Case Report

Sulfasalazine Associated Toxic Epidermal Necrolysis (TEN): A Case Series

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ABSTRACT

The important cases observed at Pharmacovigilance Programme of India (PvPI) were disseminated to all its stakeholders and public at regular basis. In this article we discuss five such cases reported to the National Coordination Centre, Pharmacovigilance Programme of India (NCC-PvPI) from the ADR Monitoring Centre's (AMCs) across the country. Toxic Epidermal Necrolysis (TEN) is also known as Lyell's syndrome is uncommon but potentially life threatening Severe Cutaneous Adverse Reaction (SCAR) with widespread epidermal detachment and mucosal erosions. Sulfasalazine is the most common drug prescribed for many diseases, which causes many potential adverse reactions. TEN is one such adverse reaction and it may be fatal if not treated promptly. Early recognition and discontinuation of responsible drug remains primary treatment of management in drug induced TEN in our cases. The immediate treatment depends upon the severity of reaction. It is very much essential that patients should be educated regarding the medication so as to avoid future complications associated with drug use which can be achieved by creating awareness about such cases among all healthcare professionals.

Key words: Sulfasalazine, Toxic epidermal necrolysis, Pharmacovigilance programme of India, Disease-modifying antirheumatic drug.

INTRODUCTION

Pharmacovigilance Programme of India (PvPI) initiated at Indian Pharmacopoeia Commission (IPC) has established regional Adverse Drug Reaction Monitoring Centers (AMCs) all over India towards patient safety by adopting spontaneous reporting of adverse drug reactions. Spontaneous Adverse Drug Reactions (ADRs) monitoring system is highly encouraged in India with increase in numbers of AMCs by National Coordination Centre-Pharmacovigilance Programme of India (NCC-PvPI). The information about TEN associated with Disease-Modifying Antirheumatic Drug (DMARDs) sulfasalazine from the data collected by NCC-PvPI from the AMCs and stakeholders is reported.

TEN is uncommon but potentially life threatening Severe Cutaneous Adverse Reaction (SCAR) with widespread epidermal detachment and mucosal erosions.[1] Sulfasalazine is the most common drug prescribed for conditions like crohn's disease, ulcerative colitis, rheumatoid arthritis. Sulfasalazine causes many potential adverse reactions like headache, nausea, anorexia, diarrhea, vomiting, gastric distress, photosensitivity in more than 10% of the patient, Stevens Johnson Syndrome, pruritis, occur in less than 3% and Sulfasalazine induced TEN is infrequent. TEN may be prove fatal if not treated promptly.[2] The average reported mortality rate of TEN is 25-35%. Herewith we are reporting a series of cases of sulfasalazine induced TEN necessitating hospitalization.

METHOD

All suspected adverse events related to Sulfasalazine which were reported to NCC-PvPI during the period from December 2011 to December 2016 were assessed and the ADRs which were serious and not listed in the Indian prescribing information were identified for further actions. TEN reports

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which were documented with causality using WHO probability scale were identified and were analyzed in detail.

RESULTS

Case Presentation

Case One

A 19- year- old female patient presented with history of bollus lesion on back of her body and spread to the entire body with hyperpigmented macules all over the body including oral and genital ulceration. The past medical history of the patient shows that she was started with sulfasalazine 1000 mg, paracetamol 650 mg twice a day which she took for 64 days for treating sacroilitis. After two months of treatment she was admitted in hospital and was diagnosed with TEN and she was given medical treatment and was recovering after cessating the Sulfasalazine.

Case Two

A 22- year- old male patient was presented with history of skin lesions and reveals that he was suffering from Seronegative Arthritis and was prescribed with Sulfasalazine 1 gm twice a day and after 3 weeks of use of Sulfasalazine he was diagnosed with TEN. The patient was admitted to hospital for 10 days and recovered after withdrawing the drug.

Case Three

A 26- year- old female patient was presented with skin lesions after taking Sufasalazine 500 mg and Cefpodoxime 200 mg twice a day for Reactive Arthritis. Concomitant medication used were rabeprazole (20 mg), indomethacin (25 mg), prednisolone (5 mg) and levofloxacin (750 mg) and patient experienced TEN after receiving medication for 11 days, and was recovering after stopping the suspected drug.

Case Four

A 34- year- old female patient was presented with rash, throat pain since one day, fever and eye pain with redness since three days. The patient past history revealed that she had joint pain since 8 months and was diagnosed with rheumatoid arthritis. The patient was prescribed with sulfasalazine 500 mg, paracetamol 650 mg and aceclofenac 100 mg BID which she took for 16 days and injection methylprednisolone IM for 20 days. She gives a history of no improvement and developed few fluid filled lesions in oral cavity, which ruptured spontaneously. She gives a history of pain and burning sensation while swallowing. Cutaneous examination revealed multiple erythematous macules and finally diagnosed with TEN. The patient showed good response to treatment and lesions, erosions decreased within span of 20 days. The patient was discharged with complete recovery after 26 days.

Case Five

A 40- year- old female patient was presented to hospital with past history revealed that she was treated with sulfasalazine 500 mg for Rheumatoid Arthritis since one year. She developed lesion in mouth which was painful and after few days she noticed red small lesions over her face and progressed to neck, arm and abdomen. The lesion then became scaly and led to erosion with oozing fluid. Patient was gradually deteriorated and condition was unstable and finally led to death due to multiple organ failure which was suspected as TEN.

DISCUSSION

Toxic epidermal necrolysis is a well-known side effect of drugs commonly used in day to day clinical practice.[3] Various studies have shown that sulfamethoxazole/trimethoprim (SMX/TMP), sulfonamides (sulfasalazine, sulfadoxine, sulfadiazine, sulfafurazole), allopurinol, phenytoin, carbamazepine, phenobarbital and Nonsteroidal anti - inflammatory drug (NSAID's) of the oxicam-type (tenoxicam, meloxicam, piroxicam) are most common drugs implicated in the causation of TEN.[1,4]

All the cases found were in adults ranging between nineteen to forty years. The cases revealed probability in 3 cases out of five and others 2 cases showed possible, which one lead to death of patient. As all the reports was very severe in nature required hospitalization for more than one week. Identifying the suspected drug is also essential to manage the patient's condition. Early recognition and discontinuation of responsible medication remains primary treatment of management in drug induced TEN. The immediate treatment necessary depends upon the severity of reaction. Emergency care, maintaining fluid and electrolyte homeostasis, mitigating temperature loss, providing adequate analgesia, preventing secondary infection. Drugs like corticosteroids, antihistamines, antibiotics, antiseptic, anti-coagulant and analgesics can be used.[1,4,5,6] Steroids have been accepted as a treatment option as they suppress the necrolytic process in the skin and internal organs. A study shows that early treatment with corticosteroids reduced morbidity and improved survival in patients of TEN. Literature search has also shown that corticosteroids may prove beneficial in cases of TEN due to their antiapoptotic effect on keratinocytes.[7]

Table 1: Causality Assessment of reported cases.

S. No.	Age (In Yrs.)	Gender	Dose received by the patients	Outcome Of reaction	Duration of use of suspected drug prior to the reaction	Causality Assessment of case reports (WHO-Probability Scale)
1	19	Female	1000 mg/Twice a day	Recovering	64 days	Possible
2	22	Male	1000 mg/Twice a day	Recovered	21 days	Probable
3	26	Female	500mg/ Twice a day	Recovering	7 days	Probable
4	34	Female	500mg/ Twice a day	Recovering	20 days	Probable
5	40	Female	500 mg/ Twice a day	fatal	11 days	Possible

Our cases showed recovering condition on cessation of the offending agent. Among five cases mentioned four patients were female which emphasises more focus to be made on female gender by HCPs during prescribing of Sufasalazine. Also concomitant medications need to be monitored as three of the cases are administered along with NSAIDs which can also cause same reaction, hence chances of possibility to aggravate the reaction. It is very essential that patients should be informed regarding the offending agent so as to avoid future complication associated with drug use and to avoid such similar conditions.

CONCLUSION

Sulfasalazine associated TEN is a rare but life threatening adverse event. These cases shows that all the patients receiving sulfasalazine should be closely monitored by HCPs, throughout the course of treatment, especially for any inception in adverse dermatological issues based on clinical manifestations, so as to avoid further complications and for prompt management. HCPs are also encouraged to report such events to nearest AMCs if they observe in their hospital settings.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

ABBREVIATIONS USED

HCPs: Healthcare Professionals; **PvPI:** Pharmacovigilance Programme of India; **AMC:** ADR Monitoring Centre; **ADR:** Adverse Drug Reaction; **TEN:** Toxic Epidermal Necrolysis; **SCAR:** Severe Cutaneous Adverse Reaction; **IPC:** Indian Pharmacopoeia Commission; **DMARDs:** DiseaseModifying Antirheumatic Drugs; **NSAID:** Nonsteroidal anti - inflammatory drug; **SMX/TMP:** sulfamethoxazole/ trimethoprim.

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