Intravenous Immunoglobulin Use in the Treatment of Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome: A 10-year Retrospective Analysis of Patients of a Single Burn Center

A thesis submitted to the University of Arizona College of Medicine -- Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

Ryan Cooper
Class of 2014

Mentors: Melissa Pressman, PhD and Kevin Foster, MD

Abstract:

Stevens - Johnson syndrome and Toxic Epidermal Necrolysis Syndrome are rare, but serious conditions affecting skin and mucous membranes that are primarily treated with supportive care. Other more specific therapies have limited evidence to support the benefit of their use; one such treatment is intravenous immunoglobulin (IVIG). The use of IVIG in the treatment of these syndromes remain controversial due to mixed results demonstrated in the literature, and at present is not considered a component of the standard of care. This study seeks to provide additional data regarding the efficacy of IVIG treatment on mortality in a small cohort of patients presenting with these syndromes at a regional burn center over a 10-year period; data was retrospectively collected from patient medical records.

On analysis of this data, IVIG use showed a potential, but not significant. improvement on mortality in comparison to the non-treatment group. Compared with the non-treatment group, odds ratios for death were 0.81 (95% CI 0.3-2.0) for IVIG.

There is ultimately no new evidence that the benefit of IVIG in the treatment of Stevens - Johnson syndrome and Toxic Epidermal Necrolysis Syndrome is anything more than potential. Further investigation should include a rigorous analysis and comparison of different dosing regimens.

Table of Contents

List of Figures and Tables

Introduction:

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis syndrome (TENS; also known as Lyell's syndrome) are related conditions characterized by fever and mucocutaneous lesions which can result in necrosis and sloughing of the epidermis that can last several weeks[1,2,3]. The etiology of these conditions are incompletely understood, although are suspected to be immunologic in nature. The skin sloughing is morphologically characterized by ongoing apoptosis of keratinocytes which results in the separation of epidermis from dermis, possibly mediated by the *Fas/FasL* death receptor and ligand[2].

While often considered together due to their clinical similarities, SJS and TENS differ based on a continuum of severity; SJS is a less severe condition in which epidermal sloughing is limited to less than 10% of the body surface area (BSA) with reported mortality ranging from 1-5%, while TENS involves sloughing >30% of the BSA with reported mortality ranging from 25-35%[2]. The two conditions overlap between 10-30% of BSA. Both conditions involve a prodrome of flu-like symptoms and fever, although temperatures often run higher in TENS, and lesion involvement of the mucous membranes. SJS/TENS can occur in all age groups, although TENS typically affects older individuals; women (60%) are more often affected than men.

By far, medications are the leading trigger of SJS/TENS; the most commonly implicated medications include antibiotics (particularly those containing sulfa), anti-psychotics and anti-epileptics, analgesics, NSAIDS and allopurinol. Mortality associated with medication-induced cases of SJS/TENS rises in correlation with increases in half-life of the agent[7]. Infection is the second leading cause, with SJS more likely to be caused by infection than TENS.

The standard of care in the treatment of SJS/TENS includes the prompt withdrawal of any suspected causative medications or agents (and future avoidance of these triggers), supportive care and possible transfer to a burn unit- particularly for extensive BSA involvement. The removal of triggers has been shown to improve prognosis and decrease mortality[7]. At least one multicenter review has suggested that transfer to a burn unit may improve outcomes and reduce mortality in TENS[8]. Supportive care includes wound care, fluid and electrolyte

management, nutritional support, pain/fever management, vigilant infection monitoring, and sub-specialist involvement as necessary.

Beyond supportive care, adjunctive medical treatments can include glucocorticoids, intravenous immunoglobulin (IVIG), and cyclosporine; all of which suffer from limited evidence given a paucity of research and a lack of controlled trials[9]. Use of plasmapheresis has also been encountered in the literature.

Early infusion of IVIG, particularly at high-doses, has been demonstrated in the literature to be a generally safe, well tolerated, and possibly effective treatment for improving the survival of patients with TENS[6]. This study is designed to assess the impact IVIG use on mortality by retrospectively reviewing patient medical records of SJS/TENS patients while hospitalized at a regional burn center. IVIG is a blood product gathered from donated plasma which contains exogenous immunoglobulins (specifically IgG), which is typically used to treat immune deficiencies, autoimmune diseases and infection by an incompletely understood mechanism of action. The logic of using IVIG in for the treatment of SJS/TENS considers that IVIG contains natural anti-*Fas* antibodies which are thought to inhibit the cellular apoptosis occurring between the dermis and epidermis in SJS/TENS[2].

Methodology:

Data collection was performed by retrospectively reviewing patient electronic and paper medical records for 86 subjects diagnosed and treated for SJS/TENS over a 10-year period. Collected demographic data included age, ethnicity, gender, physical exam and laboratory findings, suspected diagnosis, possible offending agents, estimated extent of body surface and mucous membrane involvement, IVIG use, mortality, and length of hospital stay. Inclusion criteria were that patients have a recorded clinical diagnosis or suspicion of SJS/TENS. There were no exclusion criteria.

Total body surface area (TBSA) affected was determined via chart reporting, applying specifically to the estimated amount of surface area to experience sloughing. This information was used to stratify patients based on severity of disease, and to objectively classify a working diagnosis of SJS, SJS/TENS overlap syndrome, or TENS. Because only 48 patients had documented TBSA involvement, the remaining patients were excluded when analyzing mortality in the context of a specific severity of disease.

The human subjects of this study are protected by the HIPAA, organizational privacy policies and privacy laws; appropriate efforts were taken to de-identify protected health information to protect the privacy of subjects participating in this study.

On analysis, IVIG use was compared to non-use as specific treatment for SJS/TENS. The outcome measure was patient mortality during the course of hospital admission and treatment for SJS/TENS. Mortality was reported as a percentage and an odds ratio. Because of data limitations at the time of retrospective analysis, the efficacy of combination treatments other than IVIG and supportive care was not assessed, nor was treatment stratified by dosing regimens; however all subjects were specifically assessed as to whether or not IVIG was used during treatment based on medical record documentation.

Results:

A total of 86 Patients with documented diagnoses of SJS/TENS were identified at the Maricopa County Medical Center over a 10-year period. Treatments administered by burn center physicians varied considerably, thus each patient was identified as having received IVIG or not, and assigned a 'yes' or 'no' categorical variable respectively. Multiple manufactured formulations of IVIG were used. Demographic data of the study population can be found in *Table 1*.

The majority of subjects in this study were diagnosed with higher levels of severity (60.4% having been diagnosed with TENS). Female patients (68.6%) outnumbered male patients (31.4%), consistent with previous studies published in the literature. The average age of a subject was 47 with wide variation. Overall mortality in our subject population was 32.6%. *Table 2* delineates demographic data based on treatment group; receiving IVIG or not receiving IVIG.

The majority of patients (49) received IVIG versus the non-treatment group (37). Of those patients diagnosed with SJS/TENS, 37 did not receive treatment with IVIG; of those not treated, 13 died yielding a mortality rate of 35.1%. Of those patients diagnosed with SJS/TENS, 49 received treatment with IVIG; of those treated with IVIG, 15 died yielding a mortality rate of 30.6%.

Because of data limitations on reported TBSA involvement, only 48 patients were considered when stratifying by severity of disease. The severity of disease differed moderately between the IVIG treatment group and the non-treatment group. Retrospectively, males and younger patients were found more frequently in the IVIG treatment group.

Table 3 demonstrates mortality stratified by treatment, age and disease severity.

Table 1. Demographic Data of all Patients

	n = 86 patients identified		
Severity			
	SJS	7/48	14.6%
	SJS/TENS overlap	12/48	25.0%
	TENS	29/48	60.4%
Male:Female		27/59	31.4%
Age, y, mean +/-SD		47 +/- 21	
Global Mortality		28/86	32.6%

Table 2. Demographic Data of all Patients by Treatment Group

	n = 86 patients identified			
	IVIG		No IVIG	
Severity				
SJS	15/22	68.2%	14/26	53.8%
SJS/TENS overlap	4/22	18.2%	8/26	30.8%
TENS	3/22	13.6%	4/26	15.4%
Male:Female	16/33	48.5%	10/27	37.0%
Age, y, mean +/-SD	45 +/- 20		49 +/- 23	
Global Mortality	15/49	30.6%	13/37	35.1%

Table 3. Mortality stratified by treatment, age, disease severity

	Mortality		OR	(95% CI)
Treatment				
IVIG	15/49	30.6%	0.81	(0.3-2.0)
No IVIG	13/37	35.1%	1.22	(0.5-3.0)
Age				
<35	4/27	14.8%	0.25	(0.1-0.8)
35-70	19/47	40.4%	2.26	(0.9-5.8)
>70	5/12	41.7%	1.58	(0.5-5.5)
Severity				
SJS (<10% TBSA)	0/7	0.0%	undefined	undefined
SJS/TENS overlap (10-30% TBSA)	4/12	33.3%	0.625	(0.2-2.4)
TENS (>30% TBSA)	16/29	55.2%	4.62	(1.2-17.2)

The risk of death was moderately correlated with age and strongly correlated with severity of the disease process and TBSA. Younger patients under 35 had the lowest mortality (14.8%); those patients aged 35-70 exhibited markedly increased mortality (40.4%), while those over 70 showed another slight increase (41.7%). Patients with SJS (TBSA <10%) had no mortality rate, with mortality increasing for those classified as having overlap syndromes (TBSA 10-30%), and mortality at its highest for patients classified as having TENS (TBSA >30%). TENS was associated with a 55.2% mortality rate (OR 4.62, 95% CI 1.2-17.2), the only resulting association achieving statistical significance.

Discussion:

From 86 patients with SJS/TENS, we retrospectively data-mined whether or not IVIG was utilized in treatment protocols, dividing our patient study population into those receiving IVIG as part of the treatment protocol and a control group that did not. The assignment of patients to the treatment group (IVIG) did not take into consideration the dosage; while certainly a limitation to the study and a direction for future research, it also negates any bias introduced by arbitrarily assigning maximal and minimal dose ranges in the absence of well-established, evidence-based protocols in the literature. Treatment protocols were noted to vary considerably among patients; protocols are often based on physician preference and experience given the rarity of the disease process and a standard of care consisting primarily of supportive measures. These variations could be seen between different treating physicians and at different points in time over the 10-year study period. It is assumed that all patients received equivalent supportive care, both with and without administration of IVIG.

The results of this study suggest that there may some benefit from the use of IVIG in the treatment of SJS/TENS. Mortality was decreased in the IVIG treatment group when compared with the non-IVIG treatment group; however confounding variables are potentially present and no clear statistical significance is evident from the confidence intervals. Only severity of disease in the form of a TENS diagnosis (based on TBSA involvement of >30%) was determined to have a statistically significant bearing on the measured outcome of mortality. While hinting that IVIG use in treatment protocols could result in some mortality benefit, ultimately the results of this study don't allow us to make that claim with statistical significance; thus this study contributes no new firm evidence to the body of medical knowledge that the benefit of IVIG in the treatment of SJS/TENS is anything more than potential.

From previous studies, potential benefits of IVIG use in the treatment of SJS/TENS are apparently dose-dependent. Many studies have shown benefit to using higher doses of IVIG in the treatment of SJS; in one study high-dose IVIG was found to be effective in blocking progression of SJS and reducing time to complete skin healing, while another found shortened duration of fever and hospital admission (albeit without reaching statistical significance)in

children[4, 5]. However, a retrospective study of European SJS/TENS patients receiving a lower-dose found no apparent benefit to using IVIG[3]. To help shed light on this discrepancy, subsequent analysis of this dataset and these patient records could include information on, and stratification based on, IVIG dosing. Variables that could be characterized could include quantity of dose, dosing schedule, and length of treatment.

In a study of this nature, confounding elements may always be present. For example, significant bias is can be introduced as the result of any subjective clinical assessment of TBSA involvement that may span the definitional parameters dividing SJS, TENS, and overlap syndromes. This is why the original population of 86 patients was reduced to 48 with well documented TBSA involvement when analyzing the data based on severity of disease. Other potential confounders were identified but were not able to be specifically addressed. One example is the effect of adjunct pharmacotherapies, such as corticosteroid administration, on outcome measures. Another example is non-randomization of the comparison treatment groups; without being able to identify the rationale behind when IVIG was used or not used or having a guiding standard of care, it's a distinct possibility that bias existed toward providing IVIG to the sickest of patients less responsive to supportive care. Further, the aforementioned differences in physician treatment preferences and lack of dosing stratification might also introduce bias.

This was an observational study with some strengths and inherent limitations. Strengths of the study include a well-defined population carrying working diagnoses and a clinical assessment of involved TBSA, and an analysis able to incorporate age and severity of disease. Notable limitations include results based on a small sample size of subjects included from one region of the United States, and treatment regimens that did not factor in the presence of supportive care and/or additional therapeutic modalities. Further, this study did not take into account dosing differences amongst patients treated with IVIG. While an observational study can't be used to definitively determine the efficacy of a treatment, it does provide insight into how treatments are administered, inform clinical practice, and provide data to support the design of future studies. This study begins to do that, although could be expanded in the future to stratify

based on more variables and could even consider additional outcome measures, such as inpatient hospital length of stay.

Although the only clear way to delineate to effectiveness of IVIG in the treatment of SJS/TENS is to design a controlled, prospective trial, investigating and summarizing patterns of use of IVIG in the treatment of SJS/TENS as done in this study may offer a stepping stone toward achieving that goal in the long-term, and help establish consensus treatment protocol in the short-term.

References:

[1] Bastuji-Garin, S.; et al. (1993). Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 129(1):92.

[2] French, L.E. (2006). Use of intravenous immunoglobulin in toxic epidermal necrolysis and Stevens-Johnson syndrome: our current understanding. *Int Immunopharmacol*. 6(4):543.

[3] Schneck J.; et al (2008). Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR study. *J Am Acad Dermatol*. 58(1):33.

[4] Prins, C.; et al. (2003). Effect of high-dose intravenous immunoglobin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology*. 207(1):96-9.

[5] Morici, M.V.; et al. (2000). Intravenous immunoglobulin therapy for children with Stevens-Johnson syndrome. *J Rheumatol*. 27(10):2494.

[6] Prins, C.; et al. (2003). Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol*. 139(1):26.

[7] Garcia-Doval, i.; et al. (2000). Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?. *Arch Dermatol:136*(3):323.

[8] Palmieri, T.L..; et al. (2002). A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. *J Burn Care Rehabil*. 23(2):87.

[9] Khalili B.; Bahna, S.L.. (2006). Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ann Allergy Asthma Immunol*. 97(3):272.