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Review

Cyclosporine in toxic epidermal necrolysis: a brief review of the emerging therapeutic modality

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Abstract

Toxic epidermal necrolysis (TEN) is a severe life-threatening adverse drug reaction that predominantly involve the skin and mucous membranes, and is associated with high mortality (25-35% or even higher) and with various long term sequelae. There is no universally accepted treatment for TEN, but key elements of management include rapid diagnosis, identification and interruption of the culprit drug, evaluation of the prognosis using SCORTEN, specialized supportive care ideally in an intensive care unit, and consideration of immunomodulating agents. Cyclosporine has recently emerged as a promising immunomodulating agent in the management of TEN and we have performed a brief review of evidence highlighting its role in TEN management.

Keywords: Toxic epidermal necrolysis; cyclosporine; apoptosis

Introduction

Induction of apoptosis is key to the pathogenesis of toxic epidermal necrolysis (TEN). Many molecules responsible for inducing apoptosis in TEN have been identified. One such molecule is Fas, which is a ubiquitous membrane bound protein. Activation of Fas results in apoptosis through a cascade of intracellular events culminating in the activation of caspases (the effectors of apoptosis). Fas is activated by Fas ligand (FasL), which was demonstrated in high concentrations in sera (Soluble FasL, sFasL) of TEN patients. There is some controversy regarding origin of sFasL. Cytotoxic T lymphocytes (CTL) and natural killer (NK) cells are widely believed to be source of sFasL. Some investigators have shown keratinocytes to be a source of FasL. Nonetheless, Fas-FasL play a very important role in pathogenesis of TEN as evident by blockade of lytic activity by addition of neutralizing FasL-binding monoclonal antibody or intravenous immunoglobulin (IVIG) containing Fas-binding antibodies [1, 2].

Another key molecule is granulysin, which has been found in high concentrations in TEN blisters. Also, the severity of the cutaneous lesions has been shown to correlate with granulysin levels. These observations support a role for granulysin in development of TEN. Granulysin is one of several cytotoxic proteins secreted in granules by CTL and NK cells and is a pro-apoptotic protein which permits cell-mediated cytotoxicity without direct cell-to-cell contact.

Cytokines like tumor necrosis factor alpha (TNF α) and interferon gamma (IFN γ) play a role in the amplification of apoptotic pathways. TNF α contributes to the apoptosis by activating caspases and by increasing the expression of Fas and FasL. IFN γ recruits macrophages, monocytes, and dendritic cells. These cells, in turn, produce other proinflammatory cytokines, such as TRAIL (TNF-related apoptosis-inducing ligand) and TWEAK (TNF-related weak apoptosis inducer) [1, 2].

Cyclosporine

Cyclosporine, also known as Cyclosporin A (CsA), is a cyclic peptide of 11 amino acids isolated from the soil fungus *Tolypocladium Inflatum* Gams. CsA is hydrophobic and lipophilic, and thus insoluble in water. It relies on bile, pancreatic, and small intestine secretions/enzymes for absorption. Oral bioavailability is low (<30%), ranging from 10-89%. Also, it shows high inter-individual and intra-individual variation. The microemulsified form has higher and more consistent bioavailability. It has a large volume of distribution and binds to erythrocytes, leukocytes, and lipoproteins. High concentrations are noted in fat, pancreas, liver, kidney, breast, and lymphoid tissue. Central nervous system penetration is poor. Cyclosporine is metabolized by the CYP3A4 pathway into 20 metabolites with less immunosuppressive action and toxicity compared with parent drug. Primary excretion is via bile and feces. Only 6% of cyclosporine is excreted unchanged in the urine [3, 4, 5].

Mechanism of action of cyclosporine

Cyclosporine is a calcineurin inhibitor used as an immunomodulatory agent. T cell receptor activation causes release of intracellular calcium that in turn binds to calmodulin and activates calcineurin. This calcineurin complex dephosphorylates the nuclear activator of activated T cells (NFATc), which is present within the cytoplasm allowing it to migrate into the nucleus and bind with its intranuclear counterpart (NFATn). This complex is a transcription factor for inflammatory cytokines such as interleukin (IL)-2. IL-2 receptors are also upregulated as a result of this process. Cyclosporine binds to cyclophilin. This complex blocks the dephosphorylation of NFATc and subsequent upregulation of IL-2 and IL-2 receptors, resulting in a decrease in number of CD4+ and CD8+ (cytotoxic) T cells in the epidermis. Thus cyclosporine inhibits activation of T cells by suppressing IL-2 production and antigen presentation by Langerhans cells and neutrophil chemotaxis [4].

Rationale of using cyclosporine in TEN

Cyclosporine (CsA) inhibits activation of CD4+ and CD8+ (cytotoxic) T cells in the epidermis by suppressing Interleukin-2 (IL-2) production from activated T helper cells [4]. IL-2 acts on CD8+ cells and optimizes generation of effector T cell and differentiation into memory cells [6]. Although cyclosporine A does not interfere with the intracellular events required for the activation and subsequent clonal expansion of alloreactive T cells, cyclosporine-induced lack of interleukin 2 results in an inability of T responder cells to mount cytotoxic allograft responses in vitro [7].

CsA has been shown to inhibit TNF α production, possibly by blocking translation and/or secretion of TNF α . Of note, CsA does not lower intracellular TNF α levels or TNF α mRNA [8]. Additionally, addition of CsA results in significantly decreased levels of soluble TRAIL (sTRAIL) and sFasL in the serum [9]. The effects of CsA on TEN pathogenesis is summarized in Figure 1.

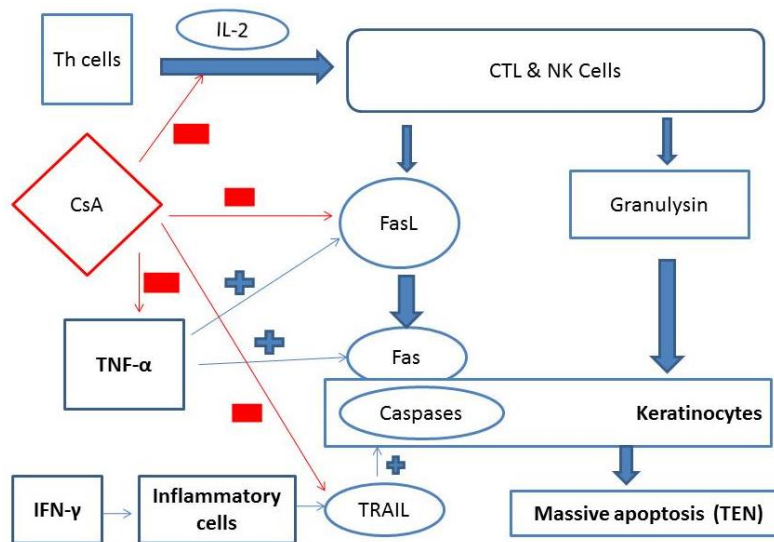


Figure 1. Pathways describing the action of cyclosporine A in toxic epidermal necrolysis pathogenesis. On activation, helper T cells release IL-2 which in turn activates cytotoxic T lymphocytes (CTL) and Natural killer cells (NK cells). On activation these cells release Fas legend (FasL) and granulysin which induces massive keratinocyte apoptosis, resulting in toxic epidermal necrolysis (TEN). TNF α , released by various cells, amplifies the apoptosis by up-regulating both FasL and Fas. Cyclosporine (CsA) inhibits release of IL-2 and thus, opposes activation of CTL and NK cells, cells responsible for secreting apoptosis inducing agents. Also, CsA inhibits action of FasL and TNF α , and inhibits amplification of apoptosis. Interferon γ (IFN γ), released predominantly by NK cells, activates other inflammatory cells to release another set of apoptosis inducing agents like TNF-related apoptosis-inducing ligand (TRAIL). CsA also opposes the actions of TRAIL and prevents apoptosis by yet another mechanism. Th cells= CD4+ helper T cells, FasL= Fas legend, Fas= CD95 surface protein, TRAIL= TNF-related apoptosis-inducing ligand.

Cyclosporine may have a protective role in of SJS to TEN by downgrading the apoptotic pathway in non-lesional skin. In a small, but interesting study, Paquet *et al* 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 Fas (CD95R) in clinically involved skin at completion of the 5-day treatment. A similar effect (reduction in Fas) was also noted in nonlesional skin. On the other hand, moderately increased Fas was observed in IVIG nonlesional skin [10].

Use of cyclosporine in TEN

Based upon the role of T lymphocytes in the pathogenesis of TEN, and the striking clinical and histologic similarity of toxic epidermal necrolysis to some cases of acute graft-vs-host disease, the use of cyclosporine in SJS/TEN was suggested [11]. In recent years, cyclosporine has gained popularity in the treatment of SJS/TEN. Many case reports, case series, open trials, and retrospective studies have documented the efficacy of CsA in SJS/TEN [12, 13, 14]. In fact, some of the reports suggest benefit of CsA over other therapies including IVIG, corticosteroids, cyclophosphamide, and supportive care. A few of the recent published reports are summarized in Table 1 [15-20].

The most widely used dose of CsA in SJS/TEN is 3-5 mg/kg body weight in divided doses. However, there is apparently no consensus on duration of therapy. Most physicians have used it for one month or until resolution of skin lesions and re-epithelization has occurred. Some authors have used CsA for a short period (around 7 to 10 days) and have reported successful outcomes. Valeyrie-Allanore *et al* have used CsA tapered over a month, based on the concern of rebound of skin lesions after a short treatment [16]. However, the case quoted by Valeyrie-Allanore *et al* (based on which Valeyrie-Allanore *et al* have raised the issue of rebound of lesions) and that reported by Hewitt *et al*, developed bullous lesions six weeks after the episode of TEN. A lesion was biopsied and the diagnosis made was erythema multiforme. Valeyrie-Allanore concluded that long-term treatment was probably unnecessary as the disease progression generally stopped before the 10th day of cyclosporine administration. Hence, it appears that short duration treatment is equally effective and is cost effective, an important issue in a developing country like India. Still, there is limited experience with CsA in SJS/TEN and hence, monitoring of patients for a few weeks after treatment seems prudent [13].

Some authors have used a combination of corticosteroid and CsA. Hewitt *et al* have treated their patients with prednisolone and methylprednisolone along with CsA. Corticosteroids were tapered off over a period of 1 month. Rai *et al* have reported successful treatment of three TEN patients with 100mg of dexamethasone in 5% glucose for an initial 2-4 days, followed by cyclosporine at a dose of 2 mg/kg body weight. They continued CsA at the same dose until improvement in the general condition of the patients and then tapered at a dose of 50mg every third day. CSA was halted after 2 weeks of remission and complete re-epithelization of skin lesions was complete. They argued that the initial high dose of steroid and subsequent cyclosporine could be a safe alternative to treat TEN, a condition associated with high mortality. Corticosteroids may have some role in the early phase, but do not have any effect after 72 hrs. Accordingly, suprapharmacologic doses of intravenous dexamethasone, given at an early stage of the disease, might contribute to a reduced rate of mortality and modify the cell-mediated immune response in the pathogenesis of TEN. However, prolonged use of same is associated with risk of septicemia and other associated complications and is associated with increased mortality. Cyclosporine is reported to be effective in TEN by interrupting the disease progression and decreasing the time taken for complete re-epithelization; hence, addition of cyclosporine to the regimen might improve treatment outcome of TEN [21].

There are some concerns about the absorption of oral CsA in TEN patients because of gastrointestinal (GI) mucosal disease. Fortunately, severe GI involvement is rare in TEN; manifestations include diarrhea, malabsorption, electrolyte disturbances, GI bleeding, and death. In fact, severe GI involvement is associated with a higher mortality rate and requires aggressive management [22, 23]. Considering the infrequent GI involvement, concerns about poor oral absorption of CsA in TEN patients should not impact its use in the majority of patients. However, data regarding the oral absorption of CsA in TEN patients with GI involvement as well as the effect of CsA on GI disease is unavailable.

Effect of cyclosporine on mortality in TEN

CsA appears to be a promising drug as far as mortality in TEN is concerned. Corticosteroid and IVIG have not shown similar effects. In one study, the expected mortality rate based on SCORTEN in 17 patients treated with CsA was calculated as 14.1%. However, the observed mortality rate was 5.9%. Similar figures for 37 patients treated with IVIG was 20.8% (expected mortality rate) and 29.7% (observed mortality rate). The standardized mortality ratio (SMR) for IVIG-treated patients was 1.43, whereas the SMR for patients treated with cyclosporine was 0.42. The calculated SMR suggests a survival benefit to cyclosporine use [20].

Table 1. Recent reports describing the use of cyclosporine in treatment of toxic epidermal necrolysis.

Authors, Year	Number of patients	Dose of cyclosporine	Outcome/ conclusion	Remarks
Arévalo <i>et al</i> , 2000 [15]	11 patients CsA, 6 patients with cyclophosphamide and steroid	3 mg/kg per day enterally every 12 hours for 2 weeks and then tapered off (10 mg a day reduction every 48 hours)	<ul style="list-style-type: none"> Time from the onset of skin signs to arrest of the disease progression and to complete reepithelialization was significantly shorter in patients treated with CSA compared with those treated with cyclophosphamide and corticosteroids. Multi (> or =4) organs failing, severe leukopenia and death were noted in fewer patients treated with CsA. 	
Valeyrie- Allanore <i>et al</i> , 2010 [16]	29 patients	Ciclosporine solution was administered orally through a nasogastric catheter at an initial dose of 1.5 mg/kg twice daily for 10 days, followed by 1 mg /kg twice daily for the 10 and finally 0.5 mg/kg twice daily for 10 days for a total treatment period of a month.	<ul style="list-style-type: none"> The progression of the disease was indeed amazingly low and stopped in the majority of patients. Sixty-two per cent of patients stopped progression at day 3 with ciclosporin instead of 35% with IVIG 11 patients had PaO₂ < 80 mmHg, which strongly suggests specific lung involvement. Still, no death was observed, which could underline a possible protective effect of ciclosporin on lung involvement. 	The treatment was prematurely stopped in three cases for side-effects, respectively at days 13, 15 and 23 for acute hallucinations suspected of being related to reversible posterior leucoencephalopathy, transitory neutropenia and severe infection (nosocomial pneumopathy).
Reese <i>et al</i> , 2011 [17]	4 patients	5 mg/kg in 2 divided doses for 5 days to 1 month	<ul style="list-style-type: none"> Noticeable symptomatic improvement within 24 hours No other notable complications during their admissions. There were no infections and no evidence of immunosuppression. 	
Firoz <i>et al</i> , 2012 [18]	82 patients (23 IVIG, 8 CsA, 51 supportive care)	<ul style="list-style-type: none"> If patients were admitted within 72hours of blistering, IVIG treatment (4 g/kg divided over 3 days) was initiated. If patients presented more than 3 days after developing the first blister, they received supportive care. Cyclosporine was used in patients with low body surface area involvement, and a SCORTEN of 0 to 1. 	When all 3 treatment options were compared, there was no significant difference in survival.	
Singh <i>et al</i> , 2013 [19]	11 patients CsA, 9 corticosteroid	Cyclosporine was administered in solution form in the dose of 3 mg/kg body weight in three divided dosage for 07 days than 2 mg/kg body weight in two divided dosage for another 07 days.	Cyclosporine had significantly reduced the time to the arrest of progression of SJS/TEN, the total re-epithelization time and hospitalization stay in comparison to corticosteroid.	One patient treated by cyclosporine developed corneal ulceration with symblepheron.
Kirchhof <i>et al</i> , 2014 [20]	35 IVIG, 15 CsA, 2 IVIG and CsA	IVIG was 1 g/kg/d for 3 days and CsA 5 mg/kg/d orally or intravenously for an average of 7 days.	<ul style="list-style-type: none"> Patients treated with IVIG had progression of epidermal detachment during admission. Cyclosporine use in the setting of SJS/TEN increases the probability of patient survival. 	28 SJS, 19 SJS/ TEN. 17 TEN

Adverse effects of cyclosporine

Most of the side effects associated with short-term therapy are reversible upon discontinuation of the drug. One of the most common adverse effects is hypertension, which is both time- and dose-related. A direct vasoconstrictive effect of cyclosporine on the kidney vasculature is responsible for the development of short-term hypertension. Modern, conservative dosing guidelines have prevented significant kidney damage in the vast majority of patients on short-term therapy. However, renal interstitial fibrosis has been demonstrated histologically even in the absence of abnormal laboratory tests in patients on appropriate dosing and monitoring regimens. Renal biopsy specimens from patients on long-term treatment demonstrate irreversible changes including renal tubular atrophy, arteriolar hyalinosis, glomerular obsolescence, and interstitial fibrosis. Although transplant recipients on high doses and prolonged courses of cyclosporine have an increased risk of certain malignancies (e.g. cutaneous squamous cell carcinoma and lymphomas), patients with skin diseases on cyclosporine for less than 2 years and on lower “dermatologic” doses have not been observed to have a similar risk. Some adverse effects are summarized in Box 1 [4, 5, 20].

Monitoring of patients on CsA are summarized in Box 2 [4, 5]. However, considering short term use of CsA in TEN patients, follow-up monitoring is not so crucial.

Box 1: Adverse effects of cyclosporine

Common	Cardiac: hypertension, dermatologic: non melanoma skin cancer, genitourinary: renal dysfunction; metabolic: hyperlipidemia; neurologic: headache, tremors
Uncommon	Dermatologic: hypertrichosis, gingival hyperplasia, sebaceous hyperplasia; genitourinary: nausea, diarrhea; neurologic: paresthesia, hyperesthesia; metabolic: hyperkalemia, hypomagnesemia, hyperuricemia
Rare	Infections; dermatologic: trichodysplasia spinulosa; musculoskeletal: myalgias, myositis; gastrointestinal: hepatotoxicity; malignancy: lymphoma; pulmonary: dyspnea, bronchospasm

Box 2: Monitoring guidelines for cyclosporine therapy

Initial screening	Follow up monitoring
Examination	Examination
Complete history and physical examination (to rule out active infections, malignancy)	Re-evaluate the patient every 2 weeks for 1–2 months, then every 4–6 weeks while on cyclosporine
Two baseline blood pressures at least a day apart	Blood pressure checked at each visit
Laboratory	Laboratory surveillance every 2 weeks for the first 1–2 months, then monthly
Baseline serum creatinine levels	Renal function – serum creatinine, BUN, urinalysis
Other baseline renal evaluation – BUN, urinalysis with microscopic examination	Complete Blood Count and liver function tests (especially SGOT/AST and SGPT/ALT)
Complete Blood Count and liver function tests (especially SGOT/AST and SGPT/ALT)	Lipids – triglycerides, cholesterol
Fasting lipid profile – triglycerides, cholesterol, HDL cholesterol	
Others- magnesium (may decrease), potassium (may increase) uric acid (mainly relevant for patients at risk for gout).	magnesium, potassium, uric acid

Use in pregnancy and lactation

Cyclosporine is not teratogenic, and is classified as a pregnancy prescribing **category C** drug. Use during pregnancy should be considered only in exceptional patients for whom the potential benefits of cyclosporine therapy dramatically outweigh the risks.

Cyclosporine is excreted into breast milk and should not be used during lactation, owing to risks of immunosuppression and possible carcinogenesis in the breastfed infant [4, 5, 20].

Use in TEN patients with HIV/AIDS

CsA has shown significant anti-HIV-1 activity and two mechanisms have been proposed. CsA inhibits gp120 and gp41 incorporation into HIV-1 virions and thus, is associated with decreased infectivity. Also, it competitively inhibits interaction of cellular protein cyclophilin A (CypA) with the capsid protein (CA) of HIV-1 and prevents CypA incorporation into virions, resulting in decreased infectivity [24, 25]. The role of CsA as adjunct to highly active antiretroviral therapy (HAART) in early HIV-1 infection is debatable [26, 27], but there is no evidence for harm in using CsA in HIV-infected persons, considering current evidence.

Conclusion

There is no widely accepted consensus on treatment of SJS/TEN. Corticosteroids and IVIG have failed to show clear cut benefit in terms of mortality in TEN. CsA appears to be a promising addition to the armamentarium. Case reports, case series, open trials, and retrospective studies have documented its efficacy, safety, and beneficial effect on expected mortality rates. A double-blind randomized trial (placebo vs. cyclosporine) would be necessary to confirm its efficacy. Such a study would be very difficult.

Considering the current published works, the usefulness of CsA in SJS/TEN is summarized in Box 3.

Box 3: Cyclosporine in Toxic epidermal necrolysis

- Cyclosporine therapy is well tolerated. No serious adverse effects are usually noted in short term therapy.
- Renal compromise, commonly noted in Stevens Johnson syndrome/Toxic epidermal necrolysis, is not a contraindication to cyclosporine therapy.
- Short duration of treatment (7 to 10 days) is effective in controlling the progression of disease.
- No progression of lesions have been noted in patients on cyclosporine therapy. The protective effect probably extends to non-lesional skin.
- More rapid re-epithelization is noted in patients on cyclosporine therapy.
- Mortality rates lower than expected, based on SCORTEN, have been reported with cyclosporine therapy.
- Short duration cyclosporine therapy is cost effective in comparison to IVIG.
- HIV/AIDS is not a contraindication to CsA therapy.

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