intervention dose	Basis of assigning treatment	Delay in start treatment Mean±SD, mean (95% CI)*, median (IQR)** days	Age Mean±SD, mean (95% CI)*, median (IQR)**, median (range)*** years	BSA Mean±SD, median (range)*** %	SCORTEN score Mean (95% CI)*, median (IQR)**, median (range)***	Total TEN sample	Expected mortality percentage	Observed mortality percentage
Cyclosporine versus supportive care										
Lee *et al.*, 2017[32]	Supportive care	NA	All consecutively admitted patients based on selection criteria received cyclosporine. Rest received supportive care only	4.0±2.7	66±17	32±30	NM	12	29.5	30
	Cyclosporine	3 mg/kg/day for 10 days than 2 mg/kg/day for 10 days and lastly 1 mg/kg/day for 10 days	-	1.8±1.7	50±21	26±20	NM	16	29.9	12.5
Mohanty *et al.*, 2017[33]	Supportive care	NA	All consecutively admitted patients based on selection criteria received cyclosporine. Rest received supportive care only	NM	41.8±9.6	32.8±20.0	3.7±1.0	8	52.5	55.5
	Cyclosporine	5 mg/kg/day for 10 days	-	NM	36.8±8.3	35.9±20.3	2.05±1.1	14	16.4	5.26
Poizeau *et al.*, 2018[35]	Supportive care	NA	NM	≤3 days	48 (39–63)**	10±14 (epidermal detachment)	NM	79	NM	NM
	Cyclosporine	3 mg/kg/day for 10 days	-	≤ 3 days	39 (2–57)**	18±18 (epidermal detachment)	NM	95	NM	NM
Steroid versus supportive care										
Brand and Rohr, 2000[20]	Supportive care	NA	Dermatologist discretion	NM	NM	NM	NM	6	NM	NM
	Corticosteroid	HS: 400 mg or PS: 30–100 mg for 3–14 days	-	NM	NM	NM	NM	6	NM	NM
Chantaphaku *et al.*, 2015[22]	Supportive care	NA	NM	NM	NM	NM	NM	5	NM	NM
	Corticosteroid	DS: IV 8–40 mg/day or PS: 30–60 mg/day for 1–10 days	NM	NM	NM	NM	NM	14	NM	NM

(*Contd....*)

Table 2: (*Continued*)

Study	Intervention	Intervention dose	Basis of assigning treatment	Delay in start treatment Mean±SD, mean (95% CI)*, median (IQR)** days	Age Mean±SD, mean (95% CI)*, median (IQR)**, median (range)*** years	BSA Mean±SD, median (range)*** %	SCORTEN score Mean (95% CI)*, median (IQR)**, median (range)***	Total TEN sample	Expected mortality percentage	Observed mortality percentage
Hirapara *et al.*, 2017[26]	Supportive care	NA	NM	NM	49 (40.–57.6)*	NM	1.8 (1.3–2.3)*,^	8	NM	NM
	Corticosteroid	Mean dose - DS: 5.6 mg or HS: 200 mg or PS: 17.5 mg. Mean duration 6.9 days	-	SJS/TEN overlap: 4.4 (3.3–5.4)* TEN: 7.1 (3.3–10.8)*	34.8 (27.4–42.2)*,^	NM	1.8 (1.5–2.1)*,^	28	NM	NM
Ioannides *et al.*, 1994[27]	Supportive care	NA	NM	NM	38.7±26.3	35.0±13.6	NM	8	NM	NM
	Corticosteroid	PS equivalent 50–120 mg/day doses of steroids	NM	NM	50.6±26.2	47.3±16.3	NM	11	NM	NM
Kaur *et al.*, 1990[29]	Supportive care	NA	NM	NM	NM	NM	NM	9	NM	NM
	Corticosteroid	PS: 1–2 mg/kg in a short course	-	NM	NM	NM	NM	21	NM	NM
Schneck *et al.*, 2008[36]	Supportive care	NA	Most patient in Germany received corticosteroid and in France supportive care)		NM	NM	NM	54	NM	NM
	Corticosteroid	PS equivalent median total dose 250 (IQR: 100–500) mg	-	4 (2–5)**	NM	NM	NM	62	NM	NM
IVIG versus supportive care										
Brown *et al.*, 2004[21]	Supportive care	NA	NM	5.6±4.7	43±29	46.3±26		21	NM	NM
	IVIG	0.4 g/kg/day for 4 days	NM	9.2±12	47±21	44.9±24.6	NM	24	NM	NM
Gravante *et al.*, 2007[25]	Supportive care	NA	Admission years	11.2±13.9	43.7±22.9	58.9±34.3	NM	15	NM	NM
	IVIG	0.4 g/kg/day for 5 days		8.9±7.1	46.1±18.7	66.5±32.1	NM	16	NM	NM
Paquet *et al.*, 2006[34]	Supportive care	NA	NM	NM	44.8±18.6	54.8±19.9	NM	5	NM	NM
	IVIG	1 g/kg/day for 3 days	-	NM	46.7±19.2	62.5±12.5	NM	6	NM	NM
Schneck *et al.*, 2008[36]	Supportive care	NA	Most patient in Germany received corticosteroid and in France supportive care)		NM	NM	NM	54	NM	NM
	IVIG	Median total dose 1.9 g/kg (IQR: 1.3–2.1)	-	5 (3–7)**	NM	NM	NM	26	NM	NM

(*Contd....*)

Table 2: (*Continued*)

Study	Intervention	Intervention dose	Basis of assigning treatment	Delay in start treatment Mean±SD, mean (95% CI)*, median (IQR)** days	Age Mean±SD, mean (95% CI)*, median (IQR)**, median (range)*** years	BSA Mean±SD, median (range)*** %	SCORTEN score Mean (95% CI)*, median (IQR)**, median (range)***	Total TEN sample	Expected mortality percentage	Observed mortality percentage
Shortt *et al.*, 2004[37]	Supportive care	NA	Historical comparator	9.1±6.9	52±20	65±27	NM	16	NM	NM
	IVIG	0.2–0.75 g/kg/day for 4 days	-	4.8±2.6	53±21	65±29	NM	16	NM	NM
Yeong *et al.*, 2011[42]	Supportive care	NA	Patients with severe manifestation, uncontrolled progression, sepsis, but not with renal failure received IVIG	NM	61.7±25.7	68.0±28.4	3.3±1.2	7	NM	NM
	IVIG	Doses NM	-	NM	55.1±23.1	64.9±30.4	3.1±1.6	9	NM	NM
Steroid+IVIG versus steroid										
Chen *et al.*, 2010[23]	Corticosteroid	HS: 100–700 mg/day IV or MPS: 40–80 mg/day. Duration NM	-	NM	34.7±15.9^	15.3^	0.8±1.0^	15	NM	NM
	IVIG+corticosteroid	IVIG: 0.7–7.4 g/kg IV for 3–15 days HS: 100–700 mg/day/ methyl prednisolone 40–80 mg/day. Duration NM	NM	8.8±4.6	42.8±15.1^	30.2^	2.0±1.7^	15	NM	NM
Jagadeesan *et al.*, 2013[28]	Corticosteroid	DS: IV 0.1–0.3 mg/ kg/day rapidly tapered within 1–2 weeks	Consecutively admitted patients alternatively allocated	NM	38.6±17.6	49.5±14.1	2.5 (2–3)**	18	26.4	16.7
	IVIG+corticosteroid	IVIG: 0.2–0.5 g/kg/day for 3 days DS: Same doses as corticosteroid arm	-	NM	35.4±17.7	52.8±11.6	3 (2–3)**	18	30.5	5.55
Lalosevic *et al.*, 2015[31]	Corticosteroid	MPS 1–2 mg/kg for 19 mean days	NM	NM	NM	NM	NM	8	NM	NM
	IVIG+corticosteroid	Total 2 g/kg over 2 or 5 days	-	NM	NM	NM	NM	6	NM	NM
Schneck *et al.*, 2008[36]	Corticosteroid	PS equivalent median total dose 250 (IQR: 100–500) mg	-	4 (2–5)**	NM	NM	NM	62	NM	NM
	IVIG+corticosteroid	Same doses for corticosteroid and IVIG group	-	NM	NM	NM	NM	29	NM	NM

(*Contd....*)

Table 2: (*Continued*)

Study	Intervention	Intervention dose	Basis of assigning treatment	Delay in start treatment Mean±SD, mean (95% CI)*, median (IQR)** days	Age Mean±SD, mean (95% CI)*, median (IQR)**, median (range)*** years	BSA Mean±SD, median (range)*** %	SCORTEN score Mean (95% CI)*, median (IQR)**, median (range)***	Total TEN sample	Expected mortality percentage	Observed mortality percentage
Stella *et al.*, 2007[38]	Corticosteroid	HS: 200–500 mg MPS: 2 g/BS: 12 mg/day. Duration NM	Historical comparator	NM	51.0±16.2	71.7±23.8	NM	6	NM	NM
	IVIG+corticosteroid	IVIG: 0.7 g/kg/day for 4 days MPS 1 g/day for initial 2 days		NM	59.3±18.4	22.4±13.8	NM	21	NM	NM
Yang *et al.*, 2009[41]	Corticosteroid	MPS 1–1.5 mg/kg/day till re-epithelialization than prompt tapering	Historical comparator	NM	43.7±23.1	41.3±11.3	2.3±1.0	35	19.2^	22.2^
	IVIG+corticosteroid	0.4 g/kg/day for 5 days and MPS as mentioned above		NM	48.2±21.5	40.0±16.1	2.3±0.9	12	17.5^	15.0^
Zhu *et al.*, 2012[43]	Corticosteroid	MPS 1.5 mg/kg/day till reepithelization than prompt tapering	Patients with progressive disease after receiving MPS for 3–5 days were given IVIG	NM	51±16	84.6±17.8	2.4±1.2	16	24.4	22.7
	IVIG+corticosteroid	IVIG: 0.4 g/kg/day for 5 days plus MPS as mentioned above	-	NM	44±20	91.7±9.1	2.3±1.2	39	23.9	12.8
IVIG versus steroid										
Kim *et al.*, 2005[30]	Corticosteroid	MPS IV 250–1000 mg/day followed by oral PS. Duration NM	NM	NM	NM	NM	NM	21	28.4	28.6
	IVIG	1.6–2.0 g/kg. Duration NM	-	NM	NM	NM	NM	14	16.8	7.1
Schneck *et al.*, 2008[36]	Corticosteroid	PS equivalent median total dose 250 (IQR: 100–500) mg	-	4 (2–5)**	NM	NM	NM	62	NM	NM
	IVIG	Median total dose 1.9 g/kg (IQR: 1.3–2.1)	-	5 (3–7)**	NM	NM	NM	26	NM	NM
Steroid+IVIG versus supportive care										
Schneck *et al.*,[36] 2008	Supportive care	NA	Most patient in Germany received corticosteroid and in France supportive care)		NM	NM	NM	54	NM	NM

(*Contd....*)

Table 2: (*Continued*)

Study	Intervention	Intervention dose	Basis of assigning treatment	Delay in start treatment Mean±SD, mean (95% CI)*, median (IQR)** days	Age Mean±SD, mean (95% CI)*, median (IQR)**, median (range)*** years	BSA Mean±SD, median (range)*** %	SCORTEN score Mean (95% CI)*, median (IQR)**, median (range)***	Total TEN sample	Expected mortality percentage	Observed mortality percentage
	IVIG+corticosteroid	Same doses for corticosteroid and IVIG group	-	NM	NM	NM	NM	29	NM	NM
Cyclosporine versus IVIG										
González-Herrada *et al.*, 2017[24]	Cyclosporine	3 mg/kg/day orally or 1 mg/kg/day IV till reepithelization and tapered off	Admission in one of two hospitals	NM	47.0±17.2^	39.3±25.8^	2.4±1.1^	23	25	7.7
	IVIG	0.75 g/kg/day for 4 days	-	NM	55.0±20.8^	29.9±26.2^	2.7±1.3^	9	33.6	45.5
Steroid+IVIG versus IVIG										
Schneck *et al.*, 2008[36]	IVIG	Median total dose 1.9 g/kg (IQR: 1.3–2.1)	-	5 (3–7)**	NM	NM	NM	26	NM	NM
	IVIG+corticosteroid	Same doses for corticosteroid and IVIG group	-	NM	NM	NM	NM	29	NM	NM
Etanercept versus steroid										
Wang *et al.*, 2018[39]	Corticosteroid	PS 1–1.5 mg/kg/day IV until skin lesion healed	Randomization with allocation concealment	NM	57.3±24.4	42.1±22.4	1.9±1.4^	17	20.3	16.3
	Etanercept	25/50 mg sc twice a week until skin lesion healed			51.6±15.7	46.3±24.2	1.8±1.3^	18	17.7	8.3
Thalidomide versus supportive care										
Wolkenstein *et al.*, 1998[40]	Placebo (supportive care)	NA	Randomization, double blind using placebo	NM	50.5 (23–58)***	30.5 (10–85)***	NM	10	NM	NM
	Thalidomide	400 mg/day for 5 days			53 (23–81)***	43.5 (26–90)***	NM	12	NM	NM

^Data of all SJS patients, TEN: Toxic epidermal necrolysis, SCORTEN: Score of TEN, SD: Standard deviation, CI: Confidence interval, IQR: Interquartile range, BSA: Body surface area, NM: Not mentioned, NA: Not applicable, IV: Intravenous, IVIG: IV immunoglobulin, MPS: Methylprednisolone, HS: Hydrocortisone, PS: Prednisolone, DS: Dexamethasone, BS: Betamethasone, SJS: Stevens–Johnson syndrome

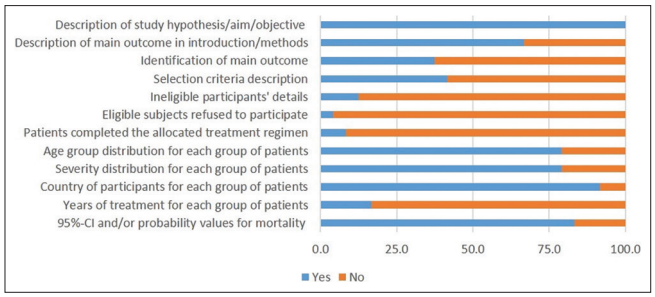

Figure 2: Risk of bias summary

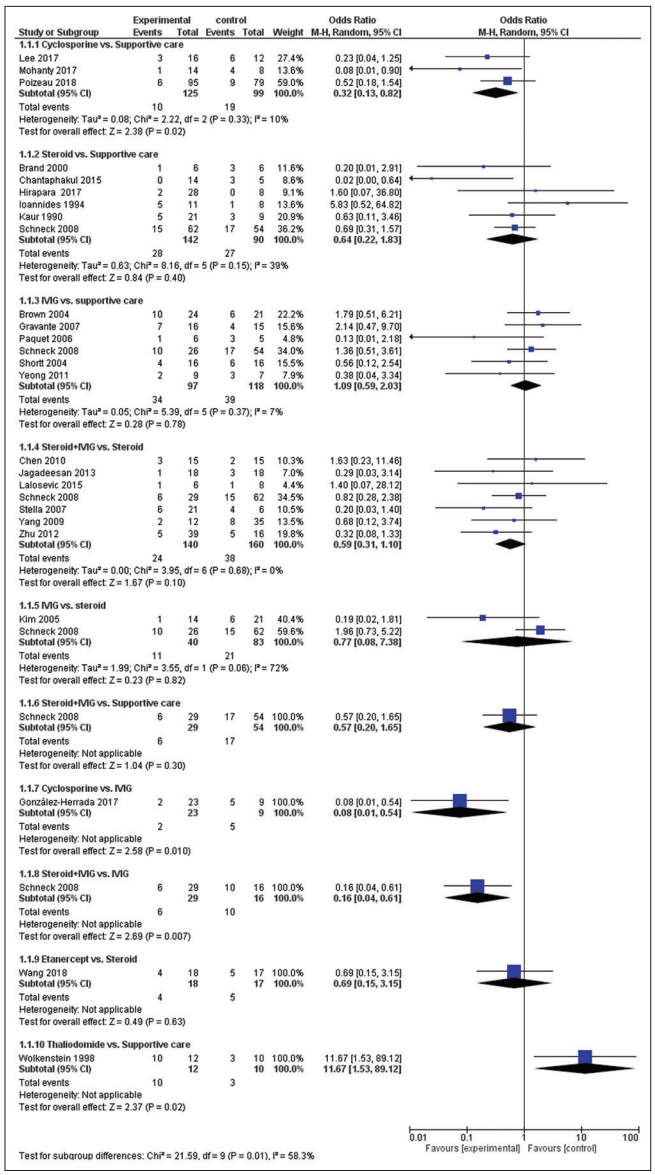

Figure 3: Meta-analytic summary of direct treatment comparisons

intravenous immunoglobulin (0.40), supportive care (0.34) and thalidomide (0.02).

Sensitivity analysis

Risk of bias assessment: The sensitivity analysis was performed by excluding high risk studies. No major differences were observed between all included studies and low-risk bias studies. As shown in Figures 6a and b, the risk of death was significantly reduced with cyclosporine as compared with supportive care, intravenous immunoglobulin and steroids. Interventions that showed a reduced risk of death as compared to thalidomide were cyclosporine, steroid+intravenous immunoglobulin, steroids, intravenous immunoglobulin and supportive care. Steroid+intravenous immunoglobulin combination also showed significantly reduced mortality as compared to intravenous immunoglobulin alone. As shown in Table 4, the most effective interventions based on SUCRA value were cyclosporine (0.96), steroid+intravenous immunoglobulin (0.78) and etanercept (0.56).

Study design: The sensitivity analysis was performed for retrospective design studies. The risk of mortality was significantly reduced with cyclosporine as compared with supportive care [OR- 0.24 (95% CrI: 0.07, 0.92)]. The most effective treatments hierarchy based on SUCRA value were cyclosporine, steroid+intravenous immunoglobulin and steroids [Table 4]. It was not possible to explore other designs due to the small number of studies in each group [prospective (3), randomized controlled trial (2) and prospective-retrospective (1)].

Study location: The sensitivity analysis was performed based on studies conducted in developed or developing countries. Cyclosporine is the most effective intervention in both developed and developing countries. The other effective treatments in developed countries were steroid+intravenous immunoglobulin and steroids, while in developing countries were intravenous immunoglobulin and steroid+intravenous immunoglobulin [Table 4].

Inconsistency assessment

Both direct and indirect evidence was available for 8 treatment pairs which were part of the closed loop of network meta-analysis. As shown in Tables 5a and b, there were no inconsistencies between direct and indirect estimates of any of the treatment pairs (all 95% CIs across zero and p>0.05) for all studies and low risk of bias studies.

The comparison-adjusted funnel plot indicated absence of major asymmetry around zero line [Figure 7].

Discussion

In this network meta-analysis, we compared the effectiveness of five immunomodulating treatment modalities for TEN patients - steroid, intravenous immnunoglobulin, combination of steroid+intravenous immunoglobulin, etanercept and cyclosporine. Our findings are based on a sample of 979 patients of TEN from 24 studies. Cyclosporine, steroid+intravenous immunoglobulin combination, etanercept, steroid and intravenous immunoglobulin were ranked above supportive care. Probabilities of being a better intervention than supportive care did not alter

Table 3: Risk of bias (quality assessment) in individual studies

Study	Description of study hypothesis/ aim/ objective	Description of main outcome in introduction/ methods	Identification of main outcome	Selection criteria description	Ineligible participants' details	Eligible subjects refused to participate	Patients completed the allocated treatment regimen	Description of following confounding factor distribution for each group of patients				Reporting of 95% CI and/ or *P* value for mortality data*	Total score
								Age	Severity	BSA	Years		
Brand and Rohr, 2000[20]	1	0	0	0	0	0	0	0	0	1	0	0	2
Brown *et al.*, 2004[21]	1	1	0	0	0	0	0	1	0	1	0	0.33	4.33
Chantaphakul *et al.*, 2015[22]	1	1	0	0	0	0	0	0	0	0	0	0.33	2.33
Chen *et al.*, 2010[23]	1	0	0	0	0	0	0	1	1	1	0	0.67	4.67
González-Herrada *et al.*, 2017[24]	1	1	1	1	0	0	0	1	1	1	0	0.67	7.67
Gravante *et al.*, 2007[25]	1	0	0	0	0	0	0	1	1	1	1	0.33	5.33
Hirapara *et al.*, 2017[26]	1	0	0	0	0	0	0	1	1	1	0	0.33	4.33
Ioannides *et al.*, 1994[27]	1	0	0	1	0	0	0	1	1	1	0	0	5
Jagadeesan *et al.*, 2013[28]	1	1	0	1	0	0	0	1	1	1	0	0.67	6.67
Kaur *et al.*, 1990[29]	1	0	0	0	0	0	0	0	0	0	0	0	1
Kim *et al.*, 2005[30]	1	1	0	0	0	0	0	0	1	1	0	0.67	4.67
Lalosevic *et al.*, 2015[31]	1	0	0	0	0	0	0	0	0	1	0	0.33	2.33
Lee *et al.*, 2017[32]	1	1	1	1	1	0	0	1	1	1	0	0.67	8.67
Mohanty *et al.*, 2017[33]	1	0	0	1	0	0	0	1	1	1	1	0.33	6.33
Paquet *et al.*, 2006[34]	1	1	1	0	0	0	0	1	1	1	0	0	6
Poizeau *et al.*, 2018[35]	1	1	1	0	0	0	0	1	1	1	1	0.67	7.67
Schneck *et al.*, 2008[36]	1	1	1	0	0	0	0	1	1	1	0	0.67	6.67
Shortt *et al.*, 2014[37]	1	1	0	1	0	0	0	1	1	1	0	0.33	6.33
Stella *et al.*, 2007[38]	1	1	0	0	0	0	0	1	1	1	0	0.67	5.67
Wang *et al.*, 2018[39]	1	1	1	1	1	0	1	1	1	1	0	0.67	9.67
Wolkenstein *et al.*, 1998[40]	1	1	1	1	1	1	1	1	1	1	0	0.67	10.67
Yang *et al.*, 2009[41]	1	1	0	0	0	0	0	1	1	1	0	0.67	5.67
Yeong *et al.*, 2011[42]	1	1	1	1	0	0	0	1	1	1	0	0.33	7.33
Zhu *et al.*, 2012[43]	1	1	1	1	0	0	0	1	1	1	1	0.67	8.67

No description of item carries score 0, Description of each point score=1 except for reporting of mortality data where description of "95% CI and *P* value both" carries score - 0.67 and "only *P* value reporting" carries score - 0.33. BSA: Body surface area, CI: Confidence interval

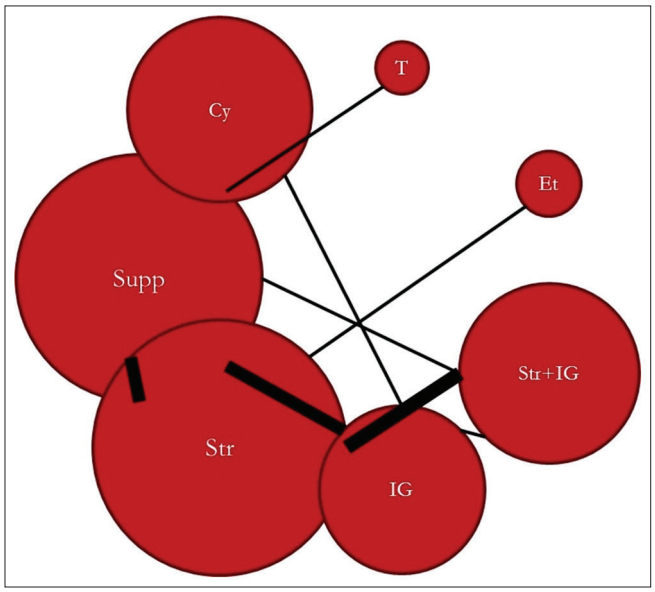

Figure 4: Network plot of treatment comparison. Cy: Cyclosporine, Supp: Supportive care, Str: Steroid, IG: Intravenous immunoglobulin, Str + IG: Steroid + intravenous immunoglobulin, Et: Etanercept, T: Thalidomide, Size of each node corresponds to number of participants. Thickness of line between nodes indicate number of comparisons

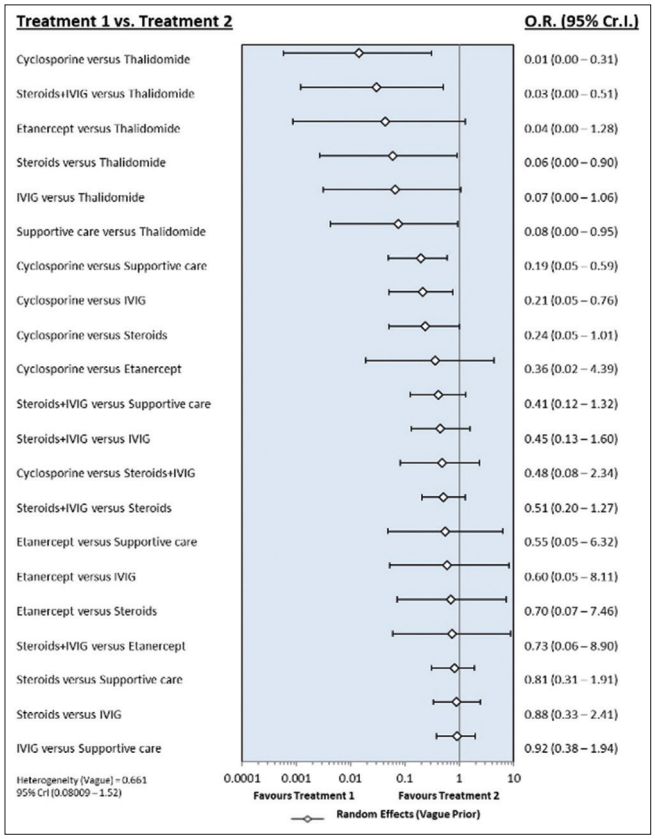

Figure 5a: Forest plot of treatment comparisons for mortality. OR: Odds ratio, CrI: Credibility interval, IVIG: Intravenous immunoglobulin

for cyclosporine, steroid+intravenous immunoglobulin combination and etanercept in sensitivity analysis.

Cyclosporine						
0.48 (0.08 – 2.34)	Steroids+IVIG					
0.36 (0.02 – 4.39)	0.73 (0.06 – 8.90)	Etanercept				
0.24 (0.05 – 1.01)	0.51 (0.20 – 1.27)	0.70 (0.07 – 7.46)	Steroids			
0.21 (0.05 – 0.76)	0.45 (0.13 – 1.60)	0.60 (0.05 – 8.11)	0.88 (0.33 – 2.41)	IVIG		
0.19 (0.05 – 0.59)	0.41 (0.12 – 1.32)	0.55 (0.05 – 6.32)	0.81 (0.31 – 1.91)	0.92 (0.38 – 1.94)	Supportive care	
0.01 (0.00 – 0.31)	0.03 (0.00 – 0.51)	0.04 (0.00 – 1.28)	0.06 (0.00 – 0.90)	0.07 (0.00 – 1.06)	0.08 (0.00 – 0.95)	Thalidomide

Figure 5b: League table of treatment ranking in order of better to worst outcome from left to right. Data indicates OR: Odds ratio, CrI: Credibility interval, IVIG: Intravenous immunoglobulin

Cyclosporine can decrease the mortality in TEN patients. It showed beneficial effects as compared with supportive care and intravenous immunoglobulin in this study. Cyclosporine was ranked first in SURCRA analysis. This is in line with three earlier meta-analyses suggesting its beneficial effect on patient survival.[10-12] Similar survival benefits of cyclosporine were also observed in other studies which are not part of included studies in this network meta-analysis.[44-49] Poizeau *et al*. observed no survival benefit with cyclosporine on propensity score adjustment. However, the authors mentioned that patients with the nonprogressive disease were more likely to have received supportive care than those with cyclosporine.[35] Our findings should be interpreted cautiously as they are based on four retrospective studies only. Moreover, included studies either did not consider patients with comorbidities (renal insufficiency, infection, cancer, etc.) or did not report this information.

Ranking analysis suggests etanercept as a promising immunomodulating option for TEN patients. This should be interpreted cautiously as it could not show significant survival benefit over other interventions. The wide confidence interval could be due to only one included study and small sample size. A double-blind randomized control clinical trial has been registered on clinicaltrial.gov (NCT02987257) which is intended to compare cyclospprin, etanercept and supportive care with the sample of 267 patients. Though mortality is the secondary objective, this trial can validate our findings of beneficial effect of cyclosporine and etanercept over supportive care in TEN patients.[50]

Intravenous immunoglobulin or steroids alone do not improve survival in TEN patients. Both the therapies showed trends of higher mortality than cyclosporine, steroid+intravenous immunoglobulin combination and etanercept. In sensitivity analysis, they showed the trend of worse outcome than supportive care. These findings are in accordance with the earlier meta-analyses.[5-8,10] In a meta-analysis by Zimmermann *et al*., steroid showed significant survival benefit in unstratified individual patient data meta-analysis. However, it was not substantiated on stratified type individual patient data and study level meta-

Table 4: Hierarchy of treatments and Surface under the cumulative ranking curves value

All studies	Low risk studies (*n*=16)	Retrospective design (*n*=18)	Developed countries (*n*=11)	Developing countries (*n*=13)
Cyclosporine (0.93)	Cyclosporine (0.96)	Cyclosporine (0.90)	Cyclosporine (0.89)	Cyclosporine (0.73)
Steroid+IVIG (0.76)	Steroid+IVIG (0.78)	Steroid+IVIG (0.76)	Steroid+IVIG (0.81)	IVIG (0.72)
Etanercept (0.59)	Etanercept (0.56)	Steroids (0.38)	Steroids (0.50)	Steroid+IVIG (0.58)
Steroids (0.46)	Supportive care (0.42)	IVIG (0.38)	Supportive care (0.46)	Etanercept (0.53)
IVIG (0.40)	Steroids (0.40)	Supportive care (0.22)	IVIG (0.32)	Steroids (0.34)
Supportive care (0.34)	IVIG (0.38)	-	Thalidomide (0.02)	Supportive care (0.11)
Thalidomide (0.02)	Thalidomide (0.01)	-	-	-

IVIG: Intravenous immunoglobulin

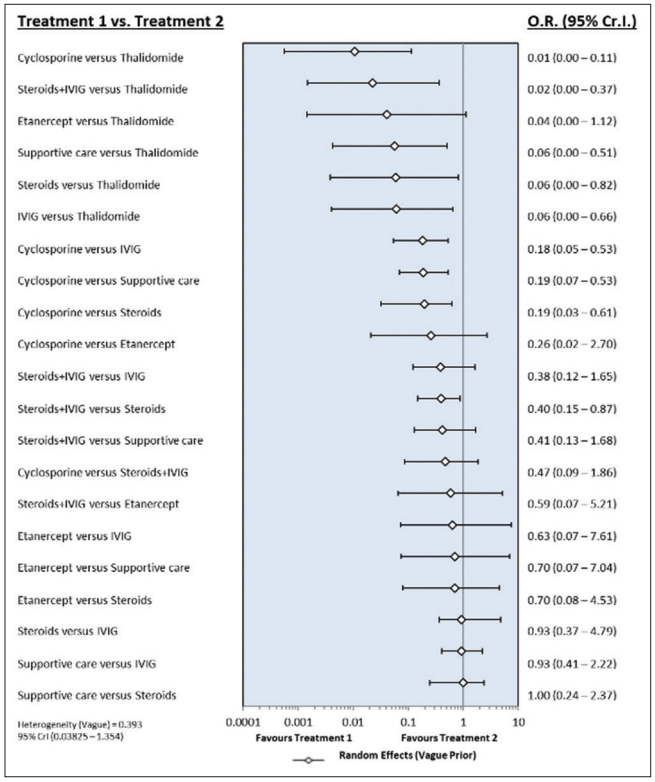

Figure 6a: Forest plot of treatment comparisons for mortality in low risk of bias studies. OR: Odds ratio, CrI: Credibility interval, IVIG: Intravenous immunoglobulin

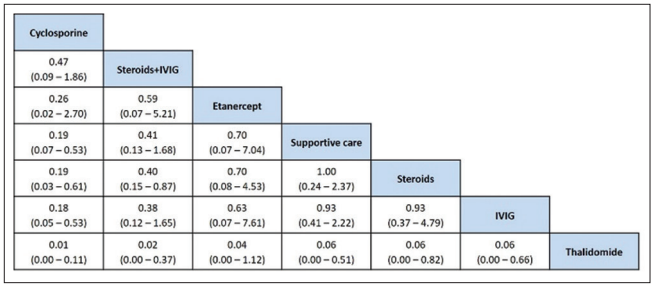

Figure 6b: League table of treatment ranking in order of better to worst outcome from left to right (low risk of bias studies). Data indicates OR: Odds ratio, CrI: Credibility interval, IVIG: Intravenous immunoglobulin

analysis.[10] Earlier meta-analyses observed contradictory mortality findings with different doses of intravenous immunoglobulin.[7,8,51] We could not evaluate high vs. low dose effect due to small sample of studies in intravenous immunoglobulin group. Similarly, we also could not evaluate the effect of individual steroids, their doses and duration of therapy on mortality.

In contrast to steroids and intravenous immunoglobulin monotherapy, their combination stands second on ranking analysis. It suggests better therapeutic effect with combination than intravenous immunoglobulin or steroids alone. In direct pairwise comparison, seven of nine included studies of combination therapy showed a trend of improved survival than intravenous immunoglobulin, steroid and supportive care alone. Though a meta-analysis by Ye *et al*. did not observe mortality benefit with steroid+intravenous immunoglobulin combination in SJS/TEN patients, the authors observed significant benefit in TEN patients irrespective of intravenous immunoglobulin dose in combination therapy.[9] This is also corroborated by a recent multicentric retrospective study from the United States with a larger sample size which observed the lowest standardized mortality ratio with combination therapy than therapy with intravenous immunoglobulin, steroid or supportive care alone.[52]

Limitations

This network meta-analysis has several limitations. Only two databases (PubMed and Google Scholar) for English language studies were searched. This could have missed some of the literature. We did not consider SJS (body surface area < 10%) cases. This prevented us from checking the effect of interventions on all severity of SJS cases. We have not included single-arm studies through matching of study characteristics. It could have strengthened the evidence. The network meta-analysis summary and ranking are mainly based on observational studies. Most studies did not describe the method of treatment allocation. There is a possibility that patients could have been treated with a corticosteroid at an outside hospital prior to admission. Most studies did not describe the time-gap between the development of symptoms and initiation of therapy. It could have affected the mortality across the treatment groups. This could also be due to differences in use of supportive care across the studies.

Table 5a: Inconsistency between direct and indirect estimates

Comparison	Number of studies	Log_ NMA	Log_ direct	Log_ indirect	Log_ difference	Log_diff_95 CI_lower	Log_diff_95 CI_upper	*P*
Cyclosporine: IVIG	1	−1.46	−2.57	−1.10	−1.48	−3.92	0.97	0.24
Cyclosporine: Supportive care	3	−1.43	−1.18	−2.65	1.48	−0.97	3.92	0.24
IVIG: Steroids	2	0.25	0.15	0.36	−0.21	−1.87	1.46	0.81
IVIG: Steroids+IVIG	1	0.83	0.87	0.79	0.08	−1.89	2.05	0.94
IVIG: Supportive care	6	0.03	0.05	−0.04	0.09	−1.75	1.92	0.93
Steroids: Steroids+IVIG	7	0.58	0.55	1.34	−0.79	−4.60	3.02	0.68
Steroids: Supportive care	6	−0.22	−0.42	0.53	−0.95	−2.73	0.84	0.30
Steroids+IVIG: Supportive care	1	−0.80	−0.57	−0.99	0.43	−1.40	2.25	0.65

NMA: Network meta-analysis, CI: Confidence interval, IVIG: Intravenous immunoglobulin

Table 5b: Inconsistency between direct and indirect estimates (low risk of bias studies)

Comparison	Number of studies	Log_ NMA	Log_ direct	Log_ indirect	Log_ difference	Log_diff_95 CI_lower	Log_diff_95 CI_upper	*P*
Cyclosporine: IVIG	1	−1.49	−2.57	−1.13	−1.45	−3.81	0.92	0.23
Cyclosporine: Supportive care	3	−1.36	−1.13	−2.58	1.45	−0.92	3.81	0.23
IVIG: Steroids	1	0.17	0.67	−0.73	1.40	−0.51	3.32	0.15
IVIG: Steroids+IVIG	1	0.96	0.87	1.09	−0.21	−2.29	1.86	0.84
IVIG: Supportive care	5	0.13	−0.07	1.82	−1.89	−4.15	0.36	0.10
Steroids: Steroids+IVIG	5	0.79	0.73	6.68	−5.94	−13.64	1.74	0.13
Steroids: Supportive care	2	−0.04	−0.06	0.04	−0.10	−2.17	1.97	0.92
Steroids+IVIG: Supportive care	1	−0.83	−0.57	−1.25	0.68	−1.26	2.63	0.49

NMA: Network meta-analysis, CI: Confidence interval, IVIG: Intravenous immunoglobulin

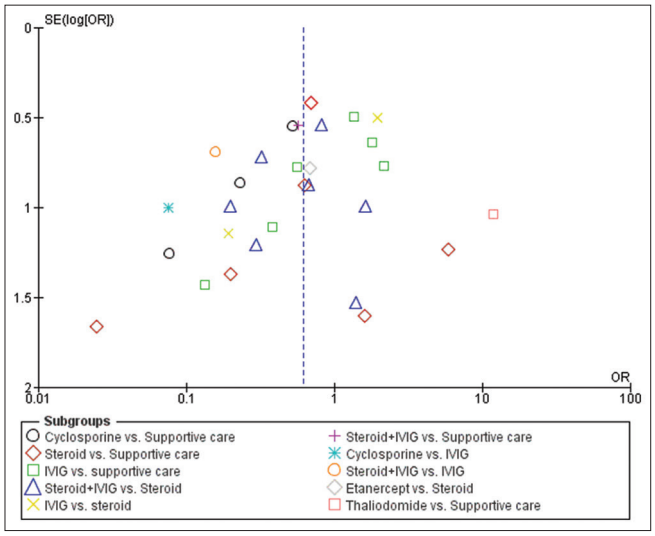

Figure 7: Funnel plot

Studies also used varied doses and duration of therapy for each intervention.

Conclusion

Cyclosporine reduces the mortality in TEN patients. Other promising interventions could be steroid+intravenous immunoglobulin combination and etanercept. Our findings could be biased as the evidence is based on analysis of retrospective studies. Double-blind randomized studies are recommended to compare the effect of interventions like cyclosporine, steroid+intravenous immunoglobulin and etanercept with supportive care. Investigators planning prospective studies should use a randomized study design. Smaller sample randomized study may not show statistically meaningful mortality differences but will definitely contribute to meta-analysis of randomized controlled studies.

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Conflicts of interest

There are no conflicts of interest.

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