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RESEARCH ARTICLE

CLINICAL PATTERN AND CAUSATIVE AGENTS IN CUTANEOUS ADVERSE DRUG REACTIONS: AN EVIDENCE BASED APPROACH

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ABSTRACT

Aim: Cutaneous adverse drug reactions (CADRs) are the commonest presentations of drug induced reactions. The present study was conducted to study the clinical pattern, causative agents and magnitude of CADRs.

Materials and Methods: A prospective hospital based study was carried out by the department of pharmacology and dermatology in SMHS hospital. The study was conducted from june 2013 to june 2016 on admitted patients of CADRs. After obtaining an informed consent, these reactions were reported on a structured questionnaire based on ADR monitoring form provided by the Central Drug Standard control Organization (CDSCO) Ministry of Health and Family Welfare, Government of India. The CADRs were analyzed for their pattern, causative agents, severity and prognosis. Causality assessment was done by using a validated ADR probability scale of Naranjo as well as WHO-Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment. The management protocols were analyzed for their clinical outcome through a proper follow up period.

Results: A total of 65 inpatients were identified as CADRs, 26% were males and 74% were females. Age group ranged from 2 – 65 years with average age of 37 years. 7 different types of CADRs were noted, most common being maculopapular drug eruption (25%), urticarias (18%), SJS(17%), TEN(14%), FDE (14%), anticonvulsant hypersensitivity syndrome(9%) and urticarial vasculitis (3%). TEN was seen in all females (100%) and in no male. Drugs implicated in causing these cutaneous reactions were identified as Phenytoin (24.6%), Fluoroquinolones (20%), Carbamazepine (15.3%), piroxicam i.m(15.3%), lamotrigine (9.2%), phenobarbitone(3%), sulfasalazine (3%), risedronate, cefixime, cefpodoxime, amoxcicillin, ayurvedic medicine and capecitabine all (1.5%). Despite higher reported mortality rates in SJS and TEN all patients survived with 2 patients surviving TEN suffered from long term ophthalmological sequelae of the disease.

Conclusion: Present study concludes that CADRs are common manifestations of various drug therapies ranging from simple nuisance rashes to rare life threatening diseases like SJS and TEN. North Indian ethnic population has great predisposition of CADRs due to aromatic antiepileptic drugs, fluroquinolones, oxicam NSAIDs, lamotrigine and other antibiotics. To ensure safe use of pharmaceutical agents and newer molecules/ biologicals post marketing voluntary reporting of severe, rare and unusual reactions remains inevitable.

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INTRODUCTION

In the present era of evidence based medicine there is a pressing need of efficient post marketing surveillance (pharmacovigilance) to optimize pharmacotherapy by maximizing therapeutic efficacy, while minimizing adverse events. Adverse Drug Reactions (ADRs) are an inevitable consequence of modern drug therapy. They are an important cause of iatrogenic illness in terms of morbidity and mortality. ADRs can cause serious harm to the patient as well as carrying medico legal and economic consequences. Cutaneous manifestations are among the most frequent adverse reactions to drugs. (Arndtka and Jick, 1976) Some CADRs are relatively mild and disappear when the drug is stopped or the dose is reduced, others are life threatening and last longer. According to certain multicentric trials acute cutaneous reactions to drugs affected 3% of hospital inpatients. Reactions usually occur a few days to 4- weeks after initiation of therapy. (Shinkai *et al*.,

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2012) It is also a matter of great concern that nowadays drugs are being used indiscriminately and there is an exceptional increase in the quantity of various drugs entering into the global market. Therefore, there is an increased susceptibility to develop different drug reactions. In addition, other risk factors which contribute for developing CADRs are extremes of age, female sex, previous history of ADRs, environmental factors, immune compromised and those on radiotherapy. In light of the above facts, a prospective hospital based study was conducted with an objective to assess the magnitude and burden of CADRs associated with the use of incriminated drugs in patients of our ethnic background. To determine the causality and severity of CADRs in patients admitted in dermatological IPD and to provide an approach to minimize their occurrence the management protocol would involve prompt identification and withdrawal of culprit drug(s) followed by vigorous supportive care. The drug therapy included systemic steroids in form of i.v dexamethasone or hydrocortisone on short term basis.

MATERIALS AND METHODS

The study was carried out by the Department of Pharmacology and Dermatology in SMHS Government Medical college Srinagar, India. A prospective study was conducted between june 2013 – june 2016 which included patients who were admitted to the hospital with a diagnosis of various patterns of CADRs. A wide variety of CADRs ranging from most common exanthamatous drug eruptions ("drug rashes" or "drug eruptions") to rare life threatening, Steven-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) were observed in the study. The study received an approval from Institution Ethical Committee.

Data collection and Drug Enquiry

After obtaining informed consent a structured questionnaire was used to interview the patients clinically diagnosed as CADRs with a definite antecedent drug history. The questionnaire included the contents based on suspected ADR reporting form provided by CDSCO, Ministry of Health and Family Welfare, Government of India. It was used to gather information on patients preceding hospitalization. The drug history included brand/generic name of drug(s) manufacturer, batch no, expiry date, timing of use, dose, indications, plasma concentration of drug if available for low therapeutic range drugs, previous exposure and previous ADR if any. For seriously ill patients and children to be interviewed patient medical record and family members provided the information. In addition, clinical examination and laboratory parameters were also recorded in questionnaire. Causality assessment was performed using a Naranjo scored algorithm (Naranjo *et al*., 1981) The method incorporates ten questions or criteria related to the ADR. every question is provided with a particular score based on the presence or absence of those criteria. Based on the scoring the probability that the adverse event was caused by the drug was classified as definite (score ≥9), probable (5-8), possible (1-4) or doubtful (≤0). Moreover, a highly dependable WHO-UMC system (http://www.WHO□UMC. org/graphics/24734.pdf) for case causality assessment has also been applied to reinforce the reliability of the study. The various causality categories based on assessment criteria are certain, probable/likely, possible, unlikely conditioned/ unclassified and unassessable /unclassifiable. The rationale for combining two tools is to overcome limitations associated with individual methods. In our study after the causality assessment is done the severity of ADRs is analysed using modified Hartwig and Siegel scale. In our study those patients with SJS/TEN were evaluated for severity and prognosis by using SCORTEN prognostic scoring system (Bastuji-Garin *et al*., 2000; Trent *et al*., 2004) that has been developed to correlate mortality with selected parameters. (Table 1)

Table I. SCORTEN: A Prognostic scoring system for patients with epidermal necrolysis

Prognostic factors	Points
Age >40 years	1
Presence of Malignancy/ Haematological malignancy	1
Epidermal Detachment >30%	1
Heart rate >120/min	1
Bicarbonate < 20mmol/L	1
Urea > 10mmol/L	1
Glycaemia >14mmol/L	1
SCORTEN	Probability of death (%)
0-1	3
2	12
3	35
4	58
≥5	90

RESULTS

A total of 65 patients were identified as CADRs. Among them 26% were males and 74% were females. Age group of subjects ranged from 2 to 65 years with the average being 37 years. Distribution of patients according to age and gender are given in (Table-2)

Table 2. Age and Gender distribution of the study subjects

Age group	Males	Females	n=65
0-10	1	Nil	1
11-20	2	12	14
21-30	2	16	18
31-40	2	8	10
41-50	3	4	7
51-60	5	7	12
61 and above	2	1	3

The study revealed that females are more prone to develop CADRs than males and the age group with high frequency of CADRs in females is 11-30 years. The various patterns of CADRs which were noticed during the study period were exanthematous drug eruption (Drug rash), urticarias, Fixed Drug eruptions, SJS, TEN, urticarial vasculitis and anticonvulsant hypersensitivity syndrome.

Table 3 reveals that the exanthematous (maculopapular) rash is the frequent skin reaction to systemically administered drugs and presents as a generalized fine maculopapular eruption. Among 65 patients of CADRs 20 cases were identified as severe cutaneous adverse reactions (SCARs) including both SJS and TEN. Both are rare acute life threatening cutaneous reactions characterized by mucocutaneous tenderness, erythema, and extensive exfoliation and detachment of epidermis (Fig. 2)

Table 3. Spectrum of CADRs noted among 65 patients

S.No.	Type of cases	Males	Females	Total % age (n=65)
1	Maculopapular drug eruption	2	14	25
2	Utricarias	3	9	18
3	Fixed Drug Eruption (FDE)	7	2	14
4	SJS	3	8	17
5	TEN	0	9	14
6	Urticarial Vasculitis	0	2	3
7	Anticonvulsant Hypersensitivity syndrome	2	4	9

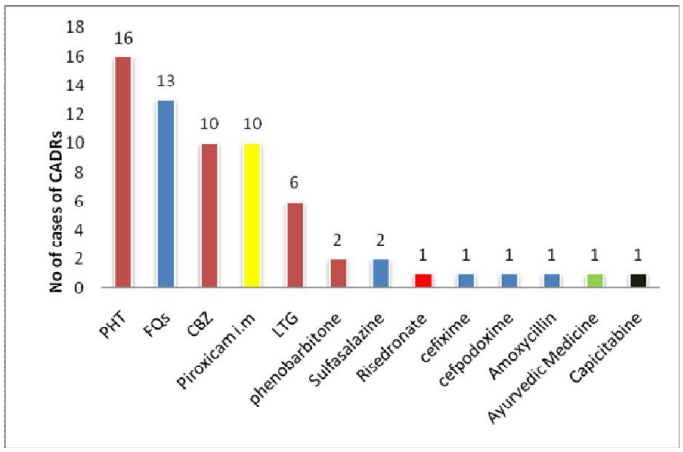

Fig. 1. Classes of drugs causing CADRs (n=65)

In the present study, we noted that these events were associated more commonly with short term therapy of most frequently implicated drugs like Antiepileptic drugs (AEDs) like phenytoin (PHT), carbamazepine (CBZ), phenobarbitone, valproic acid, lamotrigine (LTG), Fluroquinolones (FQs), (ciprofloxacin, levofloxacin, ofloxacin), oxicam NSAIDs, ibuprofen, sulfasalazine and ampicilline (Fig-1). The study also revealed that some maculopapular eruptions and urticaria's develop within a week of use of incriminated drugs. All cases of STSL/TEN develop within the months of use of aromatic anticonvulsants and within three weeks of LTG use. All the hospitalized patients of CADRs including SJS/TEN survived following discharge from the hospital. In our study, FQs, and oxicam NSAIDs were the common cause of FDE and the main presentation was solitary or few, round, sharply demarcated erythematous plaques sometimes with a central blister Fig 2: F It was also observed that all the patients recovered and survived after hospitalization.

DISCUSSION

Based on the data it was observed that the reactions were more common in females than males and the commonest age group to suffer from CADRs is 11-30 years with a mean age of 37 years. Among the CADRs identified the most common types of drug eruption were maculopapular eruptions, urticarias, fixed drug eruptions and SCARs (SJS/TEN).

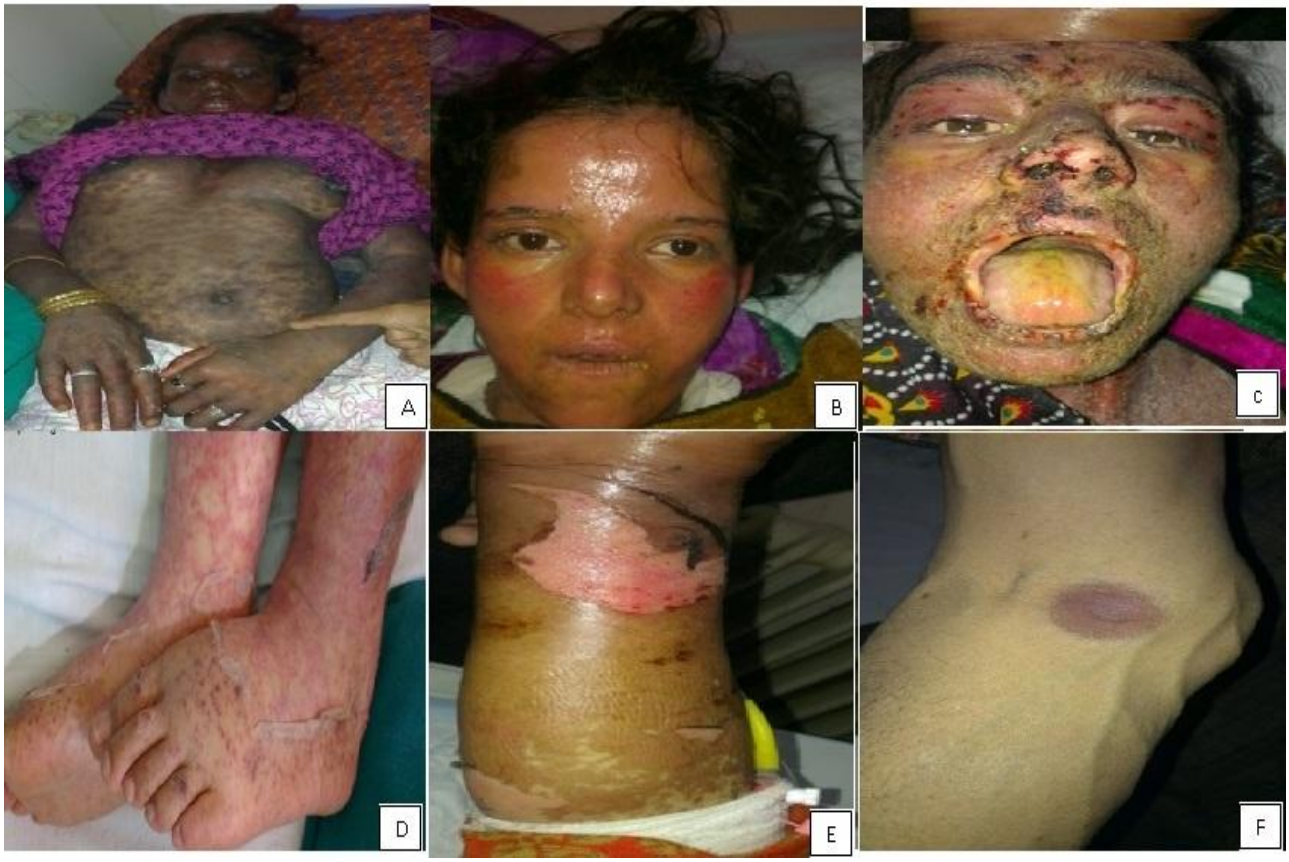

Fig. 2. A: Whole body involvement of a patient with TEN,>50%body surface area involvement with characteristic dusky red colour of early macular eruption
B: Same patient three weeks after treatment with Dexamethasone.
C: Hemorrhagic crusts with mucosal involvement in SJS.
D: Epidermal detachment of dorsal aspect of both feet in TEN
E: Epidermal detachment of forearm in TEN
F: Case of FDE. round, sharply demarcated erythematous plaque.

The exanthematous eruptions usually occur between 4 and 14 days after beginning a new therapy. However, in case of rechallenge although not recommended it can develop soon (Valeyrie-Allanore and Roujeau, 2014). These eruptions usually consists of erythematous macules or papules which are symmetric and begin on the trunk, upper extremities and progressively becomes confluent. We identified 9 cases of FDE characterized by round, sharply demarcated erythematous plaques. FDE is considered as exclusively drug induced cutaneous reaction and lesions develop usually less than 4 days after drug intake (Valeyrie-Allanore and Roujeau, 2014). Despite the rare occurrence of SJS/TEN, 11 cases of SJS (17%) and 9 (14%) cases of TEN were reported during the study period. SJS involves < 10% of body surface area of epidermal detachment. SJS-TEN overlap by 10-30% and TEN by >30%. SJS and TEN have an annual incidence of 1.2- 6 and 0.4-1.2 per million people respectively. Both effect women more frequently than men with a ratio of 1.5:1 and the incidence increases with age (Roujeau *et al*., 1990; Schopf *et al*., 1991; Chan *et al*., 1990; Naldi *et al*., 1990). The average mortality rate is 1-5% for SJS and 25-35% for TEN. The high risk medications which are commonly incriminated in CADRs include aromatic anticonvulsants, LTG, FQs, oxicam NSAIDs and sulfasalazine (Chan *et al*., 1990; Guillaume *et al*., 1987; Arif *et al*., 2007; Chang and Shear, 1992). LTG a phenyltriazine is a new anticonvulsant and has shown its efficacy for prophylaxis of depression in bipolar disorders. In our study, anticonvulsants and FQs were identified as the common causative agents for causing CADRs. LTG was associated with 2 cases of SJS and 2 cases of TEN and reaction occurred within 3 weeks after the initiation of therapy. This is in conformity with other studies where LTG has strong association with SJS/TEN. Moreover, there have been several case reports on the short term use of LTG and SJS/TEN association. (Chaffin and Davis, 1997; Duval *et al*., 1995; Sterker *et al*., 1995; Fogh and Mai, 1997; Vukelic *et al*., 1997; Page *et al*., 1998) In CADRs which have been identified a well defined temporal relationship exists between drug use and the onset of reaction. Almost all patients present with CADRs within 1-2 months time. All the patients recovered and showed improvement after the cessation of the offending drug. In North India, a prospective hospital based study was carried out over a period of 6 years recording various CADRs (Sharma *et al*., 2001). 500 patients with CADRs were enrolled in the study. The most common types of CADR patterns were maculopapular rash (34%), FDE(30%) and urticarias (14%). The drugs most often incriminated were antimicrobials (42%), anticovulsants (22%) and NSAIDs (18%). AEDs were responsible for 43% of life threatening TEN/SJS. This study is in conformity with our study in terms of patterns of ADRs and the offending agents. A retrospective study (Sushma *et al*., 2005) for 9 years (Jan 1994 –Dec 2002) involving 3541 patients were evaluated for clinical spectrum of CADRs. Only 404 (11.4%) were diagnosed as CADRs of which 52% were males and 48% females. Common age group was 21-40 years. The most common type of CADRs were maculopapular rash (42%) followed by SJS (19.5%) and FDE (11%). The drugs implicated were antibiotics (19%) and NSAIDs (19%). The study concluded that the incidence of SJS/TEN were found to be higher compared to studies published abroad. Our study also shows an increased incidence of SJS (17%) and TEN (14%) inspite of their rare occurrences.

Management begins with the identification and withdrawal of the culprit drug(s) as soon as possible (Garcia-Doval *et al*., 2000). For mild drug eruptions topical corticosteroids and antihistamines were sufficient. In case of Severe Cutaneous Adverse Reactions (SCARs) the study revealed that all the patients responded well to short term administration of systemic corticosteroids without any mortality. Some of the patients needed supportive intervention like warming of environment, correction of electrolyte disturbances, high caloric supplementation and prevention of sepsis. In patients, where AED therapy were offending agents the drugs were withdrawn immediately as a measure for prevention of drug reaction and were switched to levetiracetam and clobazam to maintain seizure free remission. Since the uncertainty persists regarding the well defined treatment modalities of CADRs and besides immunogenic mediation, use of immunosuppresants, high dose immunoglobulins (IVIG) (Viard *et al*., 1998; Prins *et al*., 2007; Rajaratnam *et al*., 2010) and anticytokine therapies like TNF antagonists has been recommended. (Hunger *et al*., 2005)

Conclusion

The dictum being prevention is better than cure. Drugs implicated in a previous reaction should be avoided, and patients should be educated about allergies, and hypersensitivity records in the notes and on prescription charts should be checked. Our ethinic population presented with great predisposition of CADRs due to aromatic AEDs, LTG, oxicam NSAIDs and FQs. These reactions need to be assessed and reported at an earliest as it has an instrumental role and forms an important component of pharmacovigilance programme. Patient education and awareness is of prime importance to yield outcome based results.

Conflict of interest: There is no conflict of interest among the authors

REFERENCES

Arndtka KA, Jick H. 1976. Rates of cutaneous reaction to drugs. *J Am Med Assoc.,* 235:918-23

Shinkai K,Stern RS, Wintroub BU. 2012. Cutaneous Drug Reactions. In: Longo DL, Favei A S, Kasper DL, Hauser SL, Jameson JL, Loscalzo, J. eds. Harrison's Principles of Internal Medicine. Mc Graw Hill. pg 432-440.

Naranjo CA, Busto U, Sellers EM, *et al*. 1981. A method for estimating the probability of adverse drug reactions. *Clin Pharmucol Ther*., 30:23945.

The use of the WHO–UMC system for standardised case causality assessment. Accessed from: http://www. WHO‐UMC.org/graphics/24734. pdf

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P: 2000. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*., 115:149-153.

Trent JT, Kirsner RS, Romanelli P, Kerdel FA. 2004. Use of SCORTEN to accurately predict mortality in patients with toxic epidermal necrolysis in the United States. *Arch Dermatol*., 140:890-2.

Valeyrie-Allanore L. Roujeau J-C. 2014. Dermatological adverse drug reactions chapter 32. In : Mann's

Pharmacovigilance, 3rd edn (Andrews EB, Moore N, eds). Chichester: Wiley Blackwell, 503-511.

Roujeau JC, Guillaume JC, Fabre JP, *et al*. 1990. Toxic Epidermal Necrolysis (Lyell syndrome): incidence and drug aetiology in France, 1981–85. *Arch Dermatol*., 126: 37–42.

Schopf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. 1991. Toxic Epidermal Necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol*., 127:839-42.

Chan HL, Stern RS, Arndt KA *et al*. 1990. The incidence of Erythema Multiforme, Stevens–Johnson syndrome, and toxic Epidermal Necrolysis: a population based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol*., 126: 43–7.

Naldi L, Locati F, Marchesi L, Cainelli T. 1990. Incidence of Toxic Epidermal Necrolysis in Italy. *Arch Dermatol*., 126:1103-4.

Guillaume JC, Roujeau JC, Penso D *et al*. 1987. The culprit drugs in 87 cases of Toxic Epidermal Necrolysis (Lyell's syndrome). *Arch Dermatol*., 123: 1166–70.

Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, Resor SR Jr, Hirsch LJ. 2007. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology*, 68:1701–1709.

Chang D, Shear N. 1992. Cutaneous reactions to anticonvulsants. *Semin Neurol*., 12: 329-37.

Chaffin JJ, Davis SM. 1997. Suspected lamotrigine-induced toxic epidermal necrolysis. *Ann Pharmacother*., 31 : 720-3.

Duval X, Chosidow 0, Semah F, Lipsker D, Franc& C, Herson S. 1995. Comment on: lamotrigine versus carbamazepine in epilepsy. *Lancet*, 345:1301-2.

Sterker M, Berrouschot J, Schneider D. 1995. Fatal course of toxic epidermal necrolysis under treatment with lamotrigine. *Int J Clin Pharmacol Ther*., 33: 595-7.

Fogh K, Mai J. 1997. Toxic epidermal necrolysis after treatment with lamotrigine (LamictaF). *Seizure*, 6:63-5.

Vukelic D, Bozinovic D, Tesovic G, *et al*. 1997. Lamotrigine and toxic epidermaI necrolysis. *Dermatology*, 195:307.

Page RL, O'Neil MG, Yarbrough DR, Conradi S. 1998. Fatal toxic epidermal necrolysis related to lamotrigine administration. *Pharmacotherapy*, 18:392-8.

Sharma VK, Sethuraman G, Kumar B. 2001. Cutaneous adverse drug reactions: clinical pattern and causative agents – a 6 year series from Chandigarh, India. *J Postgrad Med.,* 47:95-9

Sushma M, Noel MV, Ritika MC, James J, Guido S. 2005. Cutaneous adverse drug reactions:a 9 –year study from a South Indian hospital. *Pharmacoepidemiol Drug Saf*., 14: 567-70.

Garcia-Doval I, Le Cleach L, Bocquet H, *et al*. 2000. Toxic epidermal necrolysis and steven Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol*., 136: 323-7.

Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, Hunziker T, Saurat JH, Tschopp J, French LE. 1998. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science,* 282:490-493.

Prins C, Gelfand EW, French LE. 2007. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. *Acta Derm Venereol*., 87:206-218.

Rajaratnam R, Mann C, Balasubramaniam P, Marsden JR, Taibjee SM, Shah F, Lim R, Papini R, Moiemen N, Lewis H. 2010. Toxic epidermal necrolysis: retrospective analysis of 21 consecutive cases managed at a tertiary centre. *Clin Exp Dermatol*., 35(8):853-862.

Hunger RE, Hunziker T, Buettiker U, Braathen LR, Yawalkar N. 2005. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. *J Allergy Clin Immunol.,* 116:923-924.

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