Case Series

Boosting effect of cyclosporine on corticosteroids in the acute management of toxic epidermal necrolysis

Nageswaramma Siddabathuni, Sahitya Tadi, Rakesh Darla*, Premsagar Gomukonda

Department of Dermatology and Venereology, Guntur Government Hospital, Guntur, Andhra Pradesh, India

Received: 25 May 2020
Revised: 18 June 2020
Accepted: 20 June 2020

*Correspondence:
Dr. Rakesh Darla,
E-mail: sahitya.tadi@gmail.com

ABSTRACT

Toxic epidermal necrolysis (TEN) is a life-threatening dermatological emergencies. It is a rare, acute mucocutaneous disorder that usually occur secondarily as an idiosyncratic reaction to certain drugs. Prompt identification and discontinuation of the causative drug is mandatory along with adequate supportive care like proper hydration, minimize the number of skin manipulation, prevention of secondary infections. Many immunosuppressive modalities have been tried with variable results. In this manuscript, we reported 12 consecutive cases of TEN presented to our hospital over a period of 2 years from 2017 to 2019. All the cases presented with varying percentage of skin blistering and mucosal involvement secondary to an offending drug. The incriminated drug was discontinued, supportive care was initiated along with combination therapy of cyclosporine and corticosteroids as immunosuppressants. The clinical presentation, etiological drugs and treatment protocol followed and its efficacy will be described in details.

Keywords: Corticosteroid, Cyclosporin, TEN

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare and serious skin condition, often caused by an adverse reaction to medications characterized by skin peeling and blistering along with erosions of mucosal surfaces.1 World-wide, the average annual incidence of TEN is 0.4-1.3 cases per million populations.2,3 The mortality rate of Stevens-Johnson syndrome (SJS) and TEN is high; approximately, 5% for SJS and 30% for TEN.4,5 Now SJS, SJS-TEN overlap and TEN are considered a spectrum of the same condition having common risk factors and causes, differentiated only by the extent of the body surface area (BSA) involved. Patients with epidermal detachment involving less than 10% of BSA are classified as having SJS, more than 30% BSA as TEN and 10-30% as SJS/TEN overlap.6 Apoptosis is thought to be the primary reason responsible for keratinocyte death in TEN. Two probable explanation supporting apoptosis for keratinocyte death are noted. The first explanation is activation of cytotoxic T-cells drug and release of granzyme B and perforin, ultimately resulting in activating the caspase cascade and keratinocyte apoptosis.7 The second explanation proposes that Fas-Fas ligand binding activates caspase 8, which results in nuclease activation and the widespread skin blistering characteristic of this severe drug reaction.8

A prognostic score called SCORTEN has been validated to demonstrate its ability to specifically predict patient outcome in SJS and TEN.9,10 Even though, some uncertainty still persists on effector mechanisms of TEN, the resemblance to graft rejection provided a rational for using the immunomodulating agents.11 There are several studies illustrating variable results in the management of TEN. These included corticosteroids, plasmapheresis, cyclophosphamide, thalidomide.12-16 Fas-Fas ligand and cytotoxic T-cell, which plays a vital role in the pathogenesis of TEN are respectively blocked by
intravenous immunoglobulin (IVIG) and cyclosporine. Thus, theoretically making IVIG and cyclosporine effective drugs in the management of TEN. Several case reports have suggested encouraging results with IVIG in management of TEN. However, study by Bachot et al did not show any improvement with IVIG. In Indian subcontinent managing TEN by IVIG is not cost-effective and there is no literature backup to suggest IVIG is superior than other modalities. Several case reports and case series revealed encouraging result of use of cyclosporine in stopping disease progression and to prevent the mortality. In Indian subcontinent, systemic steroids have traditionally been used to manage TEN because of its easy availability and cost effectiveness. This study was designed to evaluate the efficacy of combination therapy of systemic corticosteroid and cyclosporine in tertiary health-care setting.

CASE SERIES

Study was conducted at Government General Hospital, Guntur during 01 July 2017 to 30 June 2019. Prior approval of ethical committee was taken. A total of 12 patients were enrolled into the study during this period. All cases fulfilling clinical diagnoses of TEN were included into the study. Exclusion criteria were prior treatment with any other immunosuppressive drugs, history of intolerance to cyclosporine, uncontrolled diabetes mellitus, human immunodeficiency virus (HIV) positivity and cases of multi-organ failure and sepsis.

Treatment protocol used in our study population-initially, dexamethasone was administered in the dose of 16 mg twice daily for 5 days and was followed by cyclosporine in the dose of 3 mg/kg body weight in two divided dosage for 07 days and then tapered over another 14 days. No other immunosuppressant was administered. Cases of TEN were managed in the intensive care of Department of Dermatology. Barrier nursing, ambient temperature of 30°C, fluid and electrolyte balance and high calorie containing diets were considered in each patient. Injectable antibiotics were considered in strongly suspected or evident sepsis.

Efficacy of combination therapy of corticosteroids and cyclosporine was assessed by the average number of days in stabilization of disease progress, rate of re-epithelization of skin, duration of hospitalization, safety profile of medications and mortality rate at 1 month in comparison with the mortality rate predicted by SCORTEN at admission. The SCORTEN calculation was done based on Bastuji-Garin et al. Stabilization of disease was defined when new lesions cease to appear. Progression of disease was evaluated by any increase in erosions, blistering and positive Nikolsky’s sign. Re-epithelization was defined as complete healing of the skin without any erosion. Total body surface area (TBSA) assessment was like any burn patients, following rule of nine. Monitoring of patients was like well-established intensive care unit (ICU) protocol.

Table 1: Detailed history and findings of the study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.09±15.17</td>
</tr>
<tr>
<td>Delay between onset and admission to hospital (days)</td>
<td>2.73±0.69</td>
</tr>
<tr>
<td>Total body surface area involved (%)</td>
<td>23.3±16.27</td>
</tr>
<tr>
<td>Stabilisation of disease (days)</td>
<td>3.18±1.32</td>
</tr>
<tr>
<td>Re-epithelialisation of skin (days)</td>
<td>14.5±4.08</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>18.09±5.02</td>
</tr>
<tr>
<td>Complications</td>
<td>One case developed symblepheron</td>
</tr>
<tr>
<td>SCORTEN predicted mortality rate (%)</td>
<td>10.16 (SD 9.5)</td>
</tr>
<tr>
<td>Actual mortality rate</td>
<td>Zero</td>
</tr>
</tbody>
</table>

In relation to causative drug, three cases were secondarily to dilantin and ibuprofen each, two to carbamazepine, one each to ofloxacin, ciprofloxacin and amoxicillin.
DISCUSSION

The Cochrane review on the management of Toxic epidermal necrolysis showed only one randomized controlled trial.15 This trial compared the effectiveness of thalidomide with placebo. The only trial available used thalidomide, but this trial did not show any benefit from treatment compared against placebo, but highlighted increased chances of dying from the treatment.16 Role of corticosteroids in treating patients of TEN has been debatable. Several studies had shown possible benefit of corticosteroids.12,36,37 However, off late most of the studies criticized the use of corticosteroids stating it not only prolongs the hospital stay, but also make patients susceptible for complications.38,39 A retrospective analysis of 289 patients from the EuroSCAR study found no benefit from corticosteroids or IVIG compared to supportive care alone.40 Even, the combination therapy of corticosteroid and IVIG had no positive impact on the mortality rate.18

Withdrawal of causative drugs should be a priority in the management of TEN, as there is paucity of data on effective drug for TEN. Doval et al have shown that longer the half-life of the causative drug, poorer is the prognosis and suggested early withdrawal of the causative drug.40 In order to identify the culprit drug, it is important to consider the chronology of administration of the drug and the reported ability of the drug to induce SJS/TEN. TEN is a life threatening disease and proper supervision with timely intervention is an integral part of the management.1

Our study was distinct in the way, it had evaluated the efficacy of combination therapy of corticosteroid and cyclosporine in cases of TEN. It highlighted few important results. Cyclosporine was well tolerated by all the patients. There was no death in the patients managed by combination therapy of corticosteroid and cyclosporine. All the above findings were statistically significant with p value less than 0.05. Only one patient who inadvertently continued using ofloxacin eye drops, which was the culprit oral drug for the development of TEN. The same could be the basis for continuation of BSA involvement despite being administered cyclosporine. 100% survival in cyclosporine group could be explained by probable mechanism of action of this drug, which targets cytotoxic T-cell, which plays an important role in the apoptosis of keratinocytes. Other probable reason could be strict exclusion of patients of HIV, sepsis and multi organ dysfunction, who are likely to succumb to death when they develop TEN.

Recently, Valeyrie-Allanore et al conducted an open, phase II trial to determine the safety and possible benefit of cyclosporine.11 A total of 29 patients were included in the trial (10 SJS, 7 TEN and 12 SJS/TEN overlap), and 26 patients completed the treatment protocol of oral cyclosporine at a dose of 3 mg/kg/day for 10 days and gradually tapered over one month. Results show a possible usefulness of cyclosporine in SJS and TEN, as the mortality rate and progression of the disease is much lower than the expected value.

In a case series reported by Arévalo et al in which 11 patients treated with oral cyclosporine 3 mg/kg/day observed a rapid epithelialization with no significant toxicity in comparison with patients treated with combination of corticosteroids and cyclophosphamide (n=6).31

Our study show very good results with the treatment protocol; however, comment on its efficacy cannot be made due to in built constrain of the study design. Very small sample size and exclusion of complicated cases are obvious limitations of this study, which may have added to the favourable outcome of combination therapy of corticosteroid and cyclosporine.

CONCLUSION

The present study suggest that combination therapy of corticosteroid and cyclosporine has a definite role in treating uncomplicated cases of TEN. Though a large, double-blind, placebo-controlled, randomized trial would prove the efficacy of the treatment protocol beyond any doubts, it is highly impractical.
Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES


