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In a Patient With Toxic Epidermal Necrolysis, Does Intravenous Immunoglobulin Improve Survival Compared With Supportive Care?

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Clinical Question: A 67-year-old Chinese man presented with pain and widespread skin erythema and detachment. A clinical diagnosis of toxic epidermal necrolysis (TEN) was made, which was supported by skin biopsy findings. The TEN was thought to be due to recent initiation of lamotrigine for mild epilepsy, and the drug was stopped immediately. The severity of TEN, measured by the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) scale, was 3 on admission owing to renal impairment, indicating a mortality risk of 35%. The patient was transferred to the burns unit for close monitoring of temperature, fluid balance, and appropriate dressings for his affected skin. A debate ensued among the dermatology, plastic surgery, and intensive care teams responsible for his care about whether intravenous immunoglobulin (IVIg) should be added to his treatment because improvement was slow with conservative treatment.

Background

Toxic epidermal necrolysis is a rare, life-threatening mucocutaneous disease that is caused by drugs in over 60% to 70% of cases.[1] By definition, there is epidermal detachment of over 30% of total body surface area (TBSA) as a consequence of keratinocyte apoptosis.[2] Identification and early withdrawal of the causative agent is crucial, and symptomatic and supportive care are the mainstays of treatment. Many treatments have been postulated as having possible benefit in treating this condition, but as yet no specific therapy has reached widespread acceptance through the principles of evidence-based medicine. Recent literature suggests that the use of IVIg for TEN has become accepted as standard practice in some centers.[3] The theoretical basis for the use of IVIg in TEN is that IVIg blocks Fas receptors on keratinocytes in perilesional skin, thereby preventing Fas ligand from binding and initiating keratinocyte apoptosis.[4]

See Practice Gaps at end of article

Given the differences in opinion by team members on whether IVIg should be added to best supportive care and withdrawal, we sought to review the evidence of the possible benefits and harms of IVIg in TEN, especially to consider whether our local protocol for TEN care should now include routine IVIg use.

Literature Search

We searched PubMed and the Cochrane Library using the terms *toxic epidermal necrolysis* and *TEN* and *intravenous immunoglobulin* and *IVIg* from inception until November 25, 2010. Given the vast number of case reports in the field, we restricted our article selection to include only original articles with a clinical and histological diagnosis of TEN in which IVIg had been used. We sought to primarily include systematic reviews and randomized controlled trials (RCTs). In the absence of clinical trial evidence, we agreed to scrutinize case series of more than 5 consecutive cases that included some information (eg, SCORTEN) that allowed some indirect comparison to be made with other treatments. We excluded case series or case reports of Stevens-Johnson syndrome (SJS), and those reports in which combination treatments were used.

Appraisal of the Topic

Of the 145 articles found in the literature search, only 11 met our prespecified criteria. We found only 1 systematic review,[5] published in 2001, which includes the only RCT.[6] The 1 RCT compared thalidomide vs supportive care in TEN. The trial had to be stopped early owing to increased mortality in the thalidomide arm. The use of thalidomide was postulated on a theoretical basis owing to its action on tumor necrosis factor.

One controlled cohort study, which included data on 122 patients from the EuroSCAR study,[7] found an increased risk of death (odds ratios of 1.4 for patients from France and 1.5 for patients from Germany) for the use of IVIg compared with supportive care. The main study drawback is that SJS and SJS/TEN overlap is included in the figures alongside TEN, and therefore it is not possible to assess for TEN alone. One prospective case series from Kuwait[8] documented 12 consecutive cases of TEN treated with IVIg. No deaths were reported, and 1 patient developed pneumonia.

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Table. Summary of Studies

Source	Patients in Treatment Group, No.	Dosage of IVIg	Mortality Rate, %	Comment
Schneck et al,[7] 2008 (Europe)	IVIg: 35 Control: 87	0.4-0.7 g/kg/d for 2-3 d	IVIg: 34 Control: 25	SJS, SJS/TEN, TEN-mixed data OR, 1.4-1.5
Al-Mutairi et al,[8] 2004 (Kuwait)	IVIg: 12 Control: 0	0.5-1.0 g/kg/d for 4-5 d	IVIg: 0	Arrest of progression, 2.8 d Reepithelization, 7.3 d LOS, 12.5 d
Bachot et al,[9] 2003 (France)	IVIg: 8 Control: 0	0.4-1.0 g/kg/d for 2-4 d Total dose, 2g/kg	IVIg: 25	No. of patients with TEN extrapolated from data table, based on TBSA detachment
Imahara et al,[10] 2006 (United States)	IVIg: 41 Control: 68	Dose not documented	IVIg: 21.9 Control: 19.1	46 Received prior corticosteroids SCORTEN equivalent across groups Unclear if all patients in 1999-2004 (IVIg) cohort received IVIg
Prins et al,[11] 2003 (Europe and United States)	IVIg: 38 Control: 0	0.2-2.9 g/kg/d for 1-5 d	IVIg: 16	Study also included SJS/TEN overlap 12 Received prior IV steroid Complete healing in 15 d (range, 4-40 d)
Brown et al,[12] 2004 (United States)	IVIg: 24 Control: 21	0.4 g/kg/d for 4 d	IVIg: 41.7 Control: 28.6	SCORTEN equivalent across both groups
Rajaratnam et al,[3] 2010 (United Kingdom)	IVIg: 21 Control: 7	0.4-1 g/kg/d for 4.9 d	IVIg: 21 Control: 71	Control group treated with cyclophosphamide or cyclosporine 10 Patients had IV corticosteroids prior (5 had steroid-dependent disease, GCA, BP)
Shortt et al,[13] 2004 (Canada)	IVIg: 16 Control: 16	0.7 ± 0.2 g/kg/d for 4 ± 1 d	IVIg: 25 Control: 38	Time to heal, 11.2 d (IVIg) vs 11.4 d
Trent et al,[14] 2003 (United States)	IVIg: 12 Control: 0	1 g/kg/d (0.4 g/kg/d in renal disease)	IVIg: 8 SCORTEN-predicted mortality rate, 42%	Study also included SJS/TEN overlap LOS, 20.3 d Arrest of progression, 3.75 d Reepithelization, 8.5 d
Mangla et al,[15] 2005 (India)	IVIg: 10 Control: 0	0.05-0.1 g/kg/d for 5 d	IVIg: 0	Arrest of progression, 2.1 d Reepithelization, 8.3 d Avg LOS, 13.6 d
Tristani-Firouzi,[16] 2002 (United States)	IVIg: 8 Control: 3	0.5-0.75 g/kg/d 4-7 d	IVIg: 0	Avg LOS, 19.3 d Reepithelialization, 8.1 d (11.7) Progression arrested, 2.1 d (4.5) 1 Patient received IV steroids prior

Abbreviations: Avg, average; BP, bullous pemphigoid; GCA, giant cell arteritis; IV, intravenous; IVIg, intravenous immunoglobulin (IVIg); LOS, length of stay; OR, odds ratio; SCORTEN, Severity-of-Illness Score for Toxic Epidermal Necrolysis; SJS, Stevens-Johnson Syndrome; TBSA, total body surface area; TEN, toxic epidermal necrolysis.

A further prospective case series from France[9] assessed the use of IVIg in patients with SJS, SJS/TEN overlap, and TEN. From the data provided in the article it is possible to extrapolate that 8 patients had TEN by definition of TBSA detachment greater than 30% at admission. The mean SCORTEN for these patients was 2.6, which would equate to a predicted mortality rate of 26%; however, the actual mortality rate was 25% (2 patients). Three patients of the total cohort of 34 had ocular sequelae at discharge, but no other complications were noted.

Details of 8 retrospective case series containing more than 5 patients are shown in the **Table**. Imahara et al[10] reviewed 109 patients treated for TEN from 1987 to 2004. The patients were treated according to a standardized clinical pathway, which involved removal of sloughed epidermis and dermal protection with porcine xenograft. Intravenous immunoglobulin use for TEN was introduced in 1999, and the cohort of patients treated after its initiation was compared with the cohorts treated prior to 1999. The SCORTEN was similar in all groups, but the mortality rate was marginally higher in the IVIg-treated group (21.9% vs 19.1%). No other complications were documented. Forty-six patients had received corticosteroids prior to admission. It is not clear from the information given in the article if all of the cohort of patients included in the study from 1999 onward received IVIg, because the authors state that "IVIg was considered for patients with progressive disease after its routine institution in January 1999."[10(p271)] This may affect the interpretation of the data presented.

Prins et al[11] reviewed the cases of 48 patients treated with IVIg with no comparison. Only 38 patients had TBSA detachment of 30% or greater, consistent with TEN. The mortality rate for patients with TEN was 16% (6 patients), with no other complications found. Twelve patients had received intravenous corticosteroids prior to inclusion into the study.

Brown et al[12] looked at 24 patients treated with IVIg and compared them with 21 historical TEN controls treated conservatively. SCORTEN was equivalent in both groups. The mortality rate was 41.7% in the IVIg-treated group and 28.6% in the control group. The number of complications experienced per patient was significantly higher in the IVIg-treated group (2.8 vs 1.7).

Rajaratnam et al[3] published a case series of 21 patients treated with IVIg compared with 7 historical controls who had been treated with cyclosporine or cyclo-

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phosphamide. The mortality rate in the IVIg-treated group was 21% but increased to 71% in the control group. Complications included sepsis, disseminated intravascular coagulation, renal failure, respiratory failure, and thromboembolic disease. Higher rates of these complications were seen in the IVIg-treated group.

Shortt et al[13] included 16 patients treated with IVIg and 16 historical controls (supportive care). All patients were treated with hydrotherapy and epidermal debridement, which was performed under general anesthesia or opioid and benzodiazepine sedation. Results showed a mortality rate of 25% in the IVIg-treated group compared with a mortality rate of 38% in the control group (statistically not significant owing to the small sample size). Twelve control patients and 14 patients treated with IVIg required intubation. Eleven control patients developed sepsis compared with 13 IVIg-treated patients.

Trent et al[14] included 16 consecutive patients without a control group. Twelve patients had TBSA detachment of 30% or more. SCORTEN predicted a mortality rate of 42%, but the actual mortality rate was only 8% (1 patient). One patient developed respiratory failure and required tracheostomy. Duplicate reporting of patients from this study occurred in the Prins et al study[10] discussed herein.

Mangla et al[15] reviewed the cases of 10 children with TEN treated with IVIg. No control group was used. No mortality or complications were reported. Tristani-Firouzi et al[16] reviewed 8 children who were treated with IVIg compared with 3 historical controls who were treated with plasmaphoresis and surgical debridement. No mortality was reported across either group; however, 4 patients required mechanical ventilation, and 4 required treatment for sepsis in the IVIg arm. One patient in the IVIg-treated group received intravenous corticosteroid prior to admission.

A further study was identified (Kim et al[17]) that reported a retrospective review of TEN treatment modalities. The cases of 38 patients were reviewed, 14 of whom had received high-dose IVIg treatment. The SCORTEN-predicted mortality rate in the TEN cohort was 16.8% (2.3 patients), but the actual mortality rate was lower at 7.1% (1 patient). The authors state that adverse effects of IVIg were seen in 5 patients (headache, myalgia, nausea, transient neutropenia, and Coombs positive hemolytic anemia), all of which resolved after cessation of IVIg treatment. This study has not been included in our summary of studies because it compares high-dose IVIg and corticosteroid therapy in TEN.

Limitations of the Critically Appraised Topic

To our knowledge, there is no high-quality evidence (ie, RCT data) on the use of IVIg in TEN. The data from the next best level of evidence (ie, the well-defined EuroSCAR[7] cohort study) do not suggest a reduction in mortality from IVIg use, but suggest some possible evidence of harm, although the data are limited because they include SJS and SJS/TEN overlap. The remaining case series all suffer from a high risk of selection, performance, information, attrition, and publication bias, and are almost impossible to interpret. Few of the case series described comparator treatments. Some used historical controls, which are inappropriate given the advances in intensive supportive care in acute medicine that have occurred over the past 20 years. Furthermore, many control patients were treated concurrently with other active management (cyclosporine, cyclophosphamide, surgical debridement, and plasmaphoresis), making comparison impossible. Doses of IVIg varied across the studies, as did time of initiation. Similarly, the definition of TEN by TBSA affected with epidermal detachment varied across the studies reviewed, which also makes comparisons between studies challenging. Our stated definition was "epidermal detachment of over 30% of TBSA," but we have included studies in which there is some ambiguity regarding the TBSA involved and whether that involvement is all epidermal detachment or in some cases partly erythema. Not all studies recorded SCORTEN for all patients, thus not allowing assessment of severity to be made. Some patients had received intravenous corticosteroids prior to admission, and the specific outcome for these patients were not reported separately.

The complications reported in the TEN groups were mainly infection and respiratory failure: these could be complications from TEN or IVIg. A clinical RCT of IVIg vs best conservative care is needed, and any groups or individuals interested in participating in such a study are asked to contact the authors.

Clinical Bottom Line

The evidence presented herein was discussed in a multidisciplinary setting that included the dermatology, plastic surgery, and ophthalmology departments; the pharmacy; the burns unit staff; and the intensive care unit. The majority decision was that on the basis of only high risk of bias studies being available, with potential confounding variables, as well as the possibility of IVIg causing harm, we could not confidently assert that IVIg conveys added benefit over conservative management alone in patients with TEN. Like Faye and Roujeau,[18] we will not be including IVIg for the treatment of TEN in our local protocol unless better evidence becomes available.

What Happened to Our Patient

Our patient remained an inpatient on the burns unit for 3 weeks. He did not receive IVIg and was treated conservatively as per our departmental protocol. He experienced transient renal impairment, which has resolved. He made a full recovery and experienced no other sequelae of TEN. He has full reepithelization with no scarring and remains well.

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integrity of the data and the accuracy of the data analysis. *Study concept and design:* Wootton and Patel. *Acquisition of data:* Wootton, Patel, and Williams. *Analysis and interpretation of data:* Wootton, Patel, and Williams. *Drafting of the manuscript:* Wootton, Patel, and Williams. *Critical revision of the manuscript for important intellectual content:* Wootton, Patel, and Williams. *Statistical analysis:* Wootton and Patel. *Administrative, technical, and material support:* Wootton, Patel, and Williams. *Study supervision:* Williams.

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PRACTICE GAPS

Use of Intravenous Immunoglobulin in Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is a rare, life-threatening, adverse cutaneous drug reaction with a reported mortality rate ranging from 25% to 35%.[1] Based on the reported inhibition of Fas-mediated apoptosis of keratinocytes by intravenous (IV) immunoglobulin (IVIg) in vitro, IVIg has since been considered as a potential therapeutic modality in TEN.[2] To date, 15 studies including more than 10 patients per study and analyzing the effect of IVIg in TEN have been reported in the literature. They all suffer their imperfect study designs and limitations, and none are of a randomized, controlled design. The problem with TEN to date is that a specific therapy for Stevens-Johnson syndrome/TEN that has shown efficacy in controlled clinical trials unfortunately does not exist.

In this issue of the *Archives*, Wootton et al[3] illustrate perfectly the practice gap encountered by dermatologists and burn surgeons wanting to offer the best evidence-based therapy to their patient with TEN, concluding that with only potentially biased studies being available with potential confounding variables, as well as the possibility of IVIg causing harm, they could not confidently recommend IVIg conveys over conservative management alone in patients with TEN.

We agree with Wootton et al[3] that the evidence base for the use of IVIg in TEN is not high due to the lack of clinical randomized controlled (RCTs). The practice gap includes failing to identify the ideal dosing strategy of IVIg, because the average total doses of IVIg used vary greatly from one study to another. The dose of medication given is an essential factor conditioning the chance of therapeutic response (**Table 1** and **Table 2**). To specifically address this issue, Trent et al[18] analyzed all studies performed between 1992 and 2006 and used a Cochrane-Armitage trend test to examine whether high doses of IVIg were associated with improved survival. This study showed that survival of patients with TEN treated with IVIg is strongly correlated with the total dose of IVIg administered. For each extra gram of IVIg given per kilogram of

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