Successful Use of Cyclosporine in the Treatment of Toxic Epidermal Necrolysis: A Case Series

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ABSTRACT
Toxic epidermal necrolysis (TEN) is an acute life-threatening disease associated with a high mortality. Systemic corticosteroids, cyclosporine, and intravenous gamma globulins have been used in the treatment with variable results. We report five cases of TEN treated successfully with cyclosporine monotherapy. All the patients presented with severe disease. All the patients received cyclosporine 3–5 mg/kg/day for an average duration of 5–10 days depending on the clinical response. All the patients recovered without any sequel. No significant side effects were noted in all the five patients except for one patient who developed acute nephrotoxicity. All the five patients were discharged from the hospital by the end of 2 weeks, thus decreasing the hospital stay due to a favorable outcome and early recovery. Cyclosporine in TEN patients is not only a lifesaving drug, but also it is cost-effective. This case series demonstrates the safety and efficacy of the short course of cyclosporine monotherapy in the treatment of TEN.

Key Words: Corticosteroid, cyclosporine, toxic epidermal necrolysis

INTRODUCTION
Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is an acute life-threatening disease affecting the skin and mucous membranes. Most commonly, TEN is drug-induced although infections and other causes have been implicated. In TEN, denudation of extensive areas of skin is associated with a high mortality and mortality. The role of systemic corticosteroids in the management of SJS/TEN is controversial.[1] Although many authors have claimed good success rates with corticosteroids,[2] its use in SJS/TEN management has not been universally accepted. Cyclosporine, intravenous immunoglobulins (IVIg), and cyclophosphamide have been used in the treatment of TEN with variable success rates. We report five cases of TEN who were treated successfully with cyclosporine monotherapy.

CASE REPORTS
Case 1
A 60-year-old female, known case of diabetes and chronic renal failure, was on ayurvedic treatment for 2 months. She developed multiple confluent purpuric necrotic patches followed by denudation of the skin involving more than 60% of the skin surface with severe oral and conjunctival involvement, suggestive of TEN. She had received capsule ampicillin for wound infection. She had developed TEN after 3 days of receiving ampicillin. Drug was discontinued. Apart from other supportive care, she was treated with oral cyclosporine at a dose of 150 mg/day for 10 days. She recovered completely without any sequel with cyclosporine for 10 days. She was discharged from the hospital on the 9th day of hospitalization (12th day of rash).

Case 2
A 2-year-old male child developed TEN after receiving levofloxacin, cefpodoxime, and ambroxol for fever. The child presented to us on the 3rd day of onset of severe cutaneous drug reaction with extensive skin peeling with 70% body surface area (BSA) involvement. He also had severe oral and conjunctival involvement. Cyclosporine 30 mg daily (3 mg/kg) was started on the 4th day of development of TEN. His baseline blood urea and serum creatinine levels were normal. Within 2 days, the lesions started drying, and the child showed signs of

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improvement. On the 6th day of cyclosporine therapy, the child was drowsy. Blood urea was 118 mg/ml and serum creatinine was 3 mg/dl. Cyclosporine was discontinued (received cyclosporine for 6 days) and peritoneal dialysis was started. The child was out of ICU on the 12th day and was discharged on the 15th day of admission.

Case 3
A 7-year-old child (wt-15 kg) developed TEN after receiving tablet paracetamol + nimesulide combination for fever. The child presented on the 2nd day of rash with more than 60% BSA involvement [Figure 1]. Cyclosporine 50 mg/day (3 mg/kg/day) in the syrup form (1 ml = 100 mg) was started, and the patient continued to progress. After 2 days, because of spreading nature of the disease, the dose of cyclosporine was increased to 60 mg/day. With increased dose of cyclosporine, lesions started healing. By the 7th day of hospitalization, most of the lesions were dry (4 mg/kg/day) [Figure 2]. The patient received cyclosporine for 10 days and was discharged on the 12th day (14th day of rash).

Case 4
A 34-year-old male was diagnosed to have HIV infection with CD4 count of 195/cu mm. He was started on antiretroviral therapy (ART) consisting of nevirapine, lamivudine, and zidovudine. Tablet cotrimoxazole (Septran™) was added for Pneumocystis carinii prophylaxis apart from antiretroviral therapy. On the 13th day of starting ART and cotrimoxazole, the patient developed TEN. He presented to us on the 2nd day of rash with 50% BSA involvement [Figure 3]. Both antiretroviral therapy and cotrimoxazole were stopped. Cyclosporine was started on the 3rd day at a dose of 150 mg/day (3 mg/kg/day). From the next day, lesions started showing signs of healing. On the 8th day (after completing 5 days of cyclosporine therapy), most of the lesions became dry [Figure 4]. Cyclosporine was thus discontinued. By the 16th day, the patient was discharged from the hospital.
Case 5
A 6-year-old female child received paracetamol + ibuprofen combination for suspected viral infection and developed TEN. She presented to us on the 3rd day of rash with 50% body area involvement and mucosal inflammation. She was started on syrup cyclosporine 45 mg/day in divided doses for 7 days. Lesions resolved significantly with excellent response to cyclosporine, and no side effects were noted. The child was discharged on the 10th day of hospitalization.

DISCUSSION
TEN results from extensive keratinocyte cell death, which leads to separation of large areas of the skin at the dermo-epidermal junction.[1] In TEN, keratinocyte death occurs due to apoptosis.[3] Tumor necrosis factor alpha, interleukin-6, and Fas ligand are the important mediators of keratinocyte death (apoptosis) in TEN.[3]

Apoptosis is a programmed cell death without inflammation. There are certain receptors on the cell surface which when activated can induce apoptosis (cell death). One of these receptors is Fas receptors. In TEN, keratinocytes express Fas receptors on its surface and its attachment with its ligand FasL leads to massive cell death in keratinocytes.[3] IVIg acts by blocking the interaction of FasL and Fas and thus, it is found to be effective in the treatment of TEN. Cyclosporine has been found to be effective in the treatment of TEN.[4,6] Cyclosporine is an immunosuppressant commonly used in preventing organ rejection after organ transplantation. In dermatology practice, it is commonly used in the treatment of skin disorders such as psoriasis and atopic dermatitis. Cyclosporine acts by calcineurin inhibition. By calcineurin inhibition, cyclosporine decreases the production of various inflammatory cytokines. It also has antiapoptotic action.[4,7]

In the treatment of TEN, it is not clear whether cyclosporine acts through its immunosuppressive effects or antiapoptotic effects.

TEN presents with widespread denudation or peeling of skin, and the prognosis depends on the extent of involvement and the systemic complications, if any, arising from extensive skin loss. All our patients presented with extensive involvement which is normally associated with very high mortality and morbidity rates, but all these patients recovered completely with cyclosporine at a dose of 3–5 mg/kg. The dose was adjusted as per the clinical response.

TEN is usually managed in burn unit or in the Intensive Care Unit. It usually takes more than 2 weeks for recovery of this life-threatening cutaneous drug reaction. However, with cyclosporine monotherapy in all our patients, they were out of the Intensive Care Unit after the 7th or 8th day of onset of TEN and were discharged from the hospital by the end of the 2nd week. This has not only reduced the days of hospitalization but also reduced the cost of the therapy. TEN usually leads to a large denuded area which is oozy and prone for infection; however with cyclosporine, the lesions started becoming dry very early (as evident from the figure), reducing fluid and temperature loss, and also chances of secondary bacterial infections. Eye complications are very common in TEN; however, all our patients recovered completely without any eye complication. In other studies, cyclosporine was used for about 2–4 weeks.[4,6] However, we used cyclosporine (3–5 mg/kg) for up to 10 days only, and none of these patients showed relapse due to shorter course of treatment. In all cases, cyclosporine was used in two divided doses. In the case 2, cyclosporine was discontinued after 6 days due to the development of renal toxicity. In a patient of TEN with associated HIV infection, cyclosporine was discontinued after 5 days when lesions showed sign of healing, still the disease did not relapse indicating that even the short course (less than a week) may be enough to halt the progression of the disease. However, even with this short course of cyclosporine monotherapy, one of our patients developed acute renal failure that required peritoneal dialysis for 3 days. Better treatment outcome in all our patients is also due to the fact that they presented early, i.e., <3 days.

In all the five cases, only cyclosporine was used without steroids indicating that only cyclosporine as monotherapy is effective in TEN. Several studies have confirmed the benefit of cyclosporine in TEN.[4,6] Most of the reports with successful treatment of TEN with cyclosporine have not reported any mortality, indicating its effectiveness and safety in the treatment of SJS/TEN. By shortening the recovery time, cyclosporine also reduces the cost of the treatment. As indicated in our case report, initiation of cyclosporine therapy is not a contraindication for the treatment of SJS/TEN in HIV-infected patients. However, the short course of cyclosporine therapy needs to be preferred.

In summary, our case series demonstrates that cyclosporine even without systemic corticosteroids is safe and effective for the treatment of TEN. Controlled studies of sufficient sample size are desired, however they are difficult due to ethical constraints. Multiple case reports like ours will help to establish the usefulness of cyclosporine in the management of TEN.

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Conflicts of interest

There are no conflicts of interest.

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