

Severe cutaneous adverse reactions: an evidence based approach

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Background: Severe cutaneous adverse reactions (SCAR), comprising mainly Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), although rare, constitute a severe entity with life-threatening consequences. The aetiology is multifactorial but drugs have been implicated in the majority of cases. Depending on the severity of the reaction, it has a wide spectrum of clinical presentations and there is still confusion regarding its classification. Reliable information on the incidence of drug reactions has been difficult to obtain due to lack of standardised systems for data collection and reporting. The situation is poorer in developing countries where specific epidemiological studies have not been published, largely due to the lack of a reporting system and awareness of drug reaction patterns among medical professionals and patients alike.

Method: We have reviewed available literature regarding SJS and TEN, and the hospital admission records of such patients at Tribhuvan University teaching hospital. A comparative study was done.

Results: Drugs, mainly sulfonamides and anticonvulsants have been the aetiological factors in majority of the cases, and the presentation in the patients have ranged from mild to fatal reactions. In the TU teaching hospital, in almost all cases, steroids have been used in the management.

Conclusion: Though a self-limiting disorder, patients with SCAR have a multisystem involvement, and a multi-disciplinary approach is necessary for its management. The need for intensive supportive care and the controversial role of steroids makes its management even more challenging. Thus, it is essential to develop a protocol/guidelines for the management of these disorders appropriate to our context.

Introduction

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug, which includes reactions due to overdose, predictable side-effects and unanticipated adverse manifestations.¹ It has also been defined as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.'² The criteria for assessment of potential drug reactions include

recurrence on challenge; existence of a pharmacological basis for the reactions; the occurrence of immediate acute or local reactions with a new route of administration, or of repeated rare reactions; and the presence of immunological abnormalities.^{3,4}

With atleast 90 million courses of drug treatment given yearly in the USA, the incidence of adverse drug reactions varies from 6 % to 30 %.^{5,6} The reported incidence of EM (Erythema Multiforme), SJS and TEN varies widely among different countries. A study from France estimated the incidence of TEN at 1.2 cases per million per year.⁷ Another US study estimated the incidence of EM, SJS and TEN at 1.8 cases per million person years for patients between 20

and 64 years.⁸ Various population studies in the west have reported the incidence rate of TEN between 0.4 to 1.2 cases per million annually.⁹ Reliable information on the incidence of drug reactions has been difficult to obtain due to lack of standardised systems for data collection and reporting. The situation is poorer in developing countries where specific epidemiological studies have not been published, largely due to the lack of a reporting system and awareness of drug reaction patterns among medical professionals and patients alike. It is possible that the frequency of such reactions in these countries could be much higher considering the fact that the main aetiological agent, i.e, drugs such as antibiotics, anticonvulsants and non-steroidal anti-inflammatory drugs (NSAIDs) are easily available over the counter.¹⁰

Drug reactions may arise as a result of non-immunological mechanisms, such as those caused by non-immune mediated degranulation of mast cells and basophils or immunological allergy directed against the drug itself, a reactive metabolite or some contaminant of the drug. About 80% of drug reactions are predictable non-immunological reactions, which includes overdose, side-effects, cumulation, drug interactions, metabolic alterations, etc.¹ The more serious reactions, also known as SCAR, comprises EM, SJS and TEN.

Bateman in 1814, described the target lesion. Bazin first recognised mucosal involvement and cutaneous symptoms attributed to drugs in 1862. In 1866, Ferdinand Von Hebra described Erythema exudativum multiforme and recognised these disorders as a single entity. Stevens and Johnson in 1922 first described the SJS and Lyell A in 1956 described TEN, also called 'Lyell's syndrome'.^{11,12} TEN represents the most severe form among all Types of SCAR.

Cutaneous reactions to drugs may present with varied clinical patterns of eruption. Although certain drugs are commonly associated with a specific reaction, most drugs are capable of causing several different Types of eruptions. The most frequent Type of all cutaneous reactions to drugs are the exanthematic (erythematous maculo-papular) eruptions. Other Types of clinical presentations include purpura, annular erythema, pityriasis-rosea like eruption, psoriasiform eruptions, exfoliative dermatitis, anaphylaxis, urticaria, serum sickness, drug hypersensitivity syndrome, fixed eruptions, lichenoid eruptions, photosensitivity, pigmentation reactions, acneiform and pustular eruptions, eczematous eruptions, bullous eruptions, vasculitis, lupus erythematous-like syndrome, erythema nodosum, anticonvulsant hypersensitivity syndrome, hair changes like alopecia and hirsutism and various patterns of nail changes and onycholysis.¹ It is the rare but serious reactions like SJS and TEN which contribute to significant mortality. SJS involves an illness usually of sudden onset, associated with marked constitutional symptoms of high fever, malaise, myalgia, arthralgia with skin blisters and erosions covering

less than 10 % of the body surface area. Significant involvement of the mucous membranes is present including the eyes, ano-genital mucosae and mucosa of the respiratory tract.¹³ TEN is characterised by typical sheet-like erosions of the skin involving more than 30% of the body surface area with widespread purpuric macules or flat atypical target lesions and severe involvement of the conjunctival, corneal, irideal, buccal, labial and genital mucous membranes.¹⁴⁻¹⁶

Objectives

- To determine the clinico-epidemiological pattern of patients with SCAR, admitted to the TU Teaching Hospital.
- To analyse the possible aetiology and the modalities of management in these patients.

Methodology

All available literature and texts regarding SJS and TEN were reviewed along with a review of the hospital admission records of patients admitted under various specialities of TU teaching hospital with these illnesses, between b.s 2056 and 2060, for a period of 4 yrs. The data regarding the clinical Types, age and sex distribution, the possible causes implicated and the various modalities of management were analysed and a comparative evaluation was done.

Results

A total of 33 patients (male-11: female-22) with varying severity of SCAR had been admitted to the departments of dermatology, internal medicine and ophthalmology in a period of 4 years. The patients were in the age range of 4-65 years (mean 34.5 years). Among them 6 had EM, 25 had SJS and 2 had TEN (*Fig. 1*).

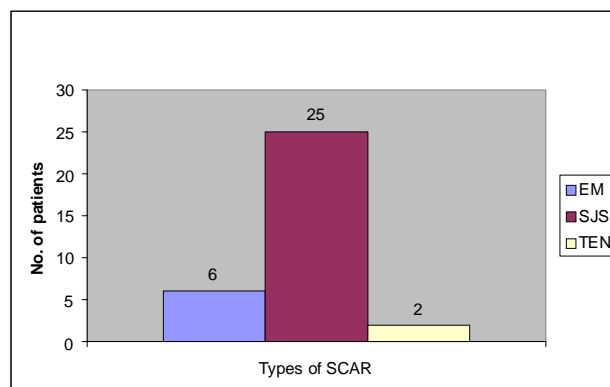


Fig. 1. Clinical types of SCAR

Severe cutaneous adverse reactions

The duration of their hospital stay ranged from 4-19 days (mean-11.5 days). Drugs were the cause in most of the patients, usually with history of antibiotic intake prior to the onset of the eruption. Reactions in 15 patients appeared to be due to antibiotics (sulfonamides, penicillins, quinolones), in 10 patients due to anticonvulsants (carbamazepine-5; phenytoin-4; phenobarbitone-1), in 4 patients due to NSAIDs, and in 4 patients no possible cause could be ascertained (Fig. 2).

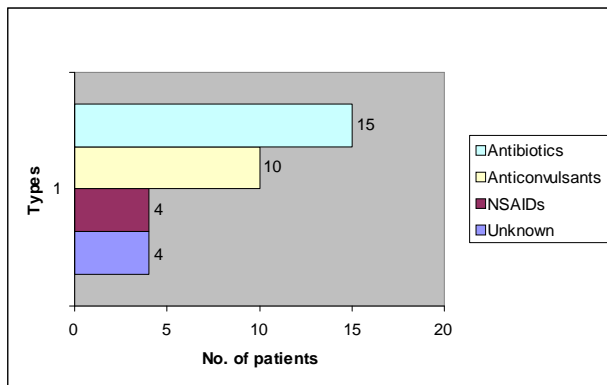


Fig. 2. Types of SCAR

All patients were treated with antibiotics and 29 of these patients had received steroids.

Discussion

The clinical picture of the SCAR spectrum appears to be a reaction pattern to many different triggering factors having an immunological basis, but the exact pathogenesis still remains largely unknown. Immune complexes have been demonstrated both in the skin and circulation and antibodies against epithelial cells and desmosomal plaque proteins desmoplakin I and II have been demonstrated in patients with EM.¹⁷⁻¹⁹ Numerous evidence suggests the important role of T cells in the pathogenesis of SCAR, and the cytotoxic lymphocyte-mediated immune reaction (CTL) aimed at the destruction of the keratinocytes expressing foreign antigens seems to be the widely accepted view.¹⁰ More recently it has been discovered that Fas-Fas ligand interactions may be directly responsible for apoptotic death of keratinocytes in TEN patients. Activated lymphocytes might induce apoptosis via an interaction between Fas antigen (CD 95), expressed by keratinocytes after exposure to IFN-gamma, and its ligand Fas-ligand (Fas L), expressed on the surface of and secreted by lymphocytes.²⁰

Drugs have been implicated as the possible aetiology in majority of the cases of SCAR, with 80-85 % of cases of TEN and more than 50 % of cases of SJS. A wide range of drugs have been suspected to be causal, but the most frequently implicated are sulfa drugs (co-trimoxazole

and other sulfonamides), anticonvulsants (phenytoin, carbamazepine, phenobarbital, valproic acid), NSAIDs (butazone, oxicam derivatives), allopurinol, anti-tubercular drugs (thiacetazone, isoniazid) and antibiotics (penicillins, quinolones).²¹ Immunisation with DPT, measles, poliomyelitis and influenza vaccines have been recorded as a cause of TEN.^{22,23} The latter has also been described with graft versus host disease.²⁴ Infections with *Mycoplasma* and *Klebsiella pneumoniae* have also been attributed as a cause of SJS and TEN. Among SCAR patients admitted to the TU teaching hospital, drugs were the cause in majority, usually with history of antibiotic intake prior to the onset of the eruption. The antibiotics commonly implicated were sulfonamides, penicillins and quinolones). In other patients, anticonvulsants (carbamazepine, phenytoin, phenobarbitone) and NSAIDs appeared to be the cause while in some no possible cause could be ascertained.

Severe cutaneous adverse reactions traditionally comprise EM, SJS and TEN. EM involves macular, papular or urticarial lesions, and the classical 'target' or iris lesions, distributed preferentially over the distal extremities. Lesions may involve the palms or trunk as well as the oral and genital mucosa with erosions. EM is most often related to Herpes simplex virus infections and occasionally to drugs. EM major usually effects younger males, frequently recurs, and has less fever and milder mucosal lesions. SJS involves skin blisters and erosions covering less than 10 % of the body surface area. TEN is characterised by detachment of the epidermis in typical sheet-like erosions involving more than 30 % of the body surface area and patients having features of both the groups who cannot be classified into either group comprise the SJS-TEN overlap syndrome. Significant differences exist between countries in the classification of SCAR, and seeing the need for precise definitions, the term 'acute disseminated epidermal necrosis (ADEN)' has been proposed. ADEN Type 1 corresponds to SJS, Type 2 to transitional SJS-TEN with epidermal detachment between 10-29 % and Type 3 to full-blown TEN.²⁵ It has also been advocated by Lyell that the term 'exanthematic necrolysis' should replace TEN.²⁶

Withdrawal of the potential causative drug/drugs should be the initial and immediate step in the management of patients with SCAR. They are an acute emergency and are life threatening if not treated promptly. Due to its unclear pathophysiology, rapid and intensive supportive care are essential for a favourable outcome.¹⁰ This involves environmental temperature control, fluid and electrolyte balance and the use of broad spectrum antibiotics since patients are at an increased risk of death due to hypothermia, dehydration, electrolyte disturbances and septicemia. Numerous reports have demonstrated a highly improved prognosis when TEN patients were treated through a multidisciplinary management in a burn center.²⁷⁻³⁰ It is now

standard treatment to admit TEN patients to a burn unit, whenever possible. If not available, then patients should be treated in an intensive care unit with reverse-isolation nursing techniques. All patients admitted to the TU teaching hospital were treated with antibiotics and 29 of these patients had received steroids. The role of corticosteroids in the management of SCAR remains controversial. Many recent studies have described prolonged wound healing and higher rate of mortality and morbidity associated with the use of corticosteroids.³¹ Cases of TEN have occurred in patients already on high doses of steroids for other illnesses, suggesting no role of steroids in preventing TEN.³² In a SCAR study, corticosteroids appeared to be an important risk factor for TEN, suggesting that epidemiologically, corticosteroids behave just as do other responsible drugs.³³ Many authorities, therefore, no longer routinely recommend corticosteroid therapy for patients with TEN. Infact, in the first international symposium on EM and Lyell's syndrome (TEN) in Creteil, France in 1985, attended by most of the world's authorities on this disease including Lyell himself, it was unanimously concluded that corticosteroids were of no particular value in the management of TEN and they condemned its use once the disease has progressed to more than 20% body surface area.³⁴ However, many authorities all over the world still use corticosteroids for the management of SJS/TEN in the early course of the disease. Besides steroids and supportive care, many other therapies have been attempted in recent times to treat TEN patients. Immunosuppressants including cyclosporine^{35,36} and cyclophosphamide^{37,38} have been claimed to prevent progression of disease in a small number of patients. However, it must be remembered that these treatments have the potential to promote infection, the main cause of death in TEN. Infusions of anti-tumor necrosis factor- α and anti-Interleukin-2 monoclonal antibodies have been used in patients with graft vs host disease related TEN. Use of recombinant granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor and hyperbaric oxygen has been reported to enhance epidermal regrowth.¹⁰ Plasmapheresis has also been used to remove the offending drug or its metabolites. Unfortunately, the efficacies of these treatments have not been tested in larger cohorts and are thus not available for universal use.¹⁰ Most recently, naturally occurring anti-Fas immunoglobulin has been used intravenously (0.2-0.75 gm/kg/day) as specific therapy to treat patients with TEN. Naturally occurring immunoglobulin in intravenous immunoglobulin preparations, which is pooled from plasma of healthy donors, may have little or no adverse effect compared to systemic corticosteroids or other immunosuppressants and it is hoped that this therapy should have tremendous potential to improve the outcome of TEN patients in the future.³⁹

Conclusion

Major developments have been made in recent years in the management of SCAR and the morbidity and mortality of patients have decreased significantly. Care of patients in a burn center or a suitable ICU involving a multi-disciplinary approach, focussing the therapeutic goal towards promotion of wound healing, aggressive correction of fluid, electrolyte and protein balance, provision of pulmonary and eye care and prevention of sepsis is essential to achieve a favourable outcome. The controversy of corticosteroid use remain but the general consensus is that steroids may be most beneficial, if the body surface area involvement is less than or equal to 20%, if started very early in the course of illness (within the first 24-48 hours), given at a relatively high dose (equivalent to 1-2 mg per kg body weight of oral prednisolone or intravenous methylprednisolone), for a brief period (not more than 3-5 days) and stopped or tapered off rapidly.^{40, 41}

In developing nations, the easy availability of potential drugs over the counter significantly increases the risk of SCAR, while the lack of standardised reporting systems and lack of awareness of SCAR contribute to the difficulty in research and formulating appropriate guidelines regarding management. Socio-economic factors and lack of or inaccessibility to healthcare facilities may also be responsible for hurdles in seeking healthcare. It is, therefore, necessary to develop guidelines/protocol for the identification, data collection and management of SCAR, appropriate to our context.

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Severe cutaneous adverse reactions

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