Review Article

NSAID Induced Stevens Johnson Syndrome or Tumor Epidermal Necrolysis

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ABSTRACT

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are the drugs which commonly prescribed and consumed by worldwide. NSAIDs are the several drugs which are having the high risk of inducing SJS or TEN. SJS or TEN are the cutaneous reactions involves in detachment of mucosal or skin membrane. Female were more affected than male. Major cause of SJS or TEN were the genetic (HLA –A and HLA- B), drugs, infection (mycoplasma pneumonia and herpes simplex virus). The exact pathogenic mechanism of SJS or TEN are uncertain. People who are having more than 40 years are the mostly affected by SJS or TEN. Due to the rarity of these diseases, sufficient evidence is still lacking to support the best choice of treatment for patients with SJS or TEN. Most of the drugs like antibiotics, anticonvulsant and NSAIDs which causes the SJS or TEN. Diagnostic test like skin prick test, PCR test, serology test was used to diagnose the SJS or TEN. Patients are treated with various drugs like immunomodulators (IVIG), Cyclosporine, systemic corticoSteroidals, TNF inhibitors, Plasmapheresis in addition to best supportive care.

Keywords: NSAIDs, Steven Johnson Syndrome, Tumor epidermal necrolysis, Drug reactions, Adverse reaction.

INTRODUCTION

Stevens John Syndrome and Toxic Epidermal Necrolysis (SJS and TEN) are adverse cutaneous drug reaction or allergic reaction involves the detachment of skin and mucosal membrane. These are rare painful blistering, skin rashes, related to variety of drugs (NSAIDS, antimicrobial) or infection (mycoplasma or herpes simplex), characterized by detachment of skin area. Based upon the severity and percentage of detachable skin area they are classified.[1-3] Stevens Johnson syndrome and toxic epidermal necrosis was first described in 1922 and 1956 respectively. Both diseases are in the same spectrum but difference in severities.[4] SJS affects nearly <10% of body surface area, TEN affects more than 30% and overlap of both SIS and TEN affects 10-30%.[5] (Table 1).

NSAIDS are the most commonly used and prescribed drug worldwide and they thought that these drugs are the leading causative agent of adverse drug reaction.[6] NSAIDS may causes SJS in 15.93% (in the study of tejask. Patel *et al*). Most of the studies reveals the NSAIDS include Acetaminophen, propionic acid, aspirin are majorly involved drugs in SJS or TEN. Mortality rate for SJS and TEN were 1-5% and 23-45% respectively.[1,6-9]

In study of Slew-EngChoon *et al*. the composition of racial in India were 15.1%.[10] In NSAIDS there are 4 cases are reported in which 1 is SJS, 1 is TEN, and remaining 2 is overlap of both SJS or TEN, (acetaminophen causes the Toxic Epidermal Necrolysis in one patient and Aspisol causes SJS in one patient, and both drugs causes SJS and TEN in two patients.[5] The general mechanism of NSAIDs were shown in Figure 1.

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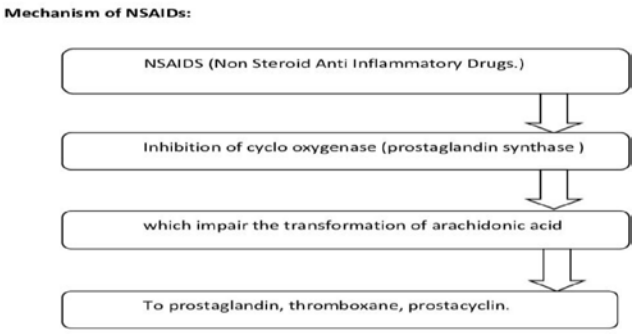

Figure 1: Mechanism of NSAIDs.

Table 1: Percentage of body surface area involved in SJS/TEN.[5,14]

	SJS	TEN	SJS-TEN
Percentage of body surface area involved	<10%	>30%	10-30%

MECHANISM OF NSAIDS[11]

Propionic acid (ibuprofen, naproxen) followed by Acetaminophen and Acetic acid are the some of the common culprit drugs leading to severe cutaneous adverse reaction.[12] According to US Food and Drug Administration in 2013 august informed that acetaminophen was the risk of causing SJS or TEN. From 1969 to 2012 USFDA were identified 91 cases of SJS or TEN. In study of Shang-Chen Yang *et al.* there are 8 cases of SJS or TEN were reported.[13] In study of Oshikoya, Ogunyinka *et al.* there are 5 cases of SJS are reported. SCORETEN was a scoring system helps to evaluate the severity and prognosis of SJS or TEN.[8]

The aim of the study is to evaluate the drugs (NSAIDS) induced SJS or TEN, Epidemiology, Etiology, Diagnostic factors, Management and therapy of SJS or TEN.

ETIOLOGY

1. ***Idiopathic***[15]

2. ***Infections*** like mycoplasma pneumonia and herpes simplex virus are majorly found to induce SJS or TEN.[15]

3. ***Genetic factors:*** Human Leukocyte Antigen class1 gene (HLA) are well known susceptibility gene. In which

   HLA-A*gene + CBZ induced SJS or TEN in a population of Japanese, Korean, European.

   HLA –B*gene + CBZ induced SJS or TEN in a population of Chinese population, although in Asian population (India, china, Malaysia).[2,3]

5. ***DRUGS:*** Some drugs like Antimicrobial (37.27%), Anti Epileptics 35.73%), Non-steroidalal Anti-Inflammatory Drugs (15.93%) are majorly causes the SJS or TEN. (Table 2)

EPIDEMIOLOGY

Gender

Women are more affected to SJS or TEN when compare to men.[17,18]

Acetaminophen was reported in 33.89% in females in the age group of 20-39 years.

Age

As per the study of Thomas harr incidence rate were 1.89 cases of TEN per million per year in a year of 1996 in western Germany and Berlin. Past 20 years SJS or TEN incidence rate were 1-2 per million per year. In the study of M. Mockenhaupt, In France TEN incidence rate were 1.2 per million per year and Germany incidence rate were 0.93 per million per year. Average age of SJS or TEN were 53.4 years (36% of patients with SJS were < 40 years) In other countries TEN/SJS incidence rate were 6 and

Table 2: These are the drugs which causes the SJS or TEN in most of the cases.[5,16]

Sl. No.	Drugs		
1.	Antibiotics	Quinolones	Levofloxacin
		Penicillin	Amoxicillin
		Carbapenem	Meropenem
		Cephalosporin	Cefuroxime Axetil
2.	Anticonvulsant	Iminostilbene	Carbamazepine
		Phenyltriazine	Lamotrigine
		Hydration	Phenytoin
		Barbiturate	Phenobarbitone
3.	NSAIDs	Acetaminophen	
		Ibuprofen	
		Aspisol	
		Naproxen	
4.	Other Drugs	Anti-tubercular drugs	
		Allopurinol	
		Omeprazole	
		Nevirapine	
		Interferon	

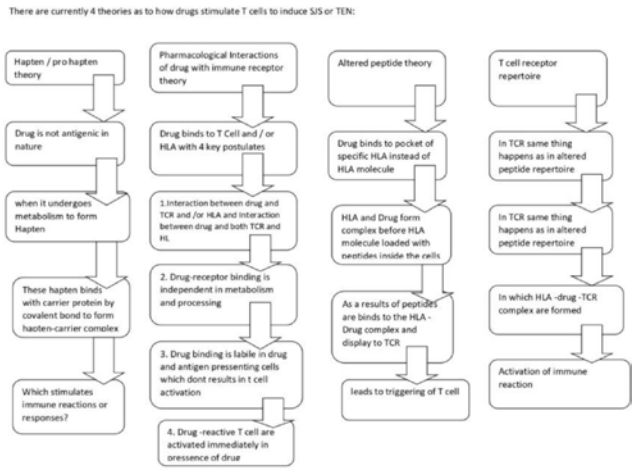

Figure 2: Theories involved in stimulation of T cells.

1.4 per million per year.[14] NSAIDs causes 9.9% of cases in that study of SiewEngchoon *et al.*[10]

Incidence rate in Europe and USA is approximately 2-3 / million population / year.[17] in japan it was 0.28-0.52 / million population /year. In the survey of 2000-2006 the mean age of age 45.7 years and later study 2000-2013 the mean age was 56.6 years.[19] A recent US pediatric database cohort study reveals that 7.5/100000 of SJS-TEN in hospitalized children's and 6.3 and 0.5 per 100000 of SJS and TEN respectively.[20] Affecting of SJS or TEN were 1-2 million each year.[21] These are the Some mechanisms involved in the stimulation of T cells were shown in the Figure 2.

These are some theories involved in stimulation of T cells[22-24]

DIAGNOSTIC METHODS

SJS or TEN were majorly diagnosed by using sings and symptoms,it will be difficult to diagnosis the particular causative agent because there is no particular diagnostic test to confirm the role of triggering agents. The ALDEN score can be used to calculate the culprit drug, it consider algorithm for 5 items those are index day, half life, prechallange / rechallange, dechallange and notoriety. Serology test and PCR for identify infections. The lymphocyte transformation test were used for the identifying the culprit drug.[25]

Skin testing

Skin prick testing and intra dermal testing were used to detect. In IDT were carried out through the dilution of 1/10 to 1/100. An increasing the diameter of area more trhan 3 mm in 20 min then it considered as positive results.[26]

Patch test were simple, fast and safe method for diagnosis of NSAIDS induced SJS or TEN. As per the mariosanchez –borges the concentration of NSAIDS for patch testing majorly Metamizole had (10-50), followed by ketoprofen, phenylbutazone, oxyphenylbutazone (1-10) and Ibuproxan, Acetyl Salicyclic Acid, Paracetamol.[27-29]

SCORETEN was a scoring system helps to evaluate the severity and prognosis of SJS or TEN.[8,22]

MANAGEMENT

Early diagnosis and management of SJS or TEN helps to prevent the prognosis or development of illness. Some of the treatment was recommended for the improving mortality.

Immediately withdrawn of causative drug is crucial and provide the supportive care and initial management of SJS or TEN. In addition, fluid balance, electrolyte, nutritional supply, pain relief (topical anesthetics) and oxygen supply.[3,21]

Topical corticoSteroidals, antibiotics were the used for the management of mild disease condition. For severe case there is an urgent replacement of amniotic membrane over the ocular surface with in a week.[30]

Intravenous immunoglobulin

IVIGs are the first treatment choice for TEN in 1998. IVIg are directly inhibits the FAS /FAS ligand interaction with the high dose of 2-4g/kg has a benefit effects in decreasing the mortality rate in SJS or TEN. The effect of IVIg were not beneficial in alone, now there are used in combinational therapy for beneficial effects of treatment.[3,22,31,33]

Cyclosporine[31]

It is a calcineurin inhibitor, it is an effective drug in transplantation, autoimmune diseases and good therapeutic benefits in SJS / TEN when compare to IVIg. It helps in the earlier re-epithelialization and prevent the onset of new lesions.[3,22,31,33,34]

Plasmapheresis

Plasmapheresis is an effective in treating of SJS /TEN. In this simple plasma exchange or double filtration is beneficial. PP is remove the pathogenic factors like drug, drug metabolism and diseases causing cytokinesis /chemokines in patient blood. PP is a safe treatment and few adverse drug reactions, Akito Hasegawa *et al.* reported for more benefits PP is combinational treatment with IVIG.[3,22,32]

Tumor Necrosis Factor Inhibitors

Very small number of studies are reported on TNF inhibitor, skin lession and blister fluids containing TNF-αin higher levels. Etanercept(25 mg/day), infliximab (5mg/kg) are the some of the drugs under TNF-αused in the treatment of SJS/TEN.[3,29,31,33]

Systemic Corticosteroidals

CorticoSteroidal is the most commonly used drug in the cutaneous infection. Short term usage of high dose of corticoSteroidal were decrease the mortality and control of infection.[3] Acute stage of pulse therapy of metyl prednisolone (500-1000mg/day) for 4 days. Followed by oral prednisolone (0.8-1mg/kg/day). High dose of corticoSteroidal (dexamethasone with dose of 4-8mg/day) for short course pulse.[5,22,25,27,29,33]

Some other drugs like Thalidomide, cyclophosphamide are used in treating the SJS/TEN. Few combinational drug therapy of IVIG and Steroidals, were used to decreased the mortality rate in patients.[13,19]

DISCUSSION

From 2005-2007 an epidemiological study on SJS or TEN in Japan reported that NSAIDs and Acetaminophen were the most suspected class of drug.[34] In evaluation of disease severity Lactate dehydrogenase (LDH) were additional useful parameter was reported recently.[35]

Medications are the common risk factor for developing of SJS or TEN. The mortality rate of SJS or TEN were high in the age of people with more than 40 years when compare to less than 40 years.[36] Sepsis is the major cause of death in SJS or TEN patients, 15% chance for occurring pulmonary complications and 30% chance for multiple organ failure system in SJS or TEN in patients.[37]

Acetaminophen is safe and mostly prescribed drug for common cold in children's, it could be a main causative drug of SJS or TEN. Acetaminophen is a main causative drug of SJS or TEN in japan and Thai population. Dipyrone is a most commonly causative drug for SJS or TEN in Brazil.[7] Incidence rate of SJS or TEN were 100 times more in the patients of HIV than general population.[38] Oxicam (NSAIDS) were the high risk of SJS or TEN when compare to other drugs of NSAIDS.[39] In previous NSAIDs have potentially associated with chronic complications in specific background of genetics and in recent study found that acetaminophen taking patients of SJS or TEN have the high rate of severe ocular surface involvement.[40]

Acetaminophen is a top five most frequently drug associated with the SIS or TEN, it was a casual drug for SJS or TEN and it is described by the ministry of health, about, welfare of Japan.[41] The patients with the age group of 21-40 years were majorly affected in India and also many other countries from the selected studies from 1995-2011.[32] In latest study the incidence ratio should be in the range of 7.6 cases per million person –year, which is variable from different countries like in study of UK the incidence ratio were 5.76 cases per million person and US study reveals that IR were 12.7 cases per million person.[42]

CONCLUSION

NSAIDs are the drugs which were increase the usage day by day in world. Over The Counter medications of NSAIDs were in dramatically increase. Acetaminophen and NSAIDs are most widely used worldwide and are also known to cause SJS or TEN in population. In this study, we were able to classify the drug and their classes, and also mechanism of drugs (NSAIDs). The use of NSAIDs should be in appropriate manner than the SJS or TEN occurrences should be decreased. Consult of Ophthalmologist and regular monitoring by corneal specialists are essential in order to prevent long-term severe visual impairment.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HLA: Human Leukocyte Antigen; **CBZ:** Carbamazepine; **SJS:** Stevens Johnson Syndrome; **TEN:** Tumor Epidermal Necrolysis; **NSAIDs:** Non-Steroidal Anti-inflammatory Drugs; **TEN:** Toxic Epidermal Necrolysis; **LDH:** Lactate dehydrogenase; **TNF:** Tumor Necrosis factor; **IVIG:** Intravenous Immunoglobulin; **PP:** Plasmapheresis; **IDT:** Intra Dermal Testing; **ALDEN:** Alogorithm of Drug Causality For Epidermal Necrolysis; **PCR:** Polymerase Chain Reaction.

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