Cyclosporine for SJS/TEN: A Case Series and Review of the Literature

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Clear guidelines for the treatment of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are lacking due to its infrequency and the absence of large controlled studies. Systemic corticosteroids and intravenous immunoglobulin (IVIG) have received considerable attention, though reports of the use of these agents have demonstrated mixed success rates in improving morbidity and mortality from SJS/TEN. We present a case series of 4 patients with SJS/TEN who rapidly responded to treatment with cyclosporin A (CsA). We discuss the proposed mechanism of action and the rationale for the use of cyclosporin based on the currently understood pathophysiologic mechanism of TEN.

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Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dermatologic emergencies most often caused by medications or infections. No clear therapeutic guidelines regarding the use of medications for the treatment of SJS/TEN exist, and optimal treatment remains an enigma. There remains a need for a rational, evidence-based treatment that can effectively halt progression and enhance wound healing in this entity. Case reports exist on the use of cyclosporin A (CsA) in SJS/TEN, which have shown promise in halting the progression and enhancing wound healing.[1] We present 4 patients with SJS/TEN treated in our burn unit with CsA (5 mg/kg daily)(Table); all of them demonstrated rapid clinical improvement. Additionally, we discuss a possible mechanism of action based on the pathophysiologic mechanism of SJS/TEN and propose a rationale for the use of CsA either alone or in combination.

Case Reports

Patient 1—A 31-year-old woman was admitted to our burn unit with a progressive generalized bullous eruption of 1 day's duration. She reported a history of allergy to penicillin and ibuprofen. In the 2 weeks preceding admission, she had been treated with naproxen, hydrocodone bitartrate and acetaminophen, trimethoprim-sulfamethoxazole, and doxycycline for a gluteal abscess. The remainder of her medical history was unremarkable. She reported ocular, nasal, genital, and oral mucous membrane pain, along with severe dysphagia and generalized pruritus that accompanied her eruption. On physical examination she had normal vital signs and a generalized distribution of dusky patches and thin plaques, many with associated flaccid or eroded bullae (Figure 1). The sclera was injected and there were hemorrhagic bullae and erosions of the oral mucosa. Total body surface area (TBSA) of involvement was estimated to be 30% with a positive Nikolsky sign. Laboratory examination was unremarkable. Skin biopsy demonstrated bulla formation with confluent epidermal necrosis consistent with SJS/TEN (Figure 2A). Possible offending medications were discontinued and she received supportive care in a specialized burn center. Additionally, the patient was started on CsA at a dosage of 5 mg/kg daily given in 2 divided doses.

Within 24 hours of treatment, she noted reduction in pain and pruritus, resolution of her dysphagia, and a halt to the progression of her eruption. By 48 hours, her symptoms had further improved

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Patient Characteristics

Patient No.	Age, y	TBSA, %	Cyclosporine Daily Dosage[a]	Other Treatments	Offending Medication	SCORTEN Score[b] at Presentation	Mortality Based on SCORTEN Score, %
1	31	30	5 mg/kg	None	TMP-SMX	1	3.2
2	21	18	5 mg/kg	None	Lamotrigine	1	3.2
3	28	15	5 mg/kg	None	TMP-SMX	1	3.2
4	31	80	5 mg/kg	None	Aceta-minophen	2	12.1

Abbreviations: TBSA, total body surface area; SCORTEN, score of toxic epidermal necrolysis; TMP-SMX, trimethoprim-sulfamethoxazole.
[a]Administered in 2 divided doses.
[b]The SCORTEN evaluates 7 independent risk factors for high mortality; a higher SCORTEN score indicates a higher mortality rate.

and she began eating solid foods with only mild discomfort. The remainder of her hospital course was unremarkable and she was discharged after completing a 5-day course of CsA. During the month following discontinuation of the CsA and discharge, the patient continued to improve and reported complete resolution of her symptoms.

Patient 2—A 21-year-old woman was admitted to our burn unit with new onset of oral and ocular mucous membrane pain along with a cutaneous eruption that presented 5 weeks after starting lamotrigine for a seizure disorder. She noted skin pain for 1 day prior to admission. She was taking no other medications. Her vital signs were normal and physical examination revealed dusky patches, erosions, and thin plaques with associated flaccid or eroded bullae on her face, chest, and back. Her TBSA was estimated at 18% with involvement of the oral and genital mucosa with erosions. Laboratory examination was unremarkable. Skin biopsy demonstrated subepidermal vesicle formation with confluent epidermal necrosis and minimal inflammatory infiltrate that were consistent with our diagnosis of SJS/TEN (Figure 2B).

Along with discontinuation of the lamotrigine and supportive care in a specialized burn center, the patient was started on CsA at a dosage of 5 mg/kg daily given in 2 divided doses. She was started on valproic acid for her seizure disorder. Within 24 hours of treatment, she noted reduction in pain and pruritus and a halt to the progression of her eruption (Figure 3A). By 48 hours, her symptoms had further improved with only mild discomfort. The remainder of her hospital course was unremarkable and she was discharged on a 1-month taper of CsA. During the months following discontinuation

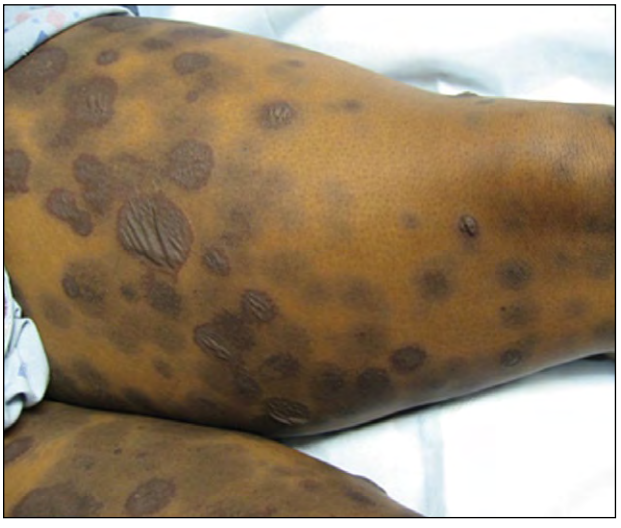

Figure 1. Flaccid bullae and dusky plaques on the thigh (patient 1).

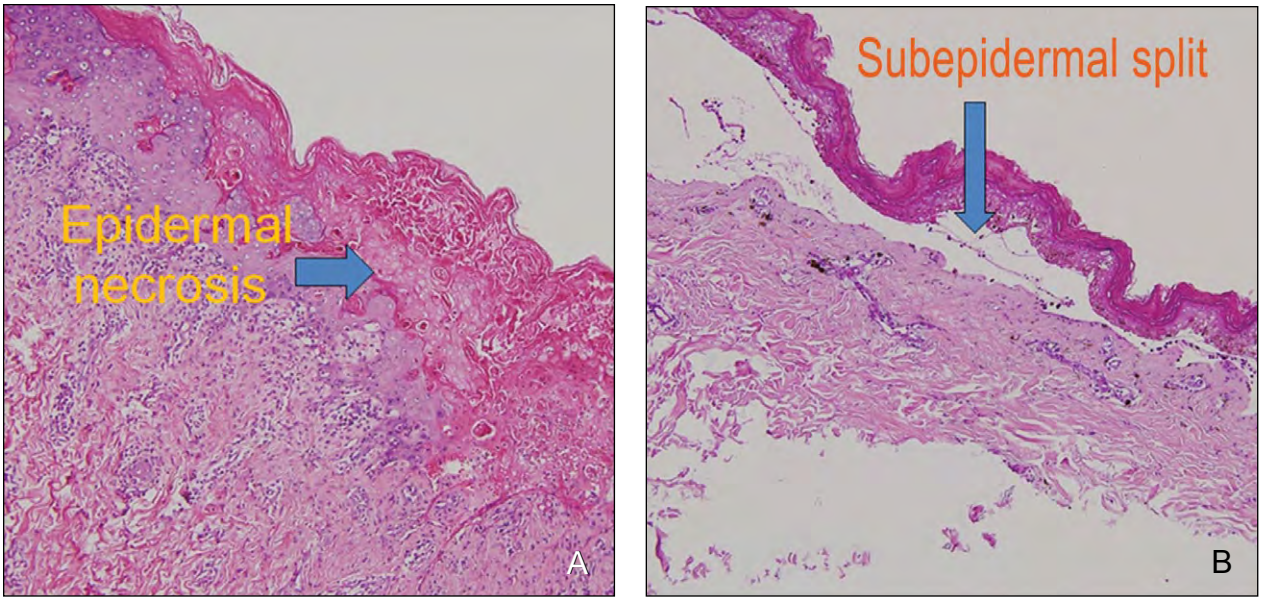

Figure 2. Full-thickness necrosis (arrow) of pathology specimen (patient 1)(H&E, original magnification ×20)(A). Biopsy specimen showing subepidermal bulla (arrow) with sparse inflammatory infiltrate and full-thickness epidermal necrosis (patient 2)(H&E, original magnification ×10)(B).

of the CsA and discharge, the patient continued to improve and reported complete resolution of her symptoms (Figure 3B).

Patient 3—A 28-year-old woman presented with a progressive painful eruption on her face, trunk, and extremities, including her palms, of 3 days' duration as well as ulceration of the oral mucosa. She had been started on trimethoprim-sulfamethoxazole for presumed sinusitis 1 week prior to presentation. The remainder of her medical history was unremarkable, with the exception of seasonal allergic rhinitis. On physical examination her vital signs were normal and she had target lesions on her palms and soles, with dusky patches, thin plaques, and flaccid bullae on the trunk and upper extremities with a positive Nikolsky sign. Her sclera was injected and there were hemorrhagic bullae and erosions of the oral, genital, and nasal mucosa. Total body surface area involvement was estimated at 15%. Her laboratory examination was normal. A skin biopsy was consistent with the diagnosis of SJS/TEN.

Her medications were discontinued and supportive care was initiated. She was started on CsA at a dosage of 5 mg/kg daily given in 2 divided doses. Within 12 hours of treatment, the progression of her eruption had halted and reepithelialization began within 48 hours. Her hospital course was unremarkable and she had no infectious complications. She was discharged on a 1-month taper of CsA. During the months following discontinuation of the CsA and discharge, the patient continued to improve and reported complete resolution of her symptoms.

Patient 4—A 31-year-old man was admitted with presumed SJS/TEN by our colleagues caring for local national patients in support of Operation Iraqi Freedom. Our department received this patient as a teleconsultation in support of this mission. This patient noted worsening skin pain of 2 days' duration as well as ocular discharge and dysuria of 1 day's duration. Two days prior to admission he took acetaminophen for a hand injury. He reported no other medical problems, with the exception of a blistering skin reaction to pain relievers 1.5 years prior to admission.

He was afebrile and on admission his vital signs were normal, with the exception of tachycardia (108 beats per minute). There was conjunctival erythema and hemorrhagic crusting of the lips. His upper extremity and flank had prominent bullae scattered diffusely with a positive Nikolsky sign and some erosions (Figure 4). Additionally, there were small, fine, dusky, and vesicular plaques and diffuse erythema with tenderness over the trunk and proximal lower extremities, as well as bullae on his distal lower extremities. His TBSA estimate was 80%. On admission his laboratory test results were normal, with the exception of a serum blood urea nitrogen level of 40 mg/dL (reference range, 8–23 mg/dL) and a creatinine level of 1.3 mg/dL (reference range, 0.6–1.2 mg/dL). Both levels improved in 24 hours with aggressive hydration (20 and 0.9 mg/dL, respectively). Because of the remoteness of the location, the inaccessibility of intravenous immunoglobulin (IVIG),

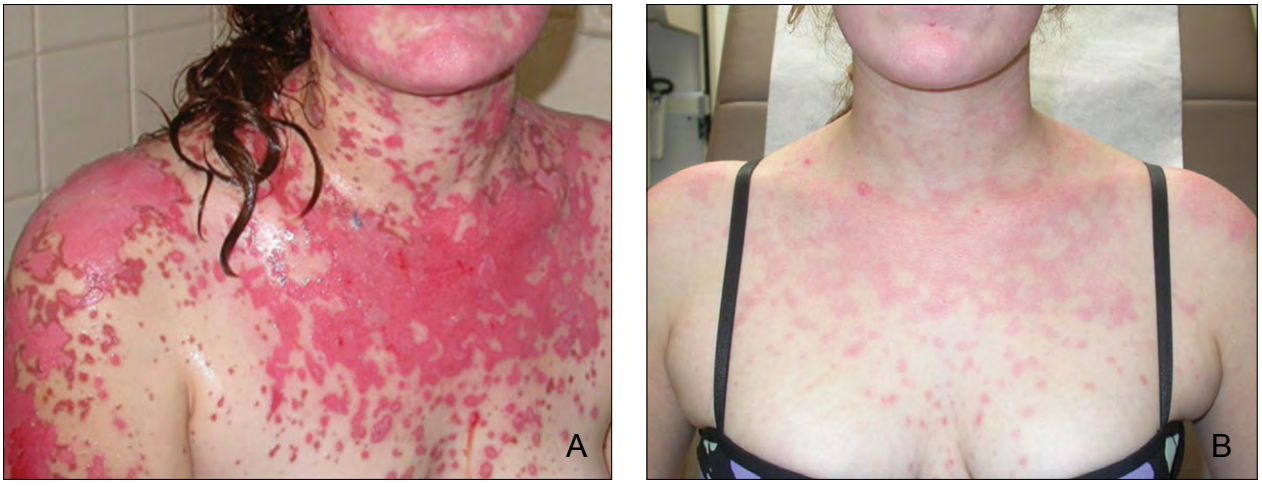

Figure 3. Patient 2 on day 2 of admission 24 hours after initiation of cyclosporin A (A) and 45 days after admission (B).

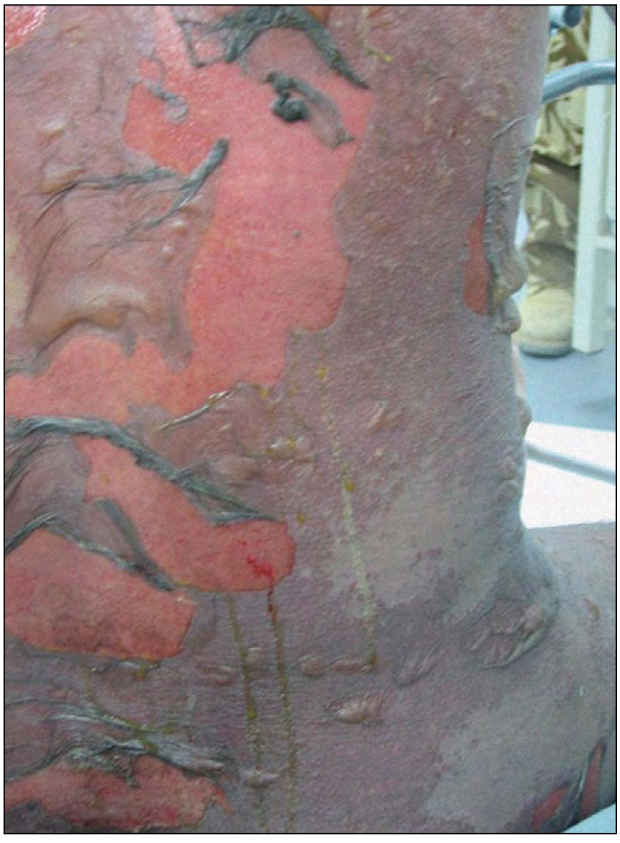

Figure 4. Patient 4 with 80% total body surface area involvement on day of admission with erosions and bullae.

and the severity of the skin involvement, our recommendation was the use of CsA at 5 mg/kg daily given in 2 divided doses. The medical team caring for this patient noted a cessation of the progression of the eruption within 12 hours of starting CsA and reepithelialization of the erosions within 96 hours. The patient was discharged and did not have a recrudescence of the eruption.

Comment

Stevens-Johnson syndrome and TEN remain severe and life-threatening dermatologic emergencies with high mortality and without a clearly effective treatment option.[2] Cessation of the offending medication and conservative management remains the standard of care and is the only intervention that shows a benefit.[2] Several treatments have been tried to halt the progression of TEN. Systemic steroids remain controversial[3-5] and have been demonstrated to worsen the outcome.[6] Intravenous immunoglobulin was promising in early small trials[2]; however, recent data have been conflicting. Both systemic steroids and IVIG have failed to show a notable benefit over conservative management.[7]

The pathogenesis of SJS/TEN is thought to be a 2-staged process in which the first stage (initiation stage) involves noninflammatory apoptosis of keratinocytes and the second stage is the amplification phase.[8] In the initiation phase, drug metabolites are thought to mediate CD95 ligand (Fas ligand) and tumor necrosis factor α (TNF-α) systems[2] stimulating apoptosis. Tumor necrosis factor α is hypothesized to promote the expression of the CD95 ligand (Fas ligand) receptor.[2] The amplification stage involves inflammatory cells[2] in which TNF-α and IL-2 act as chemotactic cytokines, recruiting $CD4^+$ T lymphocytes in the dermis and $CD8^+$ cells in the epidermis.[8] During this stage, TNF-α and IL-2 also act as messengers by stimulating the release of chemotactic factors that recruit natural killer lymphocytes and macrophages into the epidermis.[2] The hallmark of the amplification phase of TEN is massive destruction of the epidermis.

Helper T cell 1 (T_H1) cytokines, particularly IL-2, have been demonstrated to be distributed in the perivascular dermis of all lesional specimens of patients with SJS/TEN compared to healthy controls.[9] Additionally, IL-2 has been demonstrated in peripheral blood samples of patients with SJS/TEN but is absent in blister fluid.[10] Le Cleach et al[11] demonstrated IL-2 as a promoter of severe proinflammatory functions in TEN via its receptor CD25 and by way of lymphocyte proliferation and activation in the skin lesions of SJS/TEN. Apoptosis remains the key pathogenic mechanism in TEN, and TNF-α receptors mediate apoptosis through the CD95L receptor (Fas ligand) pathway. It is proposed that TNF-α acts as an autocrine factor to spread the epidermal destruction.[12]

Based on the current understanding of the pathomechanism of SJS/TEN, the ideal medication for the treatment would be one that acted against TNF-α and/or Fas ligand and reduced the inflammatory cell reaction in the amplification phase by reducing IL-2. Of the current medications available for the inhibition of TNF-α, all have a slow onset of action. Of the biologic inhibitors of TNF-α, infliximab may have the most rapid onset of action, but it is likely too slow to impact the initiation phase of TEN. Of the other systemic medications known to inhibit TNF-α, thalidomide, a systemic TNF-α antagonist, has been shown to adversely affect the outcome of TEN in 1 study.[13]

Cyclosporin A is a rapid and potent inhibitor of IL-2 and has been associated with advanced healing and improved survival in SJS in limited case reports.[1] Its suppressive action primarily is achieved by targeting T lymphocyte functions through IL-2, inhibition of macrophage activity,[14] and inhibition of the activation of the Fas receptor–Fas ligand system.[8] Fulda et al[15] have shown that in vitro CsA inhibits the drug-induced expression of CD95R (Fas receptor) and CD95L (Fas ligand) messenger RNA and is able to block drug-mediated apoptosis of some cell types. An additional mechanism of immunosuppression in CsA is the inhibition of CD8 T-cell activation, which in turn inhibits the apoptosis and destruction through either Fas ligand or perforin/granzyme pathway.[1,14]

Paquet et al[8] performed tissue sample analysis on 2 patients with TEN treated with CsA 5 mg/kg daily for 5 days and compared the results to 2 patients with TEN treated with IVIG 0.75 g/kg daily for 5 days. They found a marked reduction of CD95R (Fas receptor) in clinically involved skin at completion of the 5-day treatment. Reduction in CD95R also was documented in nonlesional skin, while the IVIG nonlesional skin showed moderately increased CD95R. Conversely, patients in this small study who were only receiving supportive care had a marked increase in CD95R level at day 5.[8] These findings support a mechanism of action of CsA in the treatment of TEN by not only reversing the apoptotic process in lesional skin but also by protecting progression of SJS to TEN by downgrading the apoptotic pathway in nonlesional skin.

In our case series, patients experienced a noticeable symptomatic improvement within 24 hours following initiation of CsA therapy at 5 mg/kg. They experienced no other notable complications during their admissions. There were no infections and no evidence of immunosuppression. Cyclosporin A may be useful in the treatment of SJS/TEN because of its inhibition of the synthesis of cytokines (IL-2) important in T-cell–mediated immunity and its documented interference with the Fas receptor–Fas ligand pathway that mediates keratinocyte apoptosis.[7,14]

In other cases, the dosage range of CsA for SJS/TEN was 3 to 10 mg/kg, with time of arrest of progression from 5 to 48 hours and a time of reepithelialization of 7 to 28 days.[1] In our case series of 4 patients, we observed a time to arrest and time of reepithelialization similar to these case reports. Of our patients, the most striking response to treatment was patient 4 who had 80% TBSA involvement. He had a time to arrest of 12 hours and a time to reepithelialization of 96 hours, which is remarkable given the extent of TBSA and the projected mortality by SCORTEN (score of toxic epidermal necrolysis) of 12.1%.

Conclusion

Stevens-Johnson syndrome/TEN is a serious, life-threatening complication of medications or infection. Although cyclosporine does not absolutely inhibit the initiation phase, there is evidence it downregulates the CD95 apoptosis pathway in the initiation phase, thereby blocking drug-mediated apoptosis. Additionally, it drastically reduces the pathogenic inflammatory cytokines in the amplification phase. The documented pharmacologic mechanism of action of CsA makes it an excellent choice for the treatment of SJS/TEN. Additional studies are needed to further evaluate its role in the management of SJS/TEN. In our experience, we have seen no adverse reactions and no increase in infection with short-term use of CsA with our patients. More studies are needed to evaluate the potential benefit of CsA alone or in combination with IVIG in the initial treatment of SJS/TEN.

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