REVIEW ARTICLE

A Literature Review on Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis and its Complications

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are delayed-type hypersensitivity reactions to medications. Early signs of identification and proper management are critical for patients' survival. The distinct features initially resemble influenza-like conditions, malaise, and fever with gradual pain and lesions in the oral, ocular, and genital areas along with other systemic symptoms. SJS/TEN can be differentiated: SJS by the degree of skin involvement and TEN by the degree of exfoliation. In SJS, skin involvement is < 10%, whereas in TEN, skin involvement is > 30%; overlapping among the two develops with 10–30% skin involvement. For the identification of culprit drugs, oral provocation tests, patch testing, and *in vitro* assay tests are used. The estimation of mortality rates for SJS/TEN has been performed by using SCORTEN- severity-of-illness score for toxic epidermal necrolysis. Sulfonamides, anti-epileptics, NSAIDs (oxicams), and allopurinol are some of the medications with a high risk of SJS/TEN development. Drug-mediated SJS/TEN is facilitated by genetic involvement particularly HLA antigens along with CYP450 genetic variants. Most frequent clinical features include mucosal involvement of nasopharyngeal, esophageal, and genital regions accompanying blisters and erosions. A multidisciplinary approach is required for the handling and treatment of SJS/TEN. It is mandatory to withdraw the contributing medicine followed by supportive therapy. Clinical management involves the use of corticosteroids, cyclosporine, and immunoglobulins.

Keywords: *Stevens-Johnson syndrome, skin involvement, toxic epidermal necrolysis, delayed hypersensitivity.*

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), described by blisters and skin exfoliation, are fatal, cutaneous, and mucosal membrane reactions [1]. The main causative sources include some drugs and infectious species like Mycoplasma [2] and the herpes simplex virus. SJS/TEN share similarities amid the disease spectrum with variations in severity and are mainly classified based on skin detachment throughout the body [3, 4]. Around 1.58 -2.26/million cases were reported in the USA which is contradictory to its high mortality rate being 4.8% (SJS) and 14.8% (TEN) [5]. Besides, sequelae are also reported after recovery like blindness, *etc.* Therefore, very precise and early diagnosis and appropriate therapeutic approach are required to initiate the management as soon as possible. Prediction of severity can be assessed with the early identification of biomarkers [3].

SJS/TEN presents purpuric macules, blisters with pain, and lesions that involve skin and mucosa. The appearance of lesions starts 4 to 28 days after exposure to the causative medication. The development of skin lesions is led by fever, weakness, and respiratory tract indications. Nearly every patient shows the involvement of mucosa in the eyes, genitalia, and mouth. Additionally, systemic involvements include the complications of cardiopulmnary, urinary tract system, and gastrointestinal tract. Sequelae and complications due to multiple organ involvement that lead to mortality were also reported and include sepsis, cutaneous infection, hepatitis, and pneumonia [4]. The recovery phase of SJS/TEN also carries events of sequelae including mucosal and dermal issues. According to one study, the prevalence of sequelae accounts for 84.3% of skin complications, 59.5% of ocular complications, and 50.8% of oral mucosal complications [5]. Neurological complications include depression associated with anxiety, along with post-traumatic stress disorder. The physical and psychological sequelae reported by a study showed that 28.2% of patients lost the ability to work whereas 30% – 68.1% of the patients were either scared of or non-compliant with medication administration [5].

SJS/TEN is a stressful illness and no standard treatment has been reported so far. The paucity of SJS/TEN is the obstacle in conducting double-blind controlled research of high-quality to interpret the effectiveness of drugs.

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Mostly, data is gathered through retrospective studies and case reports but without any obvious agreement on the usefulness of multiple therapeutic agents. This review focuses on the provision of evidence-based data about using different treatment modalities for SJS/TEN [6].

METHODOLOGY

This review article emphasizes the knowledge overview and updates on the development and management of SJS/TEN. PubMed and Google Scholar were searched from the year 2000 to 2022, using the keywords Stevens-Johnson syndrome and toxic epidermal necrolysis. The exploration was confined to articles delivering generalized data on SJS/TEN in human adults (≥18 years old) and to articles written in English. Further articles were explored after hand-searching for appropriate ones, as well as assessing the references of major articles.

We conducted a systematic review of all English language publications. We included all interventional, observational, meta-analysis, and retrospective studies and case reports. MeSH terms (medical subject headings) included Stevens-Johnson syndrome and toxic epidermal necrolysis. The article selection methodology is displayed in **Fig. (1)**.

RESULT

After applying the inclusion criteria, 12,700 articles were recognized in the search, of which 119 were incorporated in the final review.

DISCUSSION

Genetic Contribution to the Development of SJS/TEN

An incline in the evidence of genetic incidence of cutaneous adverse reactions has been described in various studies. Chung and co-investigators (2004) studied a Han Chinese populace and reported a robust association between human leukocyte antigen (HLA)-B*15:02 and carbamazepine (CBZ)-prompted SJS/TEN. There is a division of HLA alleles (class I and class II), which are specific for presenting antigenic peptides to T cells, which then activate the immune reaction. In this research, 44 cases of CBZ-prompted SJS/TEN were incorporatedand there was an HLA-B*15:02 allele in 100% of cases. More studies described the relationship between CBZ-prompted SJS/TEN and the HLA-B*15:02 allele in populaces

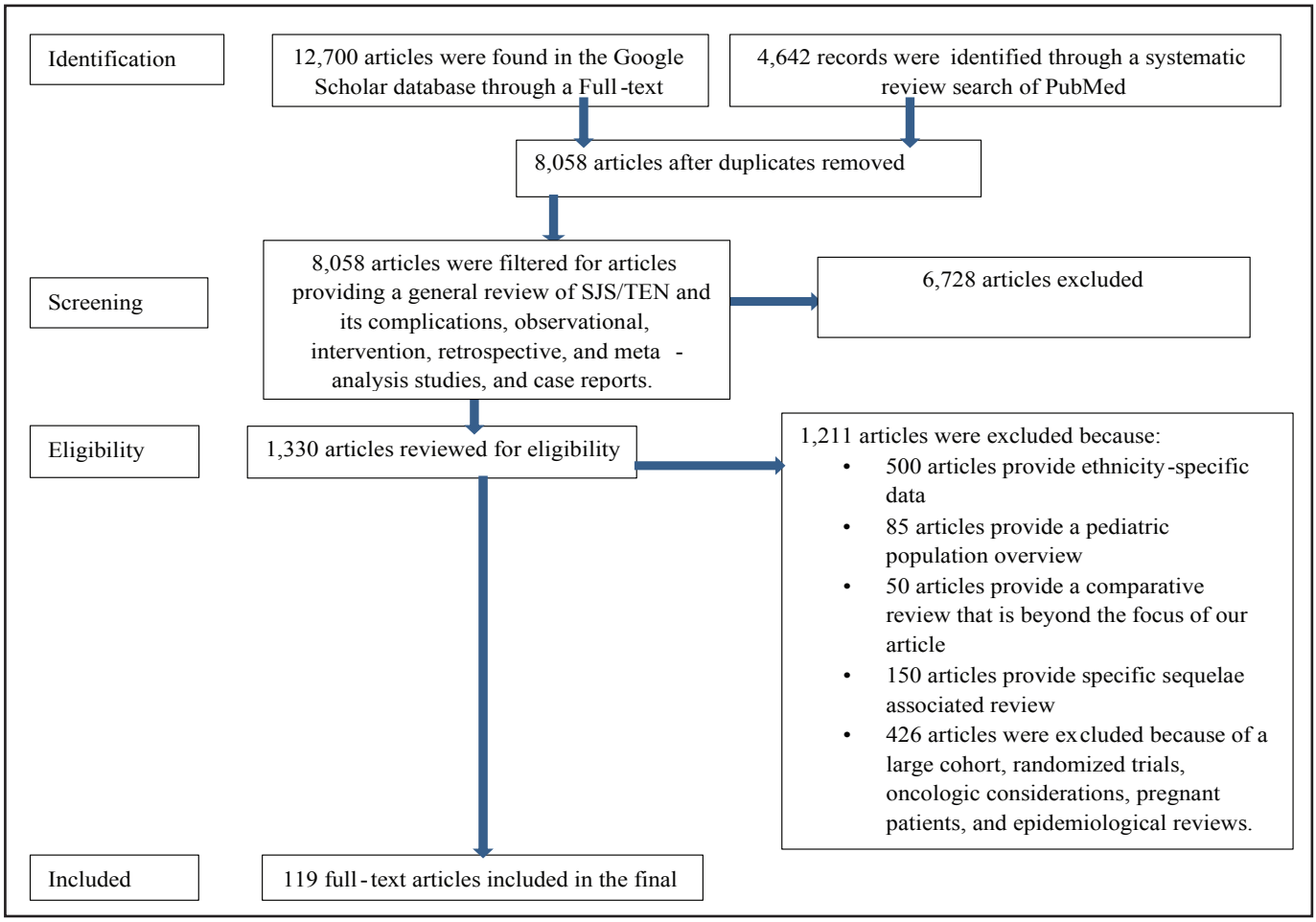

Fig. (1): Article selection flow diagram.

comprising China, Thailand, Malaysia, and India [4, 7-9].

Other than CBZ, the link between SJS/TEN and HLA-B*15:02 was established for antiepileptic medications also. Even though the occurrence was lesser than that noted with CBZ, a sturdy relationship with phenytoin-, lamotrigine- and oxcarbazepine-prompted SJS/TEN was exhibited by HLA-*15:02 [10]. On the other hand, no relationship was established amid CBZ-prompted SJS/TEN and HLA-B*15:02 in Japan, Korea, and Europe [11, 12]. The link between HLA-A*31:01 and CBZ-prompted SJS/TEN was revealed by Ozeki *et al.* [13]. HLA-A*31:01 exhibited a link with CBZ-prompted SJS/TEN in Korean, European, and Japanese populaces [14, 15] while in Asian populaces, most of CBZ-prompted SJS/TEN is linked with HLA-B*15:02; the relationship with HLA-A*31:01 is revealed in populaces of multiple ethnicities [4]. Before the administration of CBZ, the US FDA, in 2008, recommended executing HLA-B*15:02 genotyping [4]. HLA-B*15:02 screening is stated to have a sturdy relationship with a decline in CBZ-prompted SJS/TEN incidences in Taiwan [16].

Apart from antiepileptics, several other medications like allopurinol and abacavir have HLA relations. Allopurinol, which is an anti-hyperuricemic medication, is rendered as a key reason for SJS/TEN. Several ethnicities have demonstrated a link between HLA-B*58:01 and allopurinol-prompted SJS/TEN together with Korean, Thai, Taiwanese, European, and Japanese people. So, such data proposed that HLA-B*58:01 genotyping could perhaps be beneficial in the prevention of allopurinol-prompted SJS/TEN [17-20].

Cytochrome Ps (CYPs) are genetically significant elements that are involved in medication metabolism. There are 57 variants of CYP450 genes and each one displays practical variances. Cases with slow drug metabolism due to CYP450 variants have a great risk to develop ADRs (adverse drug reactions). Particular genetic factors related to phenytoin-induced SJS/TEN were identified by Chung *et al.* [21]. This study, in CYP2C9, identified 16 important single nucleotide polymorphisms. Cases with phenytoin-prompted SJS/TEN having CYP2C9*3 presented late phenytoin clearance, leading to more severe illness [4].

Clinical Presentation

Except for BSA (body surface area) involved, the clinical presentation is comparable to the spectrum of disease. In most cases, the cutaneous connection is led by a prodromal symptoms stage *i.e.* fever, sore throat, malaise, and cough [22-24]. Subsequent cutaneous and mucosal contributions are general and characteristically look like erythematous macules or uncharacteristic trunk lesions that then develop as merging erythematous regions, with shadowy midpoints, saggy blisters with a Nikolsky sign and stripped epidermal sheets [25, 26]. There is mucosal involvement in the majority of cases; 80% of cases have involvement of two or more mucosal surfaces. Dermal hyperpigmentation, scarring, alopecia, and nail dystrophy are commonly observed, too. Ocular problems comprise foreign body feelings, dry eyes, chronic conjunctivitis, trichiasis, and also loss of sight [5].

There is common involvement of the oral cavity in up to 100% of cases, with mucositis and ulceration [27]. Ocular involvement is also frequent with hyperemia of the conjunctiva and total epidermal sloughing at the surface. To avert long-term ocular sequelae, early consultation is necessary [23, 27-29]. Gynecologic involvement is noticed in about 77% of female cases but is variable in severity [27, 30].

Pathophysiology

Although medications mostly trigger SJS/TEN, however, infections (most commonly Mycoplasma pneumonia) have also been related [2, 22, 31-38]. In about 15–30% of cases, no offending cause was recognized [39]. Though the triggers of these ailments have been well-reported, their pathophysiology still requires elucidation. These are thought to be type IV hypersensitivity reactions, intervened by the T-cells. Several hypotheses exist about how medications produce an immunological reaction causing SJS/TEN [4, 40]. The foremost is the hapten theory stating that molecular medications will make a covalent complex with the serum proteins that are identified by specific HLA molecules and offered to T-cells, generating an immune reaction. Another theory is the concept of pharmacological interaction (p-i), stating that chemically inert medications and those that cannot bind covalently with serum proteins, attach directly with HLA molecules, resulting in the activation of the T cells. The last theory is the concept of altered peptide, stating that medications attach inside HLA binding sections in a manner that modifies self-protein presentation to T cells, so that they are not identified as self, resulting in the immune reaction [41, 42]. Regardless of doubt about the particular mechanism, the conclusion is T-cells activation responds to a medication or infection and subsequential epidermal necrosis. Initial theories hypothesized that keratinocyte expiry was interceded by interactions of soluble Fas ligand (sFasL) with the Fas receptor on the keratinocyte surface. Consequent

research established granulysin as a noteworthy facilitator of apoptosis [30]. More studies established granulysin's role as a foremost driver of the illness and exhibited that granulysin levels in the sore fluid were linked with the disease seriousness [43, 44]. Granulysin does not act alone though it appears to be the chief propeller of epidermal necrosis [45]. There was a study of 28 diverse cytokines and chemokines regarding their serum levels by Su *et al.* [45] and it was found that several were upregulated in SJS/TEN cases, of which granulysin and IL-15 were linked with disease seriousness. Furthermore, the character of necroptosis or programmed necrosis was studied and its contribution to keratinocyte death was revealed, that possibly has significant diagnostic inferences [46-48].

Management

Owing to the greater SJS/TEN-related morbidity and mortality, multidisciplinary attention in a dedicated burn division is suggested for such cases. The recommendations of the UK advise transfer of cases to a Burn unit with TEN and confirmation of these signs: clinical decline, further detachment of epidermis, localized sepsis, lesion conversion, and/or late curing. As per UK guidelines for SJS/TEN management, removal of the offending medication and integrative supportive care have to be lined up above systemic therapy due to the paucity of confirmation of the management effectiveness [6, 49]. Yet, Japanese SJS/TEN recommendations suggest the first-line treatment of prompt systemic corticosteroids (alone or combined with cyclosporine) [50].

Offending Drugs: their Identification and Withdrawal

Recognition and removal of the offending medication is the key element for treatment. Offending drugs were recognized in 85% of SJS/TEN patients in a study. In some patients, offending drug identification is challenging, particularly in cases of taking many drugs concomitantly. The ALDEN (Algorithm of Drug causality for Epidermal Necrolysis) algorithm is commonly employed retrospectively (not in the acute stage) for assessing medication causality [39]. Pharmacovigilance statistics have an imperative part in recognizing medications that have a much sturdy link with SJS/TEN [6].

Diagnostic Tests for the Identification of Offending Drugs

Numerous tests are available to identify the offending medication; for the offending medication of cutaneous reactions like acute generalized exanthematous pustulosis (AGEP), medication rashes with eosinophilia and systemic symptoms (DRESS), or maculopapular exanthema, patch testing has been used. Yet, no standard formulations of a testing agent are available. For AGEP, Wolkenstein and co-investigators described 50% affirmative rates, however, a positive test for only 2 cases among the 22 SJS/TEN patients was reported by them [6]. Similar results were reported with the offending medication by a multi-center study, recognized in 64% (46/72) cases with DRESS, 58% (26/45) cases with AGEP, and only 24% (4/17) cases with SJS/TEN [51]. On the contrary, Lin and co-investigators stated confirmatory patch test in 62.5% (n=10 out of 16) cases with CBZ-prompted SJS/TEN, with negative relapse of hypersensitivity response. There had been reports of cross-sensitivity to structure-associated anti-epileptics (*i.e.* oxcarbazepine, phenytoin, and lamotrigine) in CBZ-prompted SJS/TEN cases. It was proposed that those aromatic anti-epileptic agents should be evaded in such patients. It was concluded that patch testing had extremely variable sensitivity and specificity for various medications [52].

The T cell proliferation responding to medication, *in vitro*, is measured by LTT (lymphocyte transformation test) and was reported as positive in 21–56% of SJS/TEN cases [53-55]. Researchers altered the LTT to increase specificity by the addition of IL-2, IL-7/IL-15, antigen-presenting cells, or by removing regulatory T cells (CD3+ CD25+) [56]. Cytokine assays are used to evaluate cytokines levels or other arbitrators, developed by lymphocytes secondary to medication provocation. Several cytokines *i.e.* IFN- γ, IL-2, IL-4, and IL-5 are expressed and then liberated during the delayed hypersensitivity test of medication. Some new researchers have reported that IFN-γ assays and IL-4 assays could ascertain the offending medication in 78% and 50% of SJS/TEN cases, correspondingly [54]. In separate research, the offending medication was recognized in 55%, 43%, and 38% of patients with IFN-γ, IL-5, and IL-2 assays respectively. This research also proposed a combination of different assays as a more practicable method to recognize the offending medication in SJS/TEN cases. At present, cytokine assays are not usually employed in clinical practice to detect the offending medication in SJS/TEN cases [55].

SCORTEN: Severity-of-Illness Score for TEN

This score (SCORTEN) is generally employed for the evaluation and prediction of death owing to SJS/TEN [57]. SCORTEN comprises of 7 individual risk factors, *e.g.* age (> 40 years), tachycardia (> 120 beats/minute), malignancy, > 10% skin detachment, glucose (> 14 mmol/L), serum urea (> 10 mmol/L) and serum bicarbonate (< 20 mmol/L). SCORTEN has to be evaluated after admission of the patient within 24 hours and on the 3rd day [6].

Supportive Therapy

The supportive therapy is akin to the therapy of a serious burn case for SJS/TEN cases. It includes protection and restoration of the skin's barrier function, sustaining fluid balance, protection of the respiratory tract, and infection treatment. Fluid and electrolyte observation and replacement are vital along with nutritional support, owing to the high catabolic rate. Also, thermoregulation and sufficient analgesia are generally desirable [27, 58]. Clinical recommendations for the care of skin in SJS/TEN cases are unavailable. Epidermis detachment is proposed as a natural bandage for hastening re-epithelialization [59].

Integrated timely care is necessitated encompassing experts from various disciplines like gynecology, urology, ENT, ophthalmology, *etc.* to avert the SJS/TEN consequences. Referring to the optometric physician is important as most cases have an ophthalmic association. Management with combative lubrication, topical corticosteroids, topical antibiotics, and breakdown of adhesions for eyes is essential. Lately, amniotic membrane transplants displayed efficacy in the preservation of visual acuity and an intact ocular surface [27]. Since SJS/TEN may have psychological effects, proper knowledge, and emotional support are necessary [60].

In conclusion, timely diagnosis, removal of offending medication, and integrated and supportive care are the most important elements of SJS/TEN therapy. Quite a lot of immunosuppressive and immunomodulating treatments have been suggested, together with cyclosporine, corticosteroids, IVIg, and TNF-α antagonists, based on the existing information about SJS/TEN pathophysiology [6].

Systemic Corticosteroids

Corticosteroids are broadly employed as anti-inflammatory and anti-hypersensitivity drugs. Initially documented therapy for SJS/TEN was systemic corticosteroid and its effectiveness to treat SJS/TEN has long been argued. Earlier research instituted that corticosteroids to treat SJS/TEN cases may elevate infection risk, general complications, and death rate [6]. Multi-center research conducted retrospectively with n = 281 cases in Europe could not establish adequate confirmation of the benefits of corticosteroids [61]. Several meta-analyses could not prove the advantageous effects of systemic corticosteroids to reduce mortality. Yet, meta-analyses performed by Zimmermann and coworkers (2017) and Houschyar and coworkers (2021) proposed that steroids may enhance existence rates [1, 62].

In retrospective research performed by Kardaun and co-investigators in the Netherlands (2007), 12 patients with SJS/TEN were given high-dose of dexamethasone, in the short term, which reduced the mortality rate [63]. The useful effects of pulse methylprednisolone treatment for survival and deterrence of ocular problems have been established by 2 Japanese studies [64, 65]. In SJS/TEN cases, the serum levels of IFN-γ, TNF-α, IL-6, and IL-10 were reduced as reported by Hirahara *et al.* following 4 days of methylprednisolone pulse treatment, though, a statistically substantial drop was detected only in levels of IFN-γ and IL-6 [65]. In Indian research conducted prospectively, 18 TEN cases were managed with dexamethasone (1 mg/kg/day) intramuscular injection, and all cases were revived [66]. Mieno *et al.* in a retrospective research of 85 cases, instituted that administration within 4 days from the onset of pulse corticosteroids, may decrease serious ocular consequences [67]. One more retrospective research with 70 SJS/TEN cases also discovered an advantageous outcome of corticosteroids irrespective of the therapeutic plan, whether low-dose (≤2 mg/kg/day) or high-dose (>2 mg/kg/day) [68]. While the advantageous effects of systemic corticosteroids were generally established on outcomes from retrospective/ single-arm research, Japanese recommendations suggest pulse corticosteroid treatment as among the first-line management for SJS/TEN with proper infection control [50]. Systemic corticosteroids can be regarded as life-savers and a cost-effective treatment in resource-restricted circumstances [66].

Intravenous Immunoglobulin (IVIg)

Apart from antibodies having anti-infectious actions, a variety of naturally existing autoantibodies in IVIg may control vital immune activities [69].

In a retrospective study with 12 SJS cases, IVIg treatment for an average of 4 days and a mean daily dose of 0.6 g/kg, prohibited the development of epidermal necrolysis and decreased the period to total mucocutaneous cure [70]. The useful effects of IVIg have been demonstrated by 2 more single-arm and non-randomized research [71]. Yet, in 2008, a retrospective study of 281 cases revealed no noteworthy difference in deaths when corresponding with cases administered with median total dosage (1.9 g/kg IVIg) and those who got supportive management [61]. Several retrospective cohort and case series researches also described that IVIg is ineffective in decreasing deaths or the development of skin sloughing [72-75].

A complete dose of more than 2 g/ kg of body weight of IVIg is regarded as a high-dose plan for SJS/TEN, generally. Retrospective research on 48 TEN cases found that the survival rate was 88% for cases administered with high-dose IVIg [76]. A noteworthy decline in mortality rate by 17%, in a cohort of 16 TEN cases, was also reported by Trent *et al.*, by using high-dose IVIg [77]. Increasing doses of IVIg displayed

an inverse correlation with mortality even though a meta-analysis by Barron and coworkers established no useful outcome with a total dose > 2 g/kg of IVIg, in reducing the deaths related to SJS/TEN [78]. On the other hand, two meta-analyses conducted by Huang and co-investigators revealed insignificant survival gain of low-dose/ high-dose IVIg in TEN cases [79]. The varying outcomes could be due to target cells' sensitivity to Fas (FasL or CD95L or CD178), the IVIg concentration employed, and the relative proportions of agonistic and antagonistic anti-Fas autoantibodies in IVIg formulations [80].

Systemic Corticosteroids and IVIg Combination

In Chinese research done retrospectively, 20 patients administered with a combination of 0.4 g/kg/day IVIg and systemic steroid for 5 days exhibited an insignificant decline in deaths or the period to taper corticosteroids [81]. In one more Chinese retrospective research, 24 cases treated with >2 g/kg IVIg (high-dose), combined with systemic steroids, presented an insignificant decrease in standardized death ratio in comparison to those administered with corticosteroids only [81]. Both of these researches displayed insignificant benefits of combined treatment in decreasing mortality rate. Contrariwise, an Indian, prospective, open-label research with 36 TEN cases employed low-dose (0.2–0.5 g/kg) IVIg and systemic corticosteroids combined, resulting in a considerably lesser standardized death ratio in comparison to the sole corticosteroids [82]. Management with both steroids and IVIg was revealed to decrease deaths in multi-center retrospective research [83].

Ye *et al.* in 2016 performed a meta-analysis with 26 researchers and revealed that the combined IVIg and corticosteroid noticeably decreased the recovery period but not death. Subgroup investigation among Asian cases also discovered a larger outcome [84]. Moreover, Torres-Navarro *et al.* in meta-regression analysis revealed that IVIg, combined with corticosteroids, was linked with reduced mortality than anticipated by SCORTEN [85]. The greater significance of combination treatment with IVIg and corticosteroid was also ranked by 2 new network meta-analyses, for decreasing mortality among the existing systemic treatments [86, 87].

Cyclosporine A (CsA)

CsA also has anti-apoptotic actions so, it may hypothetically have an advantage for SJS/TEN cases [88]. No mortality was detected in a non-blinded, prospective, phase II clinical study, among the 29 SJS/TEN cases who were administered with 3 mg/kg/day CsA, but some cases (n = 3) necessitated termination of treatment or (n = 2) dose-tapering owing to some ADRs [89]. In further studies, the favorable effect of CsA was also seen with a first dose of 3–5 mg/kg/day following tapering [90-95].

Several meta-analyses propose advantageous effects of CsA [96, 97]. Some researchers criticized for an element of selection bias that cases with renal insufficiency, uncontrolled diabetes mellitus, arterial hypertension, severe infection, immunodeficiency or malignancy, not included in certain series. Also, the outcomes of a meta-analysis are expected to be influenced by publication biasness [98]. There are alarms relating to the renal and hepatic toxicity of CsA too, as CsA ought to be evaded or employed with attention in cases of already existent renal insufficiency, having creatinine clearance = < 60 mL/min or uncontrolled levels of diabetes [88].

TNF-Alpha (TNF-α) Inhibitors

TNFα was presented to increase HLA class I expression on keratinocytes, presenting them to be more susceptible to T cell-prompted cytotoxicity [99]. The augmented TNF-α levels have steered the suggestions to use TNF-α inhibitors in SJS/TEN cases [100]. Certain case reports and case series have defined advantageous activities of biological TNF-α inhibitors like etanercept, which is a soluble fusion protein, and infliximab, which is an anti-TNF-α monoclonal antibody [101-103]. Etanercept considerably reduced TNF-α and granulysin levels in sore fluids and plasma and augmented the regulatory T cell populace in the peripheral blood [104].

Combined Biologic Anti-TNF-α and Corticosteroids

Some case reports have defined using anti-TNF-α and corticosteroids in combination [105-110]. Sachdeva, in 2021, performed a systematic review and discovered that biological monotherapy and combination treatment both were linked with enhanced consequences in SJS/TEN [111]. AO and coworkers (2022) employed 25 SJS/TEN cases and reported that combination treatment with etanercept and corticosteroids considerably reduced acute phase period, hospitalization, and skin re-epithelialization as compared to sole corticosteroid therapy. Both therapies declined the serum levels of IL-15 significantly but combined treatment reduced the serum levels of IL-6 and IL-18, too [112]. Zhang and co-investigators conducted a study from Taiwan and China on SJS/TEN cases (n= 242) retrospectively and established that cases that were administered with combined therapy of etanercept and corticosteroids had lesser death rates as compared to corticosteroid only or IVIg combined with corticosteroids [113].

Combined Biologic Anti-TNF-α with Further Therapies

Combination treatment with anti-TNF-α and IVIg has been defined by a few cases reports [114, 115]. Adding etanercept to IVIg along with supportive care was described by Pham and coworkers in a case series of 13 cases, which improved results in comparison to IVIg with supportive care only [116].

Plasmapheresis

Through plasmapheresis, medication, its metabolites, and cytokines are removed from the sufferer. The 3 first-line treatments of choice are followed as per the Japanese recommendations: IVIg, systematic steroids, and plasmapheresis [50]. A prospective observational research enrolling 28 TEN SJS/TEN overlap cases was performed by Han *et al.* who revealed that plasmapheresis was much better than conventional treatments like IVIg or corticosteroids to reduce the deaths and the length of hospitalization [117].

Giudice *et al.* (2017), at the burn division, stated the safety and efficacy of plasmapheresis and CsA in combination with TEN therapy with 12 TEN cases [118]. The improved results with a combination of plasmapheresis and IVIg were also reported by Krajewski and coworkers and Lissia and coworkers [119].

CONCLUSION

This review article updates the knowledge about SJS/TEN by discussing genetic contribution, pathophysiology, clinical features, diagnosis and identification of culprit drugs, and pharmacotherapeutic options of SJS/TEN. Apart from genetic modulation, the adverse drug reaction mediated SJS/TEN is also discussed in detail. Evidence showed that antiepileptic drugs, allopurinol, and CYP450 can initiate this cutaneous complication with genetic involvement. However, despite the greater mortality rate, its management process is still not significantly determined. Among the therapeutic options, a dispute still exists for using systemic corticosteroids and IVIg. Nevertheless, positive treatment outcomes have been reported while using biologic anti-TNF-α and cyclosporine. Collation of further data is required to achieve a revolution for developing novel therapeutic agents.

CONFLICT OF INTEREST

The author declare no conflict of interest.

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