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STEVENS-JOHNSONS SYNDROME

Gokul Krishna A.[1]*, Sam Jeevakumar[2], Anchana Raj[3], Anusree V. S.[3] and Padmesh P.[3]

[1,3]Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, TVM, Kerla, India.

[2]Associate Professor and Head, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, TVM, Kerala, India

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***Corresponding Author**
Gokul Krishna A.
Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, TVM, Kerla, India.

ABSTRACT

Steven Johnsons Syndrome is a life threatening hypersensitivity skin reactions which is rare and affect the skin and mucous membrane. The etiology of the Stevens Johnson syndrome is mostly by drugs but also is caused by infections. Early identification and removal of causative agent play an important role to prevent the progression of the disease and also helps in reducing the severity of the disease. Supportive care is recommended more than immunomodulating treatments (Human intravenous immunoglobulin) because they helps in improvement of the patients outcome.

KEYWORDS: Steven-Johnsons syndrome (SJS), supportive care, hypersensitivity, immunomodulating.

INRODUCTON

Stevens-Johnson syndrome was first described in 1922. It was found as an extraordinary, generalized epidermal eruption. Stevens-Johnson syndrome is a disease listed under the category of erythema multiforme.[24] In 1866 Hebra was the first to describe about Erythema multiforme. They described erythema multiforme as a mild disease that did not affect mucous membranes. Hebra described a form called erythema multiforme minor in which the terms erythema multiforme minor and erythema multiforme major are currently used to differentiate the milder form of the disease from the more severe form.[1]

Stevens-Johnson syndrome is an acute inflammatory skin reaction. It can occur due to an adverse hypersensitivity reaction to drugs which results in skin and mucosal eruptions that can be fatal. The onset is usually triggered by infections of the upper respiratory tract. They

may even occur due to preceding medication, among which nonsteroidal anti-inflammatory agents, antibiotics, and anticonvulsants are the most common triggers. It is a IgE mediated hypersensitivity reaction.[2-5]

Etiology

Stevens Johnsons syndrome is usually categorized as iatrogenic, infectious, or idiopathic.[4-5] Iatrogenic causes are usually by drugs. They include antibiotics such as aminopenicillins, fluoroquinolones, tetracyclines, macrolides, cephalosporins, metronidazole. Anticonvulsants such as phenytoin, lamotrigine, carbamazepine, oxcarbazepine, phenobarbital, sodium valproate, levetiracetam. Sulfonylureas such as glipizide, diuretics such as furosemide and acetazolamide. Analgesics such as NSAIDS(diclofenac, ibuprofen and rofecoxib) and acetaminophen.

Antidepressants such as mirtazaipine and duloxetine. Tyrosine kinase inhibitors such as afatinib, imatinib and sunitinib. Xanthine oxide inhibitors such as allopurinol. Androgenic hormones such as danazole and androgenic anabolic steroids. Antineoplastic drugs such as paclitaxel, docetaxel, TS-1. Antiviral drugs, aggrenox (aspirin+dipyridamole), immunosuppressants/ immunomodulators, antihistamines such as fexofenadine, ACE inhibitors such as ramipril, antiosteoporotic agents such as strontium ranelate. Other reported non therapeutic agents include Iopentol and carbamate. Idiopathic causes may occur 18 to 22 percent of all cases.[26-29] Most common infectious causes is by Mycoplasma Pneumoniae.[30-31]

Herpes Simplex virus has also been found. It is difficult to determine whether the drug given for the infectious disease or the infectious micro organism had caused the disease.[5-7]

Pathophysiology and Clinical manifestations

Tissue damage in the form of epidermal necrolysis is a mass keratinocyte cell death through apoptosis. Cellular stress, DNA damage and intracellular cytokinesare the stimuli that can induce apoptosis. The pathologic change observed in Stevens-Johnson syndrome is an acute lymph histiocytic inflammatory infiltrate around blood vessels and degenerative changes in the endothelial cells of capillaries. Marked epidermal edema and epidermal necrosis and an immune complex process with hypocomplementic vasculitis are clearly seen. With pressure, in skin the epidermis is easily separated from the dermis (Nikolsky's sign). Skin lesions are usually preceded by a prodrome of respiratory tract. Systemic symptoms that suggest viral

illness. Symptoms may include sore throat, headache, fever, and malaise, and may be present for a week or two before cutaneous manifestations appear. Stomatitis and conjunctivitis usually occur one or two days before the onset of the exanthema.[8]

Dermatologic

Skin lesions that first appear as erythematous macules becomes edematous and papular, which forms the characteristic skin lesions of Stevens Johnson syndrome (target lesions). Target lesions are concentric rings resembling the iris of the eye and they extend over the entire body and form bullae or vesicles. They occur within 24 to 96 hours after onset of the rash. Nikolsky's sign is usually present. Sometimes the lesions may resemble a second-degree burn ie, when they are confluent. Oftentimes, sloughing of the epidermis results. Due to this burn injury the application of silver sulfadiazine is often done, which has its own complications.[8]

Infections

60 to 75 percent of cases will have complicating infections in patients with Stevens Johnson syndrome. High incidence of infection is probably by Impaired host defense.

Infections are the greatest cause of mortality in patients with Stevens Johnson's syndrome. Gram-negative pneumonias and septicemias are the common infections seen. Organisms include Pseudomonas aeruginosa, Klebsiella, Staphylococcus aureus, and Candida species. Leukopenia generally occurs within 72 hours after the skin lesions have appeared. The humoral toxins may be released into the circulation, suppressing the bone marrow.[5,8] Silver sulfadiazine may also be a cause. Skin sloughing oftentimes resembles that of a burn patient and is commonly treated with silver sulfadiazine. This may cause some complications in leukopenia patients.[9]

Respiratory manifestations

Respiratory complications and are often the cause of death and are frequent. Approximately 30 percent of cases with severe Stevens-Johnson syndrome have been reported to occur in Pneumonitis, bronchial pneumonia, and bronchiolitis. Half of the patients develop respiratory failure, requiring intubation and ventilatory support. This is to prevent increased morbidity and mortality. Respiratory failure is associated with mucus retention and sloughing of the tracheobronchial mucosa, which contributes to the prolonged need for support when such failure occurs.

Many patients having stevens Johnson syndrome experience a late respiratory deterioration. This d may be caused by immune complexes that are formed in response to an inciting antigen. During early stages Such immune complexes have been isolated from cutaneous lesions.

Immune complexes have been known to produce alveolar disease. The antigen causing the immune complexes has not been identified.[9-12]

Ocular manifestations

Range from 50 to 100 percent is reported to the incidence of serious ocular disease in Stevens Johnson syndrome. They vary from chronic conjunctivitis to complete blindness. Depending upon the degree of systemic involvement incidence and severity of chronic eye complications are classified. The most frequent ocular complication is conjunctivitis. This purulent conjunctivitis causes the eyelids to become swollen, crusted, and ulcerated, with ensuing pain and photophobia. Revascularization of ulcerated lesions may result in opacification and decreased visual acuity may occur in severe cases. Adhesions form on occasion resulting in immobilizing the eye. No long term complications occur in mild cases.

Irreversible blindness occur rarely. The occurrence of irreversible blindness is reported as 6-10 percent.[12-14]

Gastrointestinal involment

Oral and pharyngeal cavities both are involved in stevens Jonson's syndrome. Oral lesions which begins as vesicles, rupture forming a white gray membrane. The lips are painful and crusted with blood. Many patients may occur dysphagia. Oral mucous membranes are severely eroded for 10 to 14 days. Prolonged ulceration of the gastrointestinal tract months after recovery has also been reported. Oropharyngeal cavity is involved. Erosion and sloughing may extend the entire length of the gastrointestinal tract which results in malnutrition, pain, and bleeding.[8,14,15]

Fluid and Electrolyte loss

Fluid loss is not severe when compared to thermal burns, anyway fluid replacement is needed. Evaporation from skin lesions and leakage from capillaries are the factors involving massive fluid shift. This results in the loss of blood borne proteins. This may be prevented by early covering of the area by xenografts.[16,17]

Diagnosis of stevens johnson syndrome

People having stevens Johnson syndrome usually report to have constitutional symptoms including fever, malaise, arthralgia and sore throat. Targetoid lesions may be present. The lesions first involve the trunk and then spread to limbs. Recently various serum makers had been studied to detect the early case of Toxic Epidermal Necrosis. The changes that affect include < 10% of body surface area in SJS and > 30% of body surface area in TEN; involvement of 15 to 30% of body surface area is considered SJS/TEN overlap. Soluble Fas ligand, granzyme B, soluble CD40 ligand, granulysin, serum high mobility group protein B1 (HMGB1), serum lactate dehydrogenase level, Bcl-2 expression in the dermal infiltrate, thymus and activation- regulated chemokine, and glutathione-S transferase-pi expression are some of the serum markers.[18,24,16]

Drug provocation tests has been provided effective for which we can prepare the list of drugs which can be given to the patients who had been suffered from drug eruption recently. This is mostly done in day care or prolonged admission in an hospital under strict medical supervision.[25]

Prognostic factors

Risk factors are classified as seven parameters which are incorporated into a disease severity score called SCORTEN which predicts mortality[26] They are as follows

- Age over 40 years
- Malignancy
- Tachycardia (pulse > 120/minute)
- 10% < Initial epidermal detachment
- Serum urea level > 10 mmol/l
- 14 mmol/l < Serum glucose level
- Bicarbonate level > 20 mmol/

Other comorbidities can also case high mortality and have additive effect over the above factors.

Complications

The most complicated pulmonary disease caused by Stevens Johnsons' syndrome are obstructive lung diseases which include bronchiolitis, bronchiectasis and chronic obliterative bronchitis. These patients usually come with the complaints of cough, wheezing, pleurant

sputum and sometimes fever. Oesophageal strictures are commonly documented in gastrointestinal and hepatic complications which usually appear after one month on the onset of Stevens Johnson syndrome. Another report (Teo and Walsh -2016) also documented the complications such as intestinal ulcers, chronic cholestasis, ischemic hepatitis and the vanishing bile duct syndrome.[7] Majority of the patients with Stevens Johnson syndrome is involved with oral mucosal membrane and includes tooth decay, severe dental growth abnormalities as a result of bacterial infection due to low saliva production and ulceration with fibrinous exudative inflammation which leads to re-epithelialization and healing. Hypopharyngeal stenosis, nasal. Septal synechiae, pinna synechiae, acute laryngitis, epiglottitis, and ulceration of the nasal cavity which resolve with supportive therapy and airway management are the otorhinolaryngologic involvement. Gynecologic complications involve a fusion of the labia minora and majora, and labial synechiae, vulva and vaginal adenosis and renal complications involve glomerulonephritis and chronic renal insufficiency.[27,29]

MANAGEMENT

Non pharmacological treatment

The most important intervention given to the patient suffering from stevens Johnson syndrome are early and aggressive supportive care isolated preferably in Burns Intensive Care unit. The drug causing the disease should be identified and stopped immediately to Improve prognosis. Room temperature should be maintained between 30 to 32 degree Celsius, especially if larger body surface is involved. Bedding on alternating pressure mattress is also recommended. To prevent end organ hypoperfusion and shock patient should receive fluid and electrolyte replacement and a solution of albumin. In patients who are in the Intensive Care Unit should remove the damaged necrotic tissue and the exposed membrane should be covered with artificial membrane or biological dressing. Since high rate of infections are seen in Stevens Johnson syndrome regular blood skin and urine culture should be performed.[30]

Pharmacological treatment

- **Systemic corticosteroids**

Some literature states that early high doses inhibit the inflammation while some other literature states that corticosteroids increases mortality by increasing the rate of infections, risk of septicemia and delay re-epithelialisation which also prolongs hospital durability.

Pulsed intravenous dexamethasone of dose 1.5mg/kg/day given for three days may stop progression of disease and promote healing within three weeks.[31,16,30]

- **Human intravenous immunoglobulin (IVIg)**

IVIg is used for both treatment and prophylaxis of stevens Johnson syndrome.

There are many hypothesis such as IVIg inhibit Fas-mediated keratinocyte necrosis in pooled human. Creamer et al 2016 relieved that mortality in patient using IVIg has no effect when compared to the patients receiving supportive care. Mokwnhaupt (2016) also stated that this drug is not the best treatment for this disease.[16,8]

- **Cyclosporine**

Cyclosporine at the dose of 3mg/kg/day for ten days shows good result by inhibition of down regulation of NF-kB which inhibits apoptosis. Cyclosporine reduces mortality rate and Is also due to its speculated effects on granulysin.[32,16,30]

- **Plasmapheresis**

Plasmapheresis is the process in which blood is constituted by adding albumin to artificial plasma after removing the non dialyzable pathogenic component from plasma and re-infused back into the patient.[30]

- **TNF-alpha inhibitors**

Since TNF-alpha play a role in Stevens Johnson syndrome TNF-alpha inhibitors are used in the management of sjs. Infliximab, pentoxiphylline and thalidomide are some of the TNF-alpha inhibitors used in the management of Stevens Johnson on syndrome.[30]

- **Granulocyte colony stimulating factor**

For patients with stevens Johnson syndrome granulocyte colony stimulating factor boosts the count of neutrophil. It also reduce the risk of infection which is caused by neutropenia.[30]

CONCLUSION

SJS is a T-cell mediated drug reactions in which it causes rapid irreversible keratinocyte cell death. Since it is a rare disease no evidence is there for any specific treatment but supportive care in intensive care unit is found to best and effective in patients having sjs. The standard treatment includes supportive care in burns intensive care unit, analgesia, cyclosporine, fluid replacement therapy. The treatment including high-dose corticosteroids, IVIg and

plasmapheresis are not proven effective. Therefore further research is needed. Steven Johnson's syndrome is a rare and complicated disease, therefore early identification and removal of causative agents prevent the progression of the disease.

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