The Effects of Systemic Cyclosporine on Ocular Outcomes in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Scholarly Report Title: The Effects of Systemic Cyclosporine on Ocular Outcomes in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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GLOSSARY OF ABBREVIATIONS

ALT: Alanine aminotransferase

AMT: Amniotic membrane transplantation

ANOVA: Analysis of variance

AOS: Acute ocular involvement score

ASS: Acute systemic involvement score

AST: Aspartate aminotransferase

AT: Artificial tears

BCVA: Best-corrected visual acuity

COCS: Chronic ocular surface complications score

CRP: C-reactive protein

FML: Fluorometholone

IL-2: Interlukin-2

IV = intravenous

IVIG: Intravenous immunoglobulin

logMAR: Logarithm of the minimum angle of resolution [logMAR]

MEEI: Massachusetts Eye and Ear Infirmary

MF: Moxifloxacin

MGH: Massachusetts General Hospital

MMG: Mucous membrane graft

PA: Prednisolone acetate

PROSE: Prosthetic replacement of the ocular surface ecosystem

SCORTEN: Severity-of-illness scale

SJS: Stevens-Johnson syndrome

TEN: Toxic epidermal necrolysis

TNF-α: Tumor necrosis factor alpha

PROJECT QUESTION

To evaluate the effect of systemic cyclosporine on ocular disease in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) patients in a retrospective analysis. Currently here is in no clear consensus on which systemic treatments, if at all, are most effective in reducing morbidity and mortality for SJS/TEN. (Kim et al. 2015, et al, Worswick et al, 2011, Scott-Lang et al. 2014, Wolkenstein et al. 1998, Yip et al. 2004, Kirchof et al. 2014). Systemic cyclosporine in the acute phase has been found to shorten the progression of epithelial detachment as well as reduce mortality in SJS/TEN patients (Arevalo et al 2000, Reese et al. 2011, Valeyrie-Allanore et al. 2015, Ng et al, 2018). While studies have commented on the effect of topical cyclosporine on dry eye symptoms, as well as systemic cyclosporine's role in combating dermatologic changes and reducing mortality in SJS/TEN patients, there has been no study that has evaluated the effect of systemic cyclosporine in acute SJS/TEN on ocular outcomes. In this retrospective study we aim to assess the effect systemic cyclosporine in the acute phase of SJS/TEN on chronic ocular disease.

DESCRIPTION OF CONTRIBUTION OF WORK

My specific role was performing retrospective chart review to obtain the data, to analyze the data with STATA and SAS, and write a paper to discuss our findings.

TITLE: The Effects of Systemic Cyclosporine on Ocular Outcomes in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Purpose: To evaluate the effect of systemic cyclosporine on ocular disease in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) patients.

Methods: For this retrospective, comparative study patients were divided into 2 groups: those who received cyclosporine and those who did not receive cyclosporine. Best-corrected visual acuity (BCVA) and chronic ocular surface complications score (COCS; range, 0 -13) at final follow-up were compared between the two groups.

Results: The median age and follow-up period of patients was 29 years (range, 1.5 to 71 years) and 16.8 months (range, 3.67 to 91.58 months), respectively. BCVA, COCS, meibomian gland dysfunction, limbal stem cell deficiency, and the need for mucous membrane grafting and scleral lenses were not significantly different between patients who received systemic cyclosporine as compared to patients who did not receive systemic cyclosporine.

Conclusions: In this limited study we could identify no association of cyclosporine with improved ocular function or fewer chronic ocular complications later in their clinical course.

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening conditions characterized by blistering of the skin and mucous membranes. SJS/TEN is most often caused by a drug, and rarely by viral and bacterial infections (Yetiv et al. 1980, Choy et al. 1995, Stevens et al. 1978). Ocular complications occur in more than half of patients during the acute phase of SJS/TEN (Power, et al, 1995). Ocular complications can also manifest after the acute phase with 20-79% of SJS/TEN patients suffering from long-term ocular complications, which can cause visual impairment and blindness (Haber et al. 2005, Magina et al. 2003, Schwatz et al. 2013, Kohanim et al. 2016, Arstikaitis et al, 1973).

The mainstays of therapy for SJS/TEN include elimination of the offending agent, supportive care, and wound care (Kohanim et al, 2016). Because SJS/TEN is characterized by widespread apoptosis involving natural killer cells, cytotoxic T-cells, and tumor necrosis factor alpha (TNF-α) (Kohanim et al, 2016), there have been several proposed systemic immunosuppressive treatments for SJS/TEN in the acute phase. These treatments include systemic corticosteroids, intravenous immunoglobulin (IVIG), TNF-α inhibitors, and cyclosporine, all of which have been previously compared to one another in the literature. However, there is in no clear consensus on which systemic treatments, if at all, are most effective in reducing morbidity and mortality (Kim et al. 2015, et al, Worswick et al, 2011, Scott-Lang et al. 2014, Wolkenstein et al. 1998, Yip et al. 2004, Kirchof et al. 2014)

Cyclosporine is a polypeptide that inhibits transcription of interleukin-2 (IL-2), and thus inhibits IL-2's ability to attract CD4+ and CD8+ T-cells and inhibits IL-2's ability to activate natural killer cells (Reese et al, 2011). Cyclosporine may also prevent apoptosis via down regulation of nuclear factor- kB (Chave et al, 2005). Since SJS/TEN involves T-cell and natural killer cell mediated apoptosis of dermatocytes, it seems plausible that cyclosporine may be an effective treatment option (Chave et al, 2005). Systemic cyclosporine in the acute phase has been found to shorten the progression of epithelial detachment as well as reduce mortality in SJS/TEN patients (Arevalo et al 2000, Reese et al. 2011, Valeyrie-Allanore et al. 2015, Ng et al, 2018. Common adverse effects of systemic cyclosporine include nausea, headaches, hyperlipidemia, hypertension, renal dysfunction, tremors, nonmelanoma skin cancer, neutropenia, pneumonia, and leukoencephalopathy (Ng et al. 2018, Kohaim et al. 2016). Topical cyclosporine

administered to the ocular surface has been found to decrease the number of T cells in the conjunctiva and increase goblet cell density (Kunert et al, 2000, Pflugfelder et al, 2008). In particular, a prospective non-comparative interventional case series suggests that cyclosporine 0.05% eye drops are beneficial for the treatment of dry eye symptoms in the chronic phase of SJS/TEN (Prabhasawat et al, 2013). While studies have commented on the effect of topical cyclosporine on dry eye symptoms, as well as systemic cyclosporine's role in combating dermatologic changes and reducing mortality in SJS/TEN patients, there has been no study that has evaluated the effect of systemic cyclosporine in acute SJS/TEN on ocular outcomes. In this retrospective study we aim to assess the effect systemic cyclosporine in the acute phase of SJS/TEN on chronic ocular disease.

Methods

Subjects and Study Design

We retrospectively reviewed the medical records of patients who were hospitalized at Massachusetts General Hospital (MGH) with a diagnosis of SJS, SJS-TEN overlap, or TEN between August 2014 and May 2018. Medical records were obtained from both MGH and Massachusetts Eye and Ear Infirmary (MEEI). This study was approved by the institutional review board at MEEI and MGH. The study was conducted under Health Insurance Portability and Accountability Act compliance and adhered to the tenets of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) Diagnosis of SJS, SJS-TEN overlap, or TEN was confirmed in the acute phase by a dermatologist or burn surgeon on the basis of clinical exam and/or histopathologic examination of skin biopsies. SJS was defined as epidermal detachment of less than 10% of a patient's body surface area, SJS-TEN overlap as 10-30%, and TEN as greater than 30%. (2) Patients had medical records of the acute phase and chronic phase, which were fully accessible. (3) Patients were followed for at least 3 months after disease onset. (4) Patients did not report any pre-existing ocular disease and were assumed to have had BCVA of 20/20 prior to SJS/TEN onset. One patient who received cyclosporine was excluded from the study given known social factors that negatively impacted the patient's ability to receive care that adhered to institutional treatment protocol.

Twenty-eight eyes of 14 patients (5 men, 9 women; median age 25 years; range, 1.5 - 71 years) were included in the study. Seven patients received cyclosporine and seven patients received no cyclosporine. The age, sex, causative drugs or infection, follow-up period, acute ocular involvement score (AOS: range, 0-3), acute systemic involvement score (ASS; range, 0-16), amniotic membrane transplantation (AMT) in the acute phase, need for mucous membrane grafting, need for scleral lens, best-corrected visual acuity (BCVA) at final follow-up, and chronic ocular complication score (COCS; range, 0 -13) were investigated. Due to the limited sample size of the study given the low incidence of SJS/, the power of the study was 0.30.

Early Systemic Treatment during the Acute Phase of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

During the acute phase, all patients, regardless of receiving systemic cyclosporine, received treatment according to acute ocular severity as shown in Table 1. For those in the cyclosporine group, systemic cyclosporine was initiated within 7 days after onset of disease. Oral cyclosporine doses were converted to reflect IV bioavailability, and thus the median dosage of systemic cyclosporine was 2.5 mg/kg daily (range 1.6 to 5 mg/kg daily). The mean duration of time over which cyclosporine was given was 11.88 ± 8.15 days. Of the patients who received systemic cyclosporine, some only received cyclosporine (n = 2) but some received cyclosporine and systemic steroids (n=3), or cyclosporine, systemic steroids, and IVIG (n = 2) prior to admission to MGH. In the group of patients who did not receive cyclosporine, there was one patient who received 3 days of oral steroids prior to admission. Otherwise, all other patients in the no cyclosporine group did not receive any other forms of immunosuppressive therapies.

Acute Ocular and Systemic Involvement Scores

Ocular surface findings during the acute phase, defined as one month after onset of initial skin lesions, were graded as an acute ocular severity score ranging from grade 0 to 3. Eyes were graded based on presence of conjunctival, corneal, and eyelid margin disease as shown in Table 1. Acute systemic involvement was graded from 0 to 16, based on observation of the following during the patient's hospital admission: oral or genital erythema, degree of epidermal detachment, fever, respiratory disturbance, total necrosis of epidermis, liver dysfunction, anemia, elevated serum C-reactive protein concentrations, kidney dysfunction, and pneumonia. Table 2 shows the variables that contribute to the acute systemic involvement score, which were based on severity of illness score for TEN (SCORTEN) and a grading system used by Kim 2015 et al.

Table 1. Grading Scores and Suggested Management for Acute Ocular Severity of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Acute Ocular Manifestations	Grade	Suggested Management
No ocular involvement	0	Prophylactic AT 3x/day Escalation of management as necessary
Conjunctival hyperemia; no corneal conjunctional, or eyelid margin defects	1	MF 3x/day PA 6x/day FML ointment to eyelids 6x/day AT every 1 hour
Corneal, conjunctival, or eyelid margin defects without membranes	2	MF 3x/day PA 6x/day FML ointment to eyelids 6x/day AT every 1 hour If only corneal and/or bulbar conjunctival involvement, may place Prokera, otherwise perform AMT*
Corneal conjunctival, or eyelid margin defects with membranes	3	MF 3x/day PA 6x/day FML ointment to eyelids 6x/day AT every 1 hour Perform AMT*
*Decision to perform AMT based on feasibility (intubation status, cooperation, etc.). Prokera is acceptable if only bulbar conjunctival or corneal involvement or when AMT is not feasible. AT= artificial tears; MF = moxifloxacin 0.5%; PA= prednisolone acetate 1%; FML= fluorometholone 0.1%; AMT = amniotic membrane transplantation		

Table 2. Acute Systemic Involvement Score

Systemic Involvement	Scoring
Oral erosive lesions with bloody scales	1
Labial erosive lesions with bloody scales	1
Oral or labial (lips) erosive lesions only	1
Genital involvement	1
Blisters, epidermal detachment, erosions (% of total body surface area; selection of 3 items below)	*0-3*
> 30%	3
10%-30%	2
≤ 10%	1
High fever (≥ 38 °C)	1
Respiratory disturbance	1
Total necrosis of epidermis	1
Liver dysfunction (U/L; selection of the items below)	*0-2*
ALT or AST > 100	2
40 <ALT ≤ 100 or 40 <AST≤ 100	1
Anemia (hemoglobin <10 g/dL)	1
Serum CRP ≥ 5 mg/L	1
Kidney Dysfunction (serum blood urea nitrogen > 28 mg/dL)	1
Pneumonia (pneumonic infiltration in chest radiograph film)	1
Total	16
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein	

Visual Outcome and Chronic Ocular Surface Complication Score at Final Follow-up

Best-corrected visual acuity and COCS were assessed at patients' final recorded follow-up. COCS was based on the grading system establish by Sotozono et al. The 13 factors included in the score are shown in Table 3. Our study reports the presence or absence of these factors with a total of 13 points, whereas the Sotozono et al. grading system evaluates each factor on a 3-point scale with a total of 39 points.

Table 3. Chronic Ocular Complications of Stevens-Johnson Syndrome Patients

Complication	Score
Corneal complications	
Superficial punctate keratitis	1
Epithelial defect	1
Limbal Stem Cell Deficiency	1
Conjunctivalization	1
Neovascularization	1
Opacification	1
Keratinization	1
Conjunctival complications	
Hyperemia	1
Symblepharon formation	1
Eyelid complications	
Trichiasis	1
Mucocutaneous junction involvement	1
Meibomian gland involvement	1
Punctal damage	1
Total	13

Statistical Analysis

All data analyses were performed using Stata software version 12.0 (College Station, Texas, USA) and SAS version 9.4m4 (Cary, North Carolina, USA). Continuous variables are presented as mean ± standard deviation or median (range), while categorical variables are presented as frequencies. In order to ascertain the effect of cyclosporine, the following outcomes were compared between those patients who received cyclosporine and those who did not during the acute phase of disease: final BCVA (in logarithm of the minimum angle of resolution [logMAR] units), COCS, development of meibomian gland dysfunction, limbal stem cell deficiency, requirement of mucous membrane graft (MMG) and PROSE scleral lens. Generalized Estimating Equations were performed to account for non-normally distributed data and the correlated effects of paired eyes from each patient. When groups had variables with a frequency of 0, GEE could not be performed and instead Fisher's exact test was performed. We also assessed the relationship of AOS or ASS with final BCVA or COCS using Spearman's rank correlation. Of the patients who received systemic cyclosporine, some only received cyclosporine but some also received systemic steroids, IVIG, or both. An ANOVA test was performed to compare BCVA, AOS, and COCS between these 4 treatment groups. Statistical significance was defined as $p < 0.05$.

Results

Table 4 summarizes the demographics and characteristics of all patients included in the study. Median follow-up period was 16.8 months (range 3.67 – 91.58 months). Mean AOS was 1.93 ±0.60. AOS was 1 point in 6 eyes (21.4%), 2 points in 18 eyes (64.3%), and 3 points in 4 eyes (14.3%). AOS was significantly different between SJS, SJS-TEN overlap, and TEN patients (SJS 1.5 ± 0.53, SJS-TEN overlap 2 ± 0.0, TEN 2.17 ± 0.71, p = 0.043, ANOVA). However, there was no significant difference in which group received cyclosporine between SJS, SJS-TEN overlap, and TEN patients (p = 0.205, ANOVA). Median ASS was 9 (range, 5 to 12). There was no significant difference between the previously mentioned groups for ASS (SJS 7 (range 5 to 9), SJS-TEN overlap 8.5 (range 7 to 10), TEN, 9 (range 6 to 12). The etiologies of SJS/TEN included cotrimoxazole (n=4), ibuprofen (n=3), lamotrigine (n=2), amoxicillin (n=1), pseudoephedrine (n=1), Norgestrel (n=1), phenytoin (n=1), sertraline (n=1), and Mycoplasma infection (n =1).

Table 4. Patient's Characteristic According to Treatment Group

	Cyclosporine	No cyclosporine	P value
Patients (eyes)	7 (14)	7 (14)	-
Age (years)*	25 (1.5 to 71)	32 (13 to 43)	0.439
Sex (male//female)#	2//5	3//4	0.695
SJS~	1	3	0.26
SJS-TEN Overlap~	2	2	1.00
TEN~	4	2	0.29
Mean interval between disease onset and initial systemic treatment (days)	3.71 ± 2.43	-	-
AMT ~	2	3	0.58
Acute ocular involvement score Grade 1~ Grade 2~ Grade 3~	 3 10 2	 3 9 2	 1.00 1.00 1.00
Acute systemic involvement score *	9 (5 to 12)	8 (6 to 10)	0.695
Length of follow up (months) *	10 (3.67 to 20.0)	55.5 (10.7 to 91.5)	0.0001

Data are presented as the mean ± standard deviation or median (range), or frequencies.
* Wilcoxon rank-sum test
# Fisher's exact test
~ Generalized estimating equations
AMT = amniotic membrane transplantation

Final Visual Outcome and Chronic Ocular Surface Complications Score

Among all patients, the median final BCVA (logMAR) was 0.088 (range 0 to 0.602) and mean COCS was 3.07 ± 2.76. Table 5 shows that the final BCVA and COCS at final follow-up were not significantly different between the eyes that received cyclosporine and those did not receive cyclosporine. In addition, there was no significant difference with regard to meibomian gland dysfunction, limbal stem cell deficiency, and recommendation of mucous membrane grafting and PROSE scleral lenses.

Table 5. Final Visual Outcome and Chronic Ocular Surface Complication Score According to Treatment

	Cyclosporine (14 eyes)	No cyclosporine (14 eyes)	P value
Final BCVA (logMAR)~	0.215 ± 0.238	0.075 ± 0.116	0.11
COCS~	3.64 ± 3.00	2.43 ± 2.00	0.35
Meibomian gland dysfunction ~	12/14	10/14	0.52
Limbal Stem Cell Deficiency #	4/14	0/14	0.10
Required MMG ~	4/14	2/14	0.52
Required PROSE scleral lenses ~	4/14	2/14	0.52

Data are presented as the mean ± standard deviation or median (range), or frequencies.
BCVA = Best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; COCS = chronic ocular surface complication score.
MMG = Mucous membrane graft; PROSE= prosthetic replacement of the ocular surface
~ Generalized Estimating Equations
# Fisher's exact test

Relationship of Acute Ocular and Systemic Involvement with Final Visual Acuity and Chronic Ocular Complications Score

There was a significant correlation between acute ocular severity and final BCVA (r_s =0.461, p = 0.0135), as well as between acute ocular severity and the chronic ocular complication score (r_s=0.390, p =0.038). In addition, there was a significant correlation between acute ocular involvement and acute systemic involvement (r_s= 0.4952, p = 0.0074). However, there is not a significant correlation between final BCVA and acute systemic involvement (r_s=0.2669, p =0.1698). There was a significant correlation between BCVA and the chronic ocular complication score (r_s= 0.655, p= 0.0002).

TABLE 6. Subgroup Analysis of the Effect of Variables at the Acute Stage on Chronic Ocular Complications

Variables	Final Best-Corrected Visual Acuity (Logarithm of the Minimum Angle of Resolution)	p-value	Chronic Ocular Surface Complications Score	p-value
Age (yrs) (n= 28 eyes)	0.088 (0 to 0.602)	0.512	3.07 ± 2.76	0.052
Sex Male (n= 10 eyes) Female (n = 18 eyes)	 0 (0 to 0.176) 0.176 (0 to 0.602)	0.043	 2.10 ± 3.48 3.61 ± 2.20	0.170
SJS/SJS-TEN overlap/ TEN SJS (n= 8 eyes) SJS-TEN overlap (n= 8 eyes) TEN (n= 12 eyes)	 0 (0 to 0.398) 0 (0 to 0.176) 0.176 (0 to 0.602)	0.174	 2.375 ± 2.069 2.5 ± 3.16 3.917 ± 2.875	0.387
AOS (n= 28 eyes)	0.145 ± 0.197	0.098	3.07 ± 2.76	0.026
ASS (n = 28 eyes)	0.088 (0 to 0.602)	0.064	3.07 ± 2.76	0.776
AMT AMT performed (n= 10 eyes) AMT not performed (n= 18 eyes)	 0.176 (0 to 0.602) 0 (0 to 0)	0.020	 0.80 ± 0.79 4.33 ± 2.67	0.0004
Data are presented as the mean ± standard deviation or median (range). AMT = amniotic membrane transplantation; AOS = acute ocular involvement score; ASS = acute systemic involvement score; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis *Nonparametric analysis of covariance				

There was a significant relationship of female sex and final BCVA, as shown in Table 6. In addition, there was a significant relationship between amniotic membrane transplantation during the acute stage and final BCVA and COCS. Patients that received AMT had greater AOS (ANOVA, p 0.01).

Discussion

Several studies have described that systemic cyclosporine reduces the mortality rate in SJS/TEN and that local cyclosporine 0.05% eye drops reduce dry eye symptoms in the chronic phase of SJS; however, no studies have commented on the effect of systemic cyclosporine on chronic ocular outcomes (Arevalo et al. 2000, Reese et al. 2011, Valeyrie-Allanore et al. 2010, Kirchoff et al. 2014, Ng et al. 2018, Prabhasawat et al, 2013).In our limited study of 7 patients who received systemic cyclosporine during the acute phase of SJS/TEN, in comparison to 7 patients who did not, we could identify no association with improved ocular function or fewer chronic ocular complications later in their clinical course.. In all the eyes included in our study, acute ocular severity and chronic ocular complications were significantly associated; however, there was no significant difference in acute ocular severity or acute systemic involvement between those who received systemic cyclosporine and those who did not receive cyclosporine. Thus, the patients who received cyclosporine and those who did not were well matched in this regard and we can assume that the cyclosporine group did not have worse disease prompting administration of the drug. Of note, patients in the cyclosporine group had significantly less follow up time than the no cyclosporine group. This is because cyclosporine grew in use in this cohort of patients at the end of the study period.

With regard to prognostic factors, female sex was associated with poorer final BCVA, a relationship also found by Kim et al. in 2015. In addition, our data showed that AMT was associated with worse final BCVA and higher COCS than the non-AMT group; however, those patients that received AMT had higher AOS, as expected by treatment protocol shown in Table 1. Our study does not compare those who received AMT with those who did not in the setting of equivalent AOS. Given that there is a significant positive correlation between AOS and BCVA as well as between AOS and COCS, higher AOS is more of a predictor of final BCVA and COCS than whether or not the patient received AMT. AMT has been found to be effective in mitigating chronic ocular complications John et al. 2002, Hsu et al. 2012, Gregory 2016). In addition, a randomized control trial demonstrated that SJS/TEN patients who received AMT had significantly better BCVA at 6-months follow-up than SJS/TEN patients who did not receive AMT (Sharma et al. 2016).

Limitations of our study include the small sample size, which is expected given the low incidence of the disease. Our sample size was further limited by the even smaller subset of

patients who received cyclosporine. In addition, the administration of cyclosporine was not standardized, as dosing and duration of cyclosporine varied for each patient. An observational, record-based study that found that cyclosporine had a mortality benefit, all patients received 3 mg/kg for 1 to 10 days, followed by a taper over 1 month (Mohanty et al. 2017). Our sample size is too small to compare different dosages and duration of cyclosporine, but these differences may account for our non-significant findings. On the other hand, there may be a therapeutic window during which cyclosporine's effects may have positive effects on ocular outcomes, which has yet to be defined. In addition, some of the patients who received cyclosporine also received IVIG, systemic steroids, or both, often prior to admission to our burn unit. However, an ANOVA test demonstrated no significant differences in final BCVA, acute ocular severity, acute systemic involvement severity, or chronic ocular complications between the following treatment groups: cyclosporine alone, cyclosporine and IV corticosteroids, cyclosporine and IVIG, and cyclosporine and IV corticosteroids and IVIG. The sample size is small but this test may suggest that the presence of other immunomodulatory therapies did not affect our outcomes. Lastly, the limitations in clinical data collection inherent to a retrospective study are present in ours. However, all clinical data was recorded by only two clinicians at the same center who have a systematic and similar method of recording exam findings in SJS/TEN patients.

In our limited study we could identify no association between use of cyclosporine during the acute phase of SJS/TEN and improved ocular function or fewer chronic ocular complications later in their clinical course. We believe an association does indeed exist, but was not detected due to the small sample size. To have a study with a power of 0.80 and alpha of 0.05, we would require 70 eyes in the cyclosporine group and 70 eyes in the no cyclosporine group, and thus a total of 140 eyes. Such a study would require a multicenter approach given the low incidence of SJS/TEN. Female gender was associated with worse final best-corrected visual acuity. Studies with larger cohort of patients receiving standardized dosages and duration of systemic cyclosporine should be performed to ascertain the true effects of cyclosporine on ocular outcomes. Further areas of exploration should include determining the role of high-dose topical cyclosporine in mitigating chronic ocular complications when given in the acute phase of SJS.

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