Management of Toxic Epidermal Necrolysis with Plasmapheresis and Cyclosporine A: Our 10 Years’ Experience

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Background: The management of toxic epidermal necrolysis (TEN) is controversial and there is no uniform strategy.
Objective: To share our 10 years’ experience in treating severe TEN with a novel protocol based on the association of cyclosporine A and plasmapheresis.
Methods: In this case series, we retrospectively collected and assessed the 12 cases of severe TEN treated from 2005 to 2015 at the Burn Unit of the University of Bari Policlinico hospital.
Results: Average body surface area was 77; average SCORETEN was 4.3. The 12 patients had been treated with culprit drug withdrawal, systemic corticosteroids, and/or cyclosporine A with no response. The protocol was successfully administered in all 12 cases. Average time to response from protocol start was 4.9 days. Average time to remission from protocol start was 22 days; average hospital stay at our unit was 24.8 days. Four patients developed severe complications; 1 patient died. No complications linked to the protocol therapeutic measures were observed. The relatively small number of cases given the rarity of the condition is a limitation of this report.
Conclusion: Our protocol based on the association of cyclosporine A and plasmapheresis is safe and efficacious in treating severe TEN. (Plast Reconstr Surg Glob Open 2017; 5:e1221; doi: 10.1097/GOX.0000000000001221; Published online 22 February 2017.)

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The characteristics of the 12 cases are summarized in Table 1. The average body surface area (BSA) was 77%. Of the 12 cases, 4 patients presented severe mucosal involvement, defined as combined and diffuse respiratory, gastroenteric, genital, and ocular involvement. All patients showed systemic symptoms, such as fever, asthenia, pain, and dyspnea. Blood examinations varied, but common findings included lymphopenia (selective depletion of CD4 as evidenced by lymphocytogram), mild thrombocytopenia, liver and pancreatic enzymes increase, hypoproteinemia, albuminuria, and increased C reactive protein (average: 82 mg/L). Histological examination, performed in each case, confirmed the diagnosis (Fig. 1). Etiology varied, but mainly comprised antibiotics and nonsteroidal anti-inflammatory drugs. First-line therapy, defined as identification and withdrawal of the culprit medication, had been carried out in all patients. The average time from initial disease presentation (first signs and symptoms) to treatment with our protocol was 4.6 days. Each step was introduced with an original timing. In particular, at day 1 of hospitalization in our unit CsA at full dosage (intravenous 250 mg/die or 4 mg/kg/die in pediatric patients) was introduced (the dose was adjusted in those 4 patients already under CsA). At days 3, 5, and 7, CsA, at full, reduced, and minimal dosages, respectively, were introduced. At days 5 and 7, daptomycin was introduced. CsA administration continued for 15 days, daptomycin for 10 days, and the plasma exchange consisted of 7 cycles spaced by 2 days each. In the 3 cases that developed severe disease progression (cases 2, 9, and 12), we administered, topically, the anti-infective agent on the first day of admission. Treatment was tapered after an average of 9.2 days from protocol start. The average time to response, defined as halt of skin sloughing increase with apparent healing of lesions, occurred in all patients. Supportive measures were tapered. The average hospital stay was 20 days.

Table 1. Characteristics of Our Study Population and Therapeutic Results

| Case | Age | Sex | Etiology | Previous Therapies | BSA | Severe Mucosal Involvement | SCORETEN (max 7) | Time from Initial Disease Presentation to First Treatment (d) | Time from Initial Disease Presentation to Protocol Start (d) | Time from Protocol Start to Response (d) | Time from Protocol Start to Remission (d) | Hospital Stay (d) | Complications | Follow-up (mo) |
|------|-----|-----|----------|-------------------|-----|---------------------------|-----------------|-------------------|----------------|----------------|----------------|----------------|--------------|---------------|
| 1    | 47  | F   | SULFONAMIDE | Cort, CsA         | 65  | 4                         | 1               | 4                 | 2              | 5              | 20             | 23             | NA           | 24            |
| 2    | 52  | M   | EUCA LYPTOL | Cort             | 75  | 5                         | 2               | 5                 | 6              | 6              | 25             | 27             | NA           | 18            |
| 3    | 82  | F   | IBUPROFEN | Cort              | 100 | x                        | 7               | 1                 | 6              | NA             | NA             | NA             | Sepsis/Septic shock/ARDS/Exitus Interstitial pneumonia | NA           | 16            |
| 4    | 6   | F   | NIMESULID | Cort              | 100 | 4                         | 1               | 4                 | NA             | 32             | 34             | 18             | Sepsis/pancreatitis | 18            | 20            |
| 5    | 51  | F   | CEPHALOSPORIN | Cort, CsA      | 70  | 2                         | 4               | 4                 | 4              | 20             | 22             | 24             | 20           | 9             |
| 6    | 55  | M   | ALLOPURINOL | Cort, CsA         | 80  | x                        | 5               | 2                 | 6              | 6              | 22             | 22             | 24           | 24            |
| 7    | 65  | M   | CEPHALOSPORIN | Cort, CsA       | 75  | 4                         | 1               | 5                 | 5              | 18             | 20             | 20           | 20           | 9             |
| 8    | 2   | F   | AMOXICILLIN/CLAVULANICACID | Cort, CsA | 70  | 1                         | 4               | 5                 | 4              | 18             | 21             | 21           | 18           | 12            |
| 9    | 24  | M   | DICLOFENAC | Cort, CsA         | 70  | x                        | 3               | 1                 | 4              | 4              | 25             | 28             | 18           | 18            |
| 10   | 38  | M   | THIOCOLOCHELICONE | Cort, CsA | 80  | x                        | 5               | 2                 | 6              | 6              | 26             | 29             | 12           | 12            |
| 11   | 6   | F   | KETO PROFEN | Cort              | 75  | 4                         | 1               | 3                 | 5              | 20             | 24             | 24           | 8             |
| 12   | 5   | M   | AMOXICILLIN | Cort              | 60  | 3                         | 1               | 4                 | 4              | 16             | 21             | Sepsis         | 12            | 8             |

Time to response in cases 3 and 4 could not be determined because BSA = 100.

BSA, body surface area; SCORETEN, score of toxic epidermal necrolysis; ARDS, acute respiratory distress syndrome; Cort, corticosteroids; CsA, cyclosporine A; NA, not applicable.
a Nikolsky’s negative sign, and time to remission from protocol start (complete reepithelization) were, respectively, 4.9 and 22 days; the average hospital stay at our unit was 24.8 days. Four patients developed severe complications; 1 of these patients died (mortality rate 8.3%). No complications directly linked to the protocol therapeutic measures were observed. Figures 3–5 show case number 4 and 7 at time of admission at our unit, and at time of remission. After discharge, patients were scheduled for regular follow-up once every 15 days for the first month, and then once every 3–4 months. The average follow-up time was 16.2 months (min 8 – max 24).

**DISCUSSION**

The management of SJS and TEN is full of controversy and debate. The first obstacle is the difficulty of making an accurate diagnosis. Further, the precise pathophysiological mechanisms remain unclear. Authors agree only as to the strategy of management in the early stages. Such strategy involves early diagnosis, elimination of a causative factor, immediate institution of treatment, and transfer of patients to a specialist department. A decreased number of complications have been observed in individuals treated systemically, compared with the group treated supportively. The methods of systemic treatment, however, require further studies to evaluate their efficacy. Evidence is even scarcer in children, as the bulk of the literature about management in SJS and TEN include only adults or adult series. Low numbers of pediatric patients and poor quality of the reports are responsible for a lack of standardization to classify and evaluate the prognosis and evolution of this group of patients.5

**Table 2. The Therapeutic Protocol Administered in Our Cohort of Patients**

| Therapeutic | Supportive |
|-------------|------------|
| Immunosuppressive | Metabolic |
| Cyclosporine A 250 mg/die | Parenteral nutrition |
| Plasmapheresis 7 cycles (every 2 d) | Enteral nutrition |
| Antibiotics | Hydromeladone |
| Daptomycin 4 mg/kg/die for 10 days | Intravenous |
| Topical | Dextrose 5 % solution and saline |
| Detersion with chlorhexidine gluconate | Neomycin |
| Isotonic saline | Erythematous skin |
| Blood proteins | Corticosteroids |
| Hydroelectrolytic | (denuded skin, after blister de-roofing) |
| Isotonic saline | IV, intravenous |
| Venilation | Pain control |
| Invasive | Oral morphine |
| Noninvasive | IV morphine |
| Pain control | Oral methadone |
| IV, intravenous | IV, intravenous |

**Fig. 1.** TEN (hematoxylin and eosin). Notice the characteristic subepidermal detachment with full-thickness epidermal necrosis.
Topical wound care management is also far from standardized, ranging from topical immunosuppressants to epithelial substitutes and skin allografts.10,11 A recent article by Abela et al12 proposed a comprehensive wound care algorithm based on wound stage. Although our approach is similar on apparently healthy and erythematous skin areas, our personal experience in managing intermediate-superficial burns led us to prefer the use of hydrofibers in treating TEN denuded skin lesions, with satisfactory results and no need to resort to more expensive solutions. Of course comparative studies between different treatment modalities are currently lacking and would be much needed.

Finally, even though the standard SCORTEN has been validated as a prognostic indicator of mortality and morbidity in patients with SJS and TEN,13 this has lacked clinical use in general and has only recently been assessed in children.14

We herein report our 10 years’ experience in treating severe TEN. Over the years we developed our own personal protocol (Table 2), which we believe correctly addresses every key pathological aspect of TEN. In particular, such protocol comprises: hydroelectrolytic systemic re-equilibration with isotonic saline solution and blood proteins repletion; metabolic re-equilibration by means of parenteral or enteral nutrition; respiratory support with invasive or noninvasive ventilation as needed; systemic immunomodulation by administration of high-dose CsA; pathological immunogenic factors removal by plasmapheresis; prophylaxis and treatment of systemic infections by administration of daptomycin (6mg/kg/die), which based on hemoculture can be associated to other antimicrobials; control of the wound bed using a single advanced dressing made of hydrofibers with Ag ions controlled release (Aquacell AG) over denuded skin and emollients and corticosteroids over apparently healthy and erythematous skin; and pain control with intravenous morphine, later substituted with oral methadone.

In our case series, the suspected drug already withdrawn, prednisone or a combination of prednisone and cyclosporine A, did not prove efficient enough to induce remission of the clinical condition (Figs. 3, 5A), and given the deteriorating evolution despite the undergoing therapy we undertook the decision to introduce plasmapheresis associated to high-dose intravenous CsA. This, together with the other supportive and topical therapies, produced a very precocious improvement in both systemic and cutaneous...
signs (average time to response: 4.9 days), and effectively led to circulatory and respiratory stabilization with consequent patients discharge from the intensive care unit (average time to supportive measures tapering: 9.2 days). Skin lesion progression was halted, with no more sloughing increase and negative Nikolsky’s sign, and they slowly started to heal, with complete reepithelization in 22 days average after protocol start (Table 2 and Figs. 4, 5B). In Figure 2, notice the 2 key points of our therapeutic flowchart. Firstly, after institution of hospitalization, first-line therapy, topical wound care and supportive measures (liquids, nutrition, and pain), the decision to proceed with transfer to intensive care unit and protocol start was dependent on a series of parameters. In particular at least 2 parameters had to be present among: clinical evidence of disease progression/extension, a positive Nikolsky’s sign, a BSA >60, and a SCORTEN ≥3. The accompanying anti-Gram-positive prophylaxis was mandatory given the need for a central access to begin plasmapheresis. Only in cases of fever development, hemocultures were carried out and additional specific antibiotics administered. The second key point was when the Nikolsky’s sign turned negative, an indication of disease progression halt. This resulted in the decision to taper supportive measures and antibiotics, and ultimately to transfer patients to the sub-intensive care unit. Topical wound care continued until complete reepithelization.

In our case series, 1 patient died of septic shock and acute respiratory distress syndrome. This patient had the highest SCORTEN of our cohort, reflecting her elderly age, her several comorbidities (among which a
malignancy) and the BSA affected extension (100%). Of note, as reasonably expected, average time to remission and hospital stay in our cohort seemed to correlate with both the SCORTEN and the total BSA values. More interestingly, given that the average SCORTEN was 4.3, the predicted mortality rate would have been 58.3%, as per SCORTEN definition; however, in our case series the mortality rate was 8.3% (1 out of 12), significantly lower.

Although our calculations are based on a limited number of patients, we believe these data indicate the efficacy and safety of our therapeutic protocol, in both adults and children.

CsA and plasmapheresis have been individually reported in limited cases as successful second-line therapies for TEN.\(^3,7-9,15,16\) Plasmapheresis has been reported as efficacious in association to methylprednisolone and intravenous immunoglobulins in a pediatric case.\(^15\) However, to the best of our knowledge, there are no reported experiences in the literature regarding the association of CsA and plasmapheresis. What’s more, there are only 6 reported cases of children with TEN treated with plasmapheresis in the international literature.\(^3,15,16\) Among these, none employs the SCORTEN system to standardize clinical severity and prognosis.

Importantly, our choice to opt for such an uncommon therapy in our cohort came from an elevated SCORTEN value (average 4.3; range 3–7), which reflected in a unified manner the dramatic systemic and cutaneous conditions, thus predicting an unfavorable response to traditional therapies and an elevated mortality rate (58.3%). As a matter of fact we believe that correct standardization, by means of even criteria to classify, evaluate, and manage TEN, can result in better therapeutic guidelines for the care of patients affected by this condition. The decision to employ second- or third-line therapies such as the association of plasmapheresis and intravenous CsA, as effective as they may be, should always be taken on the basis of such rigorous and standardized clinical data. We also believe supportive care in terms of hydroelectrolytic and metabolic equilibration, together with specific topical therapy, do not merely constitute complementary measures, but actively and substantially concur to the clinical improvement.

Surely, further studies on larger cohorts of patients are warranted to confirm the efficacy and safety of our specific therapeutic protocol in TEN, in both adult and pediatric patients.

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PATIENT CONSENT

Patients, parents, or guardians provided written consent for the use of the patients’ images.

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