Cyclosporine - An eye opener in severe cutaneous adverse drug reactions

V. Anandan[1], P.S. Mohana Sundari[2,*], Yoga Nandhini[3], Ragini Rajan[4]

[1]Professor, [2]Senior Assistant Professor, [3]Senior Resident, [4]Junior Resident, Dept. of Dermatology, [1,2,4]Government Stanley Hospital, Chennai, Tamilnadu, [5]Thiruvannamalai Medical College, Tamilnadu, India

***Corresponding Author**
Email: psm.sundari@gmail.com

Abstract

Severe cutaneous adverse drug reactions (sCADR) comprise the life-threatening Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Aim: The aim of this study was to assess the efficacy and safety of cyclosporine in treating sCADR.

Materials and Methods: A retrospective study was done from data collected over a three year period at the department of dermato-venereo-leprology at a tertiary care centre in South India. Out of thirty-four in-patients with adverse drug reactions (ADRs), twenty who fulfilled the inclusion criteria (one DRESS, ten SJS and nine TEN patients) were taken for the study. Fixed drug eruption and TEN with multiorgan failure were excluded.

Methodology: Patients were evaluated, screened for multiorgan involvement, offending drug/drugs were withheld, routine investigations done and the severity assessed based on SCORTEN. Treatment was initiated with injection dexamethasone 1mg/kg/day and supportives. In those with unsatisfactory response in three days, if not contra-indicated, oral cyclosporine was added at a dose of 100mg bid for 2 weeks, tapered by 50mg/week and stopped once the lesions healed. Efficacy of cyclosporine was assessed using the average number of stabilization days, the rate of cutaneous re-epithelialization and the duration of hospitalization.

Results: For SJS, the mean duration of stabilization was 2 days, re-epithelialization 7.9 days and hospital-stay 18.1 days. For TEN, the mean duration of stabilization was 3.9 days, re-epithelialization 12.8 days and hospital-stay 29.2 days.

Conclusion: With the use of cyclosporine, patients stabilized early, re-epithelialization occurred early; concomitant use with steroids helped in early tapering of steroid dose. Recovery time and duration of hospital stay were shortened. Cyclosporine was well tolerated, no significant toxicity was noted; there was no mortality.

Keywords: Cyclosporine, Severe cutaneous adverse drug reactions, DRESS, SJS, TEN.

Introduction

Adverse drug reactions (ADRs) are undesirable clinical manifestations resulting from administration of drugs. They include predictable side effects and unanticipated adverse manifestations. ADRs account for 5-8% of hospitalization worldwide and are the fifth leading cause of death.[1] The most frequently reported are cutaneous adverse drug reactions (CADRs) -30-45%[2] accounting for 2% hospital admissions.[3] CADRs range from transient erythema to severe CADRs (sCADR); their incidence varies from 1-3% in developed to 2-5% in developing countries.[4] Of this, 2-7% are life-threatening severe cutaneous adverse drug reactions (sCARD) {SJS, TEN, DRESS}[5] that may affect anyone taking the medication. Patients with less than 10% body surface area epidermal detachment are classified as SJS, more than 30% as TEN and 10-30% as SJS/TEN overlap. Mortality rate varies from 5-10% for SJS[6] and 25-30% for TEN.[7] Skin failure secondary to sCADR with loss of the protective cutaneous barrier is associated with a high risk of mortality and morbidity. Pathogenesis involves antigenic moiety/metabolite peptide-induced T cell activation leading to keratinocyte apoptosis acting through soluble Fas ligand, perforin/granzyme B, tumor necrosis factor-α (TNFα), nitric oxide, the recently proposed granulysin mediated keratinocyte death[8] and necroptosis mediated by annexin A1 acting through formyl peptide receptor1.[9] Some of these patients may be refractory to systemic corticosteroids when additional immunotherapy, e.g., cyclosporine, intravenous immunoglobulin, plasmapheresis, cyclosporine, TNFα inhibitors, N-acetylcysteine and granulocyte colony-stimulating factor, is required to halt the destructive process. Cyclosporine is a calcineurin inhibitor that inhibits T-cell activation and chemotaxis. The present study was done to assess the safety and efficacy of cyclosporine in sCADR patients not responding to systemic corticosteroids.

Materials and Methods

A retrospective study was done from data documented over a three year period at the department of dermato-venereo-lepology of a tertiary care hospital in South India. Patients presenting with acute severe cutaneous adverse drug reactions who fulfilled the criteria for SJS, SJS-TEN Overlap, TEN and DRESS were included; those with a history of prior treatment with any other immunosuppressive drug, intolerance to cyclosporine, uncontrolled hypertension, renal failure, multi-organ failure, sepsis and seropositivity for HSV and HIV were excluded. Twenty in-patients treated for sCADR were taken for the study. This included one DRESS, ten SJS and nine TEN cases.

Upon admission, patients were evaluated, screened for multi-organ involvement; routine investigations

were done and the severity assessed based on SCORTEN. After withdrawing the offending drug/drugs, patients were started on systemic corticosteroid (injection dexamethasone 1mg/kg body weight) and supportives with appropriate topical therapy. In those with unsatisfactory response in 48-72 hours, oral cyclosporine was added at a dose of 100mg bid for 2 weeks and tapered to 150 mg/day (1 week), 100 mg/day (1 week) and maintained at 50mg/day until lesions healed. Thereafter the dose of systemic corticosteroids was also gradually tapered.

The response to treatment was noted as one of three outcomes, namely, 1) progression of the disease- increase in erosions, blistering and positive pseudo Nikolsky's sign 2) stabilization of the disease- new lesions cease to appear or there was no increase in the size of existing lesions. 3) re-epithelialization - complete healing of the skin without any erosion/denudation. Stabilization was indicated by cessation of new lesions followed by re-epithelialization. Efficacy of cyclosporine was assessed using the average number of stabilization days, the rate of re-epithelialization of skin and the duration of hospitalization.

Results

Among the twenty cases of sCARDs, 10 patients had SJS (50%), 9 had TEN (45%) and one had DRESS (5%). (Graph. 1)

35% were males, 65% were females and one was a male child (5%). There were an overall female preponderance with six females and 4 males with SJS (F: M :: 3:2), five females and 4 males with TEN (F: M :: 5:4) and one female patient with DRESS. (Graph. 2)

Overall, most patients were in their forties and fifties, 20% aged less than 20 years, 35% between 21 and 40 years and 45% between 41 and 60 years. The age of SJS patients ranged from 18-60 years, TEN patients from 12-51 years with one male child while one case of DRESS was aged 17 years. (Graph. 3)

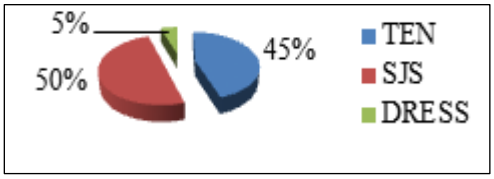
In SJS, the mean time for stabilization was 2 days (1-4 days), reepithelialization 7.9 days (4-12 days) and duration of hospital stay 18.1 days (11-32 days). There were no complications of SJS or adverse reactions to cyclosporine. (Table 1)

Among the TEN patients, SCORTEN was 1 in one patient, 2 in four and 3 in four patients. Total body surface area involved ranged from 40-90%. The mean time for stabilization was 3.9 days (2-7days), re-epithelialization 12.8 days (9-20 days) and duration of hospital stay 29.2 days (18-60 days). One patient had ocular complications. There was no adverse reaction to cyclosporine. (Table 2)

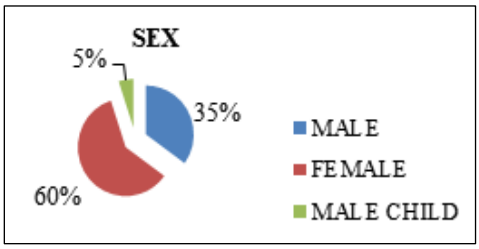
In the patient with DRESS, the mean time for stabilization was 2 days, re-epithelialization 5 days and duration of hospital stay 19 days. There was no complication or adverse reaction to cyclosporine. (Table 3)

In this study, 4 patients had a SCORTEN of 3; there was no mortality.

Graph 1: Disease Categorisation - Type of drug reaction



Graph 2: Gender Distribution



Graph 3: Age Distribution Age incidence

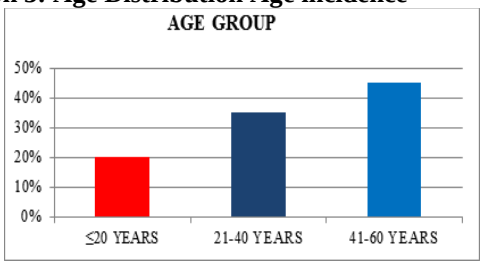


Fig. 1: Case of TEN

Fig. 2: Case of SJS

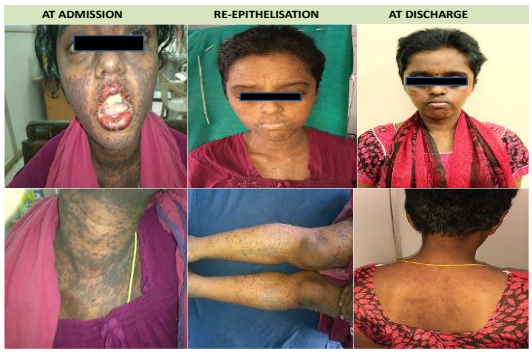


Fig. 3: Case of TEN

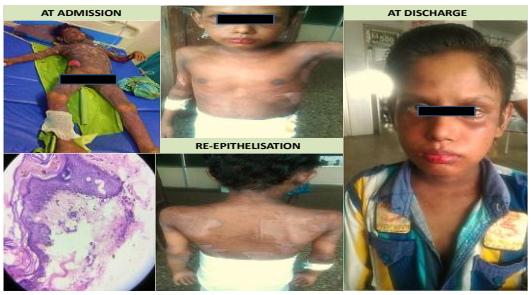


Fig. 4: Pediatric Case of SJS0

Table 1: SJS

S.No	Age (yr)	Sex	Stabilisation (days)	Re-epithelisation (days)	Duration of hospital stay (days)	Complications	Adverse effects of drug
1	44	F	2	5	24	NIL	NIL
2	18	F	1	8	16	NIL	NIL
3	29	F	4	10	32	NIL	NIL
4	32	M	3	12	29	NIL	NIL
5	47	F	2	9	12	NIL	NIL
6	50	M	1	7	11	NIL	NIL
7	48	M	1	6	14	NIL	NIL
8	60	F	1	4	11	NIL	NIL
9	56	M	3	10	19	NIL	NIL
10	28	F	2	8	13	NIL	NIL
MEAN	41.2	F>M	2.0	7.9	18.1	NIL	NIL

Table 2: TEN

S.No	Age (yr)	Sex	Scorten	TBSA (%)	Stabilisation (days)	Re-epithelisation (days)	Duration of hospital stay (days)	Complications	Complications of drug
1.	20	F	3	85	7	20	60	**Ocular**	NIL
2.	44	M	2	48	2	12	25	NIL	NIL
3.	12	M	3	90	5	15	42	NIL	NIL
4.	35	F	2	56	3	9	20	NIL	NIL
5.	51	M	3	44	2	10	18	NIL	NIL
6.	32	F	2	59	4	13	27	NIL	NIL
7.	34	M	1	40	2	11	18	NIL	NIL
8.	24	F	2	62	4	10	24	NIL	NIL
9.	48	F	3	71	6	15	29	NIL	NIL
Mean	**30.4**	**F>M**	**3.0**	**61.7**	**3.9**	**12.8**	**29.2**	**NIL**	**NIL**

Table 3: DRESS

S.No	Age (yr)	Sex	Stabilisation (days)	Re-epithelisation (days)	Duration of hospital stay (days)	Complications	Complications of drug
1.	**17**	**F**	**2**	**5**	**19**	**NIL**	**NIL**

Table 4: Results of Study

	SJS		TEN	
	Range	Mean	Range	Mean
Stabilisation days	1-4	2.0	2-7	3.9
Re-epithelisation days	4-12	7.9	9-20	12.8
Duration of hospital stay	11-32	18.1	18-60	29.2

Discussion

Adverse drug reactions are undesirable, noxious and unintended clinical manifestations resulting from administration of a particular drug, occurring at doses used in humans for the prophylaxis, diagnosis or therapy of disease or for the modification of physiologic function, purposely excluding therapeutic failures, overdoses, drug abuse, non-compliance and medication errors.[10] They are of 5 types - Type A (predictable from known pharmacology) - (80%) common, dose-dependent extensions of pharmacological actions, Type B (unpredictable) - rare, dose-independent, idiosyncratic or immunologic reactions, unrelated to pharmacological actions, Type C - uncommon, associated with long-term use involving dose accumulation, Type D - dose-independent delayed effects like carcinogenicity or teratogenicity and Type E - resulting in termination of treatment.[11]

Non-immunological reactions include overdosage, side effects, cumulative toxicity, delayed toxicity, facultative effects, drug interactions, enzyme stimulation or inhibition, drug displacement from carrier or receptor, intestinal drug interactions, teratogenicity and effect on spermatogenesis. Immunological reactions can be of Type I - immediate/ anaphylactic (IgE-mediated) e.g., anaphylaxis with penicillins, Type II - cytotoxic (IgG, IgM-mediated) e.g., methyldopa-induced hemolytic anemia, Type III- immune complex (IgG, IgM) e.g., serum sickness, procainamide-induced lupus erythematosus and Type IV- delayed hypersensitivity (T cell-mediated) e.g., contact dermatitis with topical antihistamine.[12]

Of these, cutaneous ADRs are the most frequently reported, ranging from transient erythema to sCARDs. sCARDs include the potentially life-threatening SJS, TEN and DRESS.

SJS and TEN form a clinical spectrum characterized by widespread skin and mucous membrane blistering with full-thickness epidermal necrosis (keratinocyte apoptosis). Genetic associations with molecules critical to T-cell activation, strong drug-specific association between certain HLA class I alleles and risk of TEN and faster onset of TEN on accidental re-exposure to the causative drug suggest a T-cell-mediated pathogenesis. Three pathogenetic mechanisms have been proposed, namely 1) medication-induced upregulation of surface Fas L by keratinocytes that interacts with constitutive keratinocyte Fas receptors leading to death receptor mediated apoptotic pathway and keratinocyte apoptosis, 2) drug interaction with MHC1-expressing cells inducing accumulation of drug-specific CD8 cytotoxic T-cells within epidermal blisters that release perforin & granzyme B to kill keratinocytes[13] and 3) drug-triggered activation of CD8 T cells, natural killer cells (NK cells) and NKT cells to secrete a soluble mediator granulysin, that induces keratinocyte death without cell contact.[14] FasL is induced by T-cell interferon γ (IFN-γ)- and TNFα-mediated keratinocyte nitric oxide secretion. Granulysin-induced cell death may coexist with FasL-mediated keratinocyte apoptosis, possibly in a sequential manner. Other mechanisms include CD40/CD40L activation, perforin and granzyme release and a bystander role of TNF-α activating apoptotic pathway through the death receptor TNF-R1.

The cardinal features of DRESS (drug-induced hypersensitivity syndrome-DIHS / hypersensitivity syndrome-HSS) include an exanthem-like eruption, oedema and systemic inflammation - fever, organ dysfunction, haematological abnormalities and lymphadenopathy, mimicking a viral infection.[15] *In vitro* demonstration of drug-specific T cells indicates a T-cell-mediated hypersensitivity reaction. A more complicated pathogenesis is suggested by reactivation of viruses, especially EBV, HHV-6 and HHV-7, detected in about 75% of cases, a useful diagnostic marker of DRESS. Herpesvirus reactivation is proposed as causing disease flares despite withdrawal of the culprit drug. Drug-specific Th2 immune response may induce regulatory T cells to impair host virus control with viral reactivation, antiviral CD8+ T cells upsurge and disease flare. Alternatively, virus replication induction may be primarily responsible, as many proliferating CD8+ T cells from the skin, blood or other organs are virus-specific and causative drugs specifically enhance viral replication and production in patients' B cells[16].

Cyclosporine, isolated from soil fungus *Tolypocladium inflatum gams* in 1970, is a neutral cyclic polypeptide with 11 amino acids. Available as 50 mg capsule, this calcineurin inhibitor was the first immunosuppressant to act selectively on T cells. Cyclosporine complexes with cyclophilin to inhibit the intracellular enzyme calcineurin, leading to reduced activity of nuclear factor of activated T cells (NFAT-1) that regulates transcription of IL-2 needed for activation and proliferation of CD4 T helper and CD8 T cytotoxic cells; impaired IL-2 production leads to a decline in the number of epidermal activated CD4 and CD8 cells.

The only FDA approved indication of cyclosporine is severe recalcitrant psoriasis; off- label uses are atopic dermatitis, pyoderma gangrenosum, chronic urticaria, drug reactions, bullous dermatoses, connective tissue disorders and granuloma annulare.

Adverse effects of cyclosporine are renal dysfunction, hypertension, tremor, headache, paresthesia, hyperesthesia, hypertrichosis, gingival hyperplasia, nausea, abdominal discomfort, diarrhoea, myalgia, lethargy, arthralgia, hyperkalemia, hyperuricemia, hypomagnesaemia and hyperlipidemia. Absolute contraindications are significantly decreased renal function, uncontrolled hypertension, hypersensitivity to cyclosporine, clinically cured or persistent malignancy (except nonmelanoma skin cancers) and cutaneous T-cell lymphoma. Relative contraindications are age under 18 or over 64 years,

controlled hypertension, plan to receive live attenuated vaccination, concomitant use of medications interfering with cyclosporine metabolism or potentiating renal dysfunction, concomitant phototherapy, methotrexate, or other immunosuppressive agents, active infection, evidence of immunodeficiency, pregnancy and lactation. Drug interactions wherein there are increased cyclosporine levels are with anti-fungal azoles, macrolides, ciprofloxacin, doxycycline, cimetidine, diuretics and oral contraceptives. Cyclosporine levels are decreased by anticonvulsants, griseofulvin, isoniazid, rifampicin and bexarotene.

The meager data available in literature for definitive management of sCADRs has paved the way for identifying newer life-saving management choices. Various modalities are now available as part of treatment protocol. Immediate withdrawal of the causative drug is the priority in management, but it is often difficult to identify it. The latency period between drug intake and onset of drug reaction can range from 5 – 28 days.[17] The studies available in relation to drugs previously used for treatment, like thalidomide and corticosteroids, have failed to inspire a concrete protocol for definitive management of sCARD. The disadvantages of thalidomide are prolonged hospital stay with no positive effect in reducing fatality rate.[18] Corticosteroid usage is controversial; some authors consider it useful in halting disease progression,[19-21] whereas others find risks outweighing benefits.[22, 23]

The proven benefits of cyclosporine are earlier re-epithelialization, normally 3 weeks,[17] shortened recovery time and duration of hospital stay and reduced mortality; it is well tolerated by patients and no significant toxicity is noted. In our study, the average duration of re-epithelialization was 7.9 and 12.8 days for SJS and TEN (mean 10.35), average hospital stay was 18.1 and 29.2 days (mean 23.65), there were no adverse reactions for the drug proper and no fatality.

Arevalo et al, in a case series of 6 patients, reported faster re-epithelialization and absence of significant toxicity in patients treated with oral cyclosporine.[24] Reese et al have also reported similiar findings in their study with 4 patients.[25]

In a phase II trial by Valeyrie-Allanore et al, orally administered cyclosporine (3mg/ kg / day for 10 days), SCORTEN-predicted mortality of 2.75 did not occur as there were nil deaths. They proposed its usefulness in SJS and TEN management as it decreased the progression of detachment of skin with a sharp reduction in case fatality.[26]

Similar observation of using cyclosporine as monotherapy for TEN has also been noted by Vikrant Saoji et al.[27]

Kirchof et al[28] compared cyclosporine with IVIG in management of TEN. SCORETEN mortality rate in cyclosporine treated patient was 0.43 and 1.43 in IVIG treated patients. This proves cyclosporine effectively reduces the mortality rate. Swosti Mohanty et al[29] have reported the benefit of using cyclosporine in faster re-epithelialization; time for stabilization and duration of recovery was lower in cyclosporine treated group as against a comparative group of supportive management. The mortality rate was 3.3 times lower than the comparative group.

Singh et al[30] comparing cyclosporine to retrospective cohort treated with corticosteroids reported a decreased mean duration of hospital stay, faster re-epithelialization and stabilization with no mortality in the group treated with cyclosporine.

Limitations of our study were the limited number of patients, chosen cases were devoid of complications and the results were not compared with other modalities of management.

Conclusion

sCARD was more common in females aged 40-60 years. With the use of cyclosporine, patients were stabilized earlier, re-epithelialization occurred earlier, recovery time, duration of hospital stay and mortality rate was reduced. Concomitant use with steroids helped in reducing the dose of steroids and favored early tapering. It was well tolerated by patients and no significant toxicity was noted.

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