Suprapharmacologic doses of intravenous dexamethasone followed by cyclosporine in the treatment of toxic epidermal necrolysis

Sir,

Toxic epidermal necrolysis (TEN) is a widespread, life-

threatening, mucocutaneous disease usually due to drugs, but vaccinations, malignancy, and graft versus host disease (GVHD) have also been implicated.[1] It may also be idiopathic in which it is not possible to identify any cause. TEN represents epidermal detachment involving more than 30%. The pathogenesis involves cytotoxic-mediated immune reaction targeted at the destruction of keratinocytes expressing foreign antigens.[2] It has been shown that in the fluid contained in the bullae of patients with TEN, T-lymphocytes predominate in the initial phases, while subsequently the cells of the monocyte-macrophagic line prevail and probably contribute to the progression of the necrosis through TNF production.[3] Epidermal keratinocytes express large amounts of Fas ligand (CD95L), and interaction between these and Fas (CD95) on the effector cells are directly in epidermal necrolysis.[4] The role of genetic factors in the pathogenesis of TEN remains to be clarified. The onset of TEN usually occurs 7-21 days after the beginning of medical treatment, and the rare cases of relapse initiate within 48 hrs of taking the drug, thus suggesting the existence of an immunological memory. The various modalities of treatment include steroids, cyclosporine, intravenous immunoglobulin, thalidomide, cyclophosphamide, pentoxifylline, N acetyl cysteine, and plasmapherisis.[5] The use of corticosteroids is a much-debated question.

Some reports have described a dramatic improvement in patients with TEN treated with corticosteroids.[6,7] Steroids can be given intravenously or as suprapharmacologic doses intravenously. Short-term use of suprapharmacologic intravenous doses of dexamethasone, at an early stage of the disease, may contribute to a reduced mortality rate in SJS/TEN without increasing the healing time.[8] Use of steroids modifies the cell-mediated immune response in the pathogenesis of TEN. Cyclosporin inhibits the principal cellular populations involved in the pathogenesis of TEN (activated T-lymphocytes, macrophages, keratinocytes), interferes with the metabolism of TNF, and possesses an anti-apoptosis property that causes the death of keratinocytes in TEN.[9] We report three patients of TEN who were treated with suprapharmacologic doses of intravenous dexamethasone followed by cyclosporine.

Case 1: A 40-year-old male presented with TEN after therapy with phenytoin for epilepsy since 1 month. The diagnosis was confirmed by histopathology with frozen sections and H and E-stained sections. He was nursed in isolation and was administered intravenous with 100mg of dexamethasone in 5% glucose for 4 days till no new lesions appeared. Cyclosporine was started on day 5 at the dose of 2 mg/kg weight till the patient's general condition improved, and then tapered at the dose of 50mg every 3rd day, and stopped after 2 weeks when the patient had complete remission and re-epithelization of skin lesions.

Case 2: A 55-year-old female presented with TEN after carbamazepine. After confirmation of the diagnosis by frozen section, she was administered 100mg of dexamethasone in 5% glucose for 2 days, when no new lesions appeared. Cyclosporine was administered on day 3 in the same regime as in Case 1.

Case 3: A 22-year-old female presented with TEN after ciprofloxacin. After confirming the diagnosis on frozen sections and H and E-stained sections of skin biopsy, she was administered suprapharmacologic doses of intravenous dexamethasone in the form of 100mg of dexamethasone in 5% glucose for 2 days, when no new lesions appeared. Cyclosporine was administered on day 3 in the same regime as in Case 1.

All three patients were taken in succession and treated in isolation in a tertiary care hospital, where the clinical diagnosis of TEN was confirmed by frozen and H and E sections of skin biopsy. Once the diagnosis of TEN was confirmed by frozen sections, treatment was started on the same day, even when new lesions were appearing. In all patients, electrolytes and input-output chart were monitored. In addition, supportive treatment like antibiotics, fluid replacement, daily dressing, and nutritional support was given.

The treatment of TEN in a burn unit or in isolation has considerably improved patients' prognosis and survival. Appropriate care and nursing, such as protection of the cutaneous and mucosal surfaces involved, monitoring of the electrolytic balance, fluid replacement, nutritional support, and the prevention and treatment of infection, are the mainstays of treatment. Steroids help to arrest the disease progress by modifying the cell-mediated immune response and preventing the progression of the disease when given within 72 hours.[6] By administering steroids early and for a short duration, the side-effects like gastrointestinal bleeding, delayed wound healing, and increased risk of infection can be prevented. Since cyclosporine has anti-apoptosis property and decreases the time taken for complete re-epithelization, it helps arrest further progression of the disease.[10,11]

Although steroids could have been continued till the person recovered, the risk of septicemia and other associated complications due to steroids is reported to increase mortality. Since the role of steroids is in the early phase and

does not have any effect after 72 hrs, the steroids given early and for a short duration may help improve the prognosis. Since cyclosporine is reported to be effective in TEN by interrupting the disease progression and decreasing the time taken for complete re-epithelization, we feel that the combination of initial high dose of steroid and subsequent cyclosporine will be a safe alternative to treat this condition associated with high mortality.

Hence, to reduce mortality in toxic epidermal necrolysis, suprapharmacologic doses of intravenous corticosteriods at an early stage of the disease, followed by cyclosporine, appear to be a rational option to influence the immune system, which leads to apoptosis and necrolysis, and results in early recovery.

Suprapharmacologic doses of intravenous dexamethasone, given at an early stage of the disease, contribute to a reduced mortality rate and modify the cell-mediated immune response in the pathogenesis of TEN. Cyclosporin possesses an anti-apoptosis property that causes the death of keratinocytes in TEN. By using a combination of both, the immune response is modified and the side-effects of steroids are minimized, and the disease progression is interrupted by cyclosporine. This combination may be a safe alternative in the management of TEN.

Reena Rai, C. R. Srinivas
Department of Dermatology, PSG Hospitals, Coimbatore, India

Address for correspondence: Dr. C. R. Srinivas, Department of Dermatology, PSG Hospitals, Peelamedu, Coimbatore - 641 004, India.
E-mail: srini_cr_1955@yahoo.com

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