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Topical treatment for Stevens - Johnson syndrome and toxic epidermal necrolysis: a review

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ABSTRACT

Background: Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are currently regarded to be same disease entity which differs only in the extent and severity of epidermal sloughing. Both are potentially life-threatening mucocutaneous immunologic reaction, which are most frequently induced by drug consumption. The epithelial destruction of skin and mucosal membrane can cause both acute as well as chronic/ long term outcomes in term of late sequelae during the course of the disease. Sequelae often occur during the late phase of SJS/TEN and become a significant problem due its chronicity and severe degree of impairment, which leads to deterioration of quality of life for the patients. This may prevented or decreased in terms of intensity if the patient's received prompt and sufficient topical therapy, particularly in managing lesions on the mucosa of the eye, oral, and genital.

Objective: This review underlines topical therapies which could be delivered for management of mucocutaneous lesions from SJS/ TEN, aimed to prevent late sequelae due to SJS – TEN in order to improve the life quality of SJS – TEN survivors.

Conclusion: SJS/ TEN frequently lead to late sequeale which includes skin, ocular, oral, and genital involvement. These sequelaes are often severe and chonic. Thus, may cause significant decrease in quality of life of SJS/TEN survivors. It is therefore most important to detect them early in order to manage them adequately. To date, we still have an impression that the specific sequelae of SJS – TEN are often late diagnosed and insufficiently treated. Finally, we want to emphasize that for mucosal involvement in particular, such as ocular, genital and oral involvement, a careful topical treatment have to be taken into special consideration in order to prevent severe late sequelae.

Keywords: Stevens Johnson Syndrome (SJS), Toxic Epidermal necrolysis (TEN), topical therapy.
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INTRODUCTION

Stevens-Johnson syndrome (SJS) is a mucocutaneous immunologic reaction which may be potentially life-threatening, this disease are mostly induced by drug consumption.[1] In 1956 Alan Lyell, a dermatologist reveals a severe condition affecting skin and mucosal membrane which is resembles SJS, a condition now known as Toxic Epidermal Necrolysis (TEN) or Lyell's syndrome.[2]

After prolonged debate over the years, SJS and TEN are now stated as the same disease entity which differs only in the degree of severity and the extent of epidermal detachment.[1,2]

Data from observational studies estimated incidence of TEN to be 1-1.4 cases per million populations. More than 60% cases of SJS are strongly suggested etiology correlation to drugs exposures. However, other causes, such as Mycoplasma pneumonia as well as other infections have been suspected to play certain role in the development of this mucocutaneous disease, while the etiology of up to 20% SJS cases remains unexplained.[3]

SJS and TEN shares the same pathophysiologic process, erupting as severe erosion both on skin and mucosa. Skin lesion may start as erythematous macules or atypical target lesions, which frequently become confluent, followed by epidermal detachment, often showing positive Nikolsky sign. The epithelial destruction of skin and mucosa may cause acute effects during the course of the disease. Nevertheless, this may also bring long term outcomes in form of late sequelae.[4] Sequelae often occur during the late phase of SJS/TEN and become a significant problem due its nature of chronicity as well as severe degree of impairment which further deteriorate the patient's quality of life. [1] Sequelae can be prevented or decreased in the intensity if the patient's management integrates sufficient topical therapy, particularly in treating lesions on the mucosa of the eye, oral, and genital.

STEVENS JOHNSON SYNDROME/ TOXIC EPIDERMAL NECROLYSIS

Etiology and risk factors

Over 100 drugs had been suspected as the potential inducers of SJS/TEN. Some of the most famous associated drugs with the incidence of SJS/TEN are antibiotics of sulfonamide group, antiepileptic drugs (such as phenytoin, carbamazepine, phenobarbital

lamotrigine), nevirapine, allopurinol, nonsteroidal anti-inflammatory drugs (such as meloxicam, piroxicam). Interestingly enough, acetosal/ aspirin, has never been associated with the incidence of SJS/ TEN, unlike other NSAIDs.[3,4,5]

Recent studies are still far from explaining the risk significance of cross-reaction in between medications with structural similarity. Locharernkul et al conducted a study, observing patients with SJS from carbamazepine and or phenytoin therapy. The conclusion of the study was that the patients were having good tolerance to other kinds of antiepileptics (valproic acid, lamotrigine, phenytoin, carbamazepine and/or phenobarbital). It found 90% of patients with SJS/TEN due to phenytoin or carbamazepine therapy in the study were safely treated with valproic acid.[6] These indicate that the risk of having cross-reactivity is of lesser magnitude than as predicted before. Nevertheless further investigations are still required to confirm the findings.

Infection with HIV significantly increases the risk for having SJS – TEN, up to 1000 times. Other predisposing disorder of autoimmune nature, namely systemic lupus erythematosus, collagen vascular disease, cancer and genetic tendencies due to HLA gene polymorphisms may also augmenting the risk of having SJS.[7]

Pathophysiology and Genetic

The specific pathophysiology of SJS and TEN remains unclear to date. Several theories emerge, such as the key players of immunologic process in the incidence of SJS/ TEN, together with prolonged discussion over whether it's the parent drug or drug metabolite which triggers the activation of the immune cells. Studies on genetic susceptibilities have begun to reveal the potential cause of why some people develop such a severe mucocutaneous reaction while most people are unaffected. Research have implicated that the presence of certain genotypes in human leukocyte antigen are correlated with an increased risk of SJS/TEN when a person is exposed to a certain drug.[8]

Latest research have pointed out an association of the presence of HLA-B*1502 and carbamazepine induced SJS/TEN in the descendant of Southeast Asians.[9] This does not occur in European populations. Furthermore, in a European study, most of the patients with positive HLA-B*1502 and having SJS/TEN due to carbamazepine were of Southeast Asian origin. Therefore, genetic screening for HLA-B*1502 is only recommended for patients with Southeast Asian descendent.[9,10]

HLA-B* 5801 is another allele, correlating allopurinol consumption with SJS/TEN. To date, there is no recommendation by FDA for HLA-B*5801 testing before taking allopurinol therapy as HLA-B*5801 is distributed equally in all ethnic groups, making genetic screening less useful.[11,12]

The development of epidermal necrosis leading to characteristic cutaneous lesions are thought to result from massive keratinocytes apoptosis, suspected to occur due to a cytotoxic reaction which is cell-mediated. Previous investigations had confirmed the existence of various cytotoxic cells, in the early skin lesions which includes natural killer T cells (NK) and drug-specific CD8+ T lymphocytes.[8] The cytotoxic cells are suspected to start the amplification and cytokines release (granulysin, perforin, and granzyme B) process. This cytokines play a separate role in apoptosis process.[11,13]

Concentrations of perforin, granzyme B and soluble Fas ligand (sFasL) in the blister fluid were insufficient to produce significant cytotoxicity. Unlike granulysin, where granulysin concentration levels in the blister fluid is directly associated with the clinical severity of the symptoms; TEN lesions have higher granulysin concentrations compared to SJS. This correlation was proven further when a mice skin was injected with granulysin and soon clinical features of SJS/TEN developed.[13] Granulysin has a direct effect, causing keratinocytes apoptosis and now is thought as the key mediator in keratinocytes apoptosis.[7,8]

Clinical Manifestation

Epidermal detachment in SJS involves less than 10% of the total body skin surface; transitional SJS-TEN has an epidermal detachment between 10 and 30% and TEN is defined when there is an epidermal detachment of greater than 30%. In pathological examination full-thickness epidermal necrosis may be observed. The clinical definition differentiates SJS-TEN from erythema multiforme (EM) major.[4]

There are significant differences between SJS/ TEN and EM in etiology and recurrence rates. The most frequent etiology of EM is the infection of herpes simplex virus (HSV), which opposite the drug causality of SJS/TEN. As a consequence to the viral infection etiology in EM, there are 30% recurrence rates of EM, while in SJS/TEN, no recurrence when unless there is a reexposure to the causative drug.[14]

The clinical appearance of the skin lesions is another feature differentiating EM from SJS/TEN. EM have a target lesion with a dark center and concentric rings of red hue, while lesions in SJS/ TEN had a dark center with irregularly shapes which may coalesces progressively. The skin of SJS/ TEN patients normally came up with flat macules (spots), which cannot be seen in EM. Deaths are

rarely occur in EM, while in patients with SJS mortality rate is roughly 10%.[3,14]

Clinical course, typical of SJS starts in 8 weeks (around 4 to 30 days) following a first exposure to the causative drug. In very rare incidence where re-administration of causative drugs occurs, symptoms appear in a few hours. Patients having SJS/ TEN may came up with varying levels of manifestations from the skin, extracutaneous, as well as mucous membrane.[15] Nearly 30% of patients will have prodromal symptoms (e.g., malaise, headache, fever, sore throat, and cough) as well as burning sensation of the eyes followed by the appearing skin lesion as well as mucosal lesions of the eyes, mouth, genitals, and urinary tract in 1 to 3 days.[1] Another thirty percent of patients will come up with lesions of the mucous membrane. The rest of the patients may have a diffuse rash. After the emerging of the diffuse rash, the lesions soon developed into flaccid blisters, which break easily and spread with pressure, resulting in an extensive epidermal sloughing. The epidermal sloughing can be effortless, usually due to a frictional trauma and pressure points. SJS/ TEN patients often show a positive Nikolsky's sign, which is epidermal detachment with lateral pressure.[1,7]

Nearly all patients having mucosal lesions will have hemorrhagic erosions which is painful and covered by gray-white pseudomembranes and crusts on the lips border and in the oral cavity.[1] Ocular involvement frequently occurred, affecting up to 80% of patients, which may result in severe blepharitis and conjunctivitis together with a decrease of visual acuity and photophobia[16] Edema of the eyes may occur with erythematous conjunctiva, and crusting due to excessive ocular discharge.[1,16] Gastrointestinal (GI) tract can also be affected, involving esophagus, small bowel, and colon, which may lead to a defect in enteral nutrition and oral medications absorption as well as defecation process. Involvement of genital and anal mucosa may lead to strictures.[17]

Complications

Septicemia is the most frequent serious complication which may lead to mortality in SJS/TEN cases. Normally skin and mucosal epithelium provides natural barrier against systemic bacterial invasion, but this barrier is impaired during an extensive epidermal dislodgement. Extensive skin detachment may result in intravascular fluid accumulation in the peritoneal or pleural cavity (intravascular fluid third spacing), leading to intravascular fluid and protein loss which leads to hypotension and organ failures.[15,17]

Late sequelae are frequent features of late phase TEN. Based on the study of Magina et al, the following symptoms may be found: hyper- and hypopigmentation of the skin (62.5%), nail dystrophies (37.5%) as well as ocular complications.[17] According to the study by Yip et al. Half of the TEN patients will develop late ocular squelae including, severe dry eyes (46% of cases), trichiasis (16%), symblepharon (14%), districhiasis (14%), visual loss (5%), entropion (5%), ankyloblepharon (2%), lagophthalmos (2%), and corneal ulceration (2%).[18] In a small observational study, seven out of nine post SJS/TEN patients had either keratoconjunctivitis or xerostomia or both, which resembles Sjögren-like syndrome.[19]

Hypertrophic scars are very rare and only seen in a few patients.[20] Chronic sequelae of mucosal membranes occur in 73% of patients who present mucosal lesions during the acute phase, this sequela mainly involve oral and oesophageal mucosa, and to a lesser extent genital and lung mucosa.[21] Vulvar and vaginal complications of SJS/ TEN occur in about 25% of cases. Dyspareunia frequently happens and related to vaginal dryness, itching, pain and bleeding. Genital adhesion may lead to the requirement for surgical treatment. Esophageal, intestinal, urethral and anal strictures may also develop in rare cases.[17]

Prognosis

Severe cutaneous adverse drug reactions may lead to a significant mortality rate where TEN has the highest rate (30-35%); while overlap forms has mortality rates of 10-15% and only 5% with SJS.[22]

Epidermal detachment of TEN are often extensive, even may involve the skin surface entirely. Similar with severe burn cases, a massive fluid loss occurred, resulting in imbalance of electrolyte. Secondary infections, thermoregulation dysfunction, excessive loss of energy, immunologic functions alteration and abnormalities of hematologic values are frequently occurred systemic complications. Mucous membrane lesions (eyes, oropharynx, anal and genitalia) may be severe and demanding a careful nursing care. Involvement of tracheobronchial epithelium and to a lesser extent gastrointestinal epithelium may lead to a high morbidity. Prognostic factors of SJS/ TEN include patient's age, extent of epidermal detachment, serum urea nitrogen level, neutropenia, as well as visceral involvement. A specific assessment system (SCORTEN) has been elaborated and validated recently. Furthermore, SJS and TEN may result in long-term sequelae, due to mucosal involvement which significantly deteriorate the quality of life. Post healing, pigmented alterations as well as corneal lesions are the most frequent long-term sequelae.[23]

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TOPICAL THERAPY FOR SJS/TEN

Skin lesion care

The main symptomatic treatment for SJS / TEN are similar to those of burns. Hence, the treatment experiences from burn care units are mostly applicable for treating SJS/ TEN cases: This includes control of room temperature, prudent aseptic – antiseptic handling, maintaining an aseptic clean ambience, and avoiding any adhesive material.

Nevertheless, TEN and burn cases are not perfectly identical: burns occurred in a relatively short period time and dont extend thereafter. In contrast, TEN-SJS process is progressing for several days, even after hospitalization. Skin necrosis degrees are more variable and frequently are deeper in burns, compared to TEN. Due to the restriction of lesion location in the epidermis and usually without hair follicles involvement, epidermis regrowth is quite fast in patients with SJS-TEN. This required a different topical treatment approach.[24]

Conservative skin care

There has not been any consensus on topical care for SJS/ TEN. Approaches for patient care can be either conservative or aggressive (involving large operative debridement). In many expert's opinion, based on many clinical experiences, the conservative care is considered superior to any surgical method, despite there has not been any study to support this. They observe the areas with positive Nikolsky sign, which is potentially denuded by any friction. The experts found that the skin healed much faster where the epidermis are left to cover the denuded site than on areas where the epidermis had been removed. This indicates that the vesicle roof and the denuded epidermis are capable to function as biologic dressing in SJS/TEN, thus need to be leave in place and use dressings only to protect it. Operative debridement in SJS/TEN, unlike in burn cases, is not necessarily required due to the re-epithelialisation ability of epidermis if it is maintained in place.[25]

Skin topical antiseptics

Topical skin antiseptics such as silver nitrate 0.5% or chlorhexidine 0.05% are utilized either to bathe, dress or paint, the patients. Non adhesive dressings which may be gauzed with silver nitrate 0.5%, petrolatum, polyvidoneiodine, or hydrogels can be applicate on areas of the body with skin denudations. Topical antibiotic and anti-infection with sulfa moiety (such as silver sulfadiazine) should not be administered, particularly when there is a suspicion of sulfa derivative as the causative drug.[16]

In accordance with recent strategies to improve systemic outcome by targeting the management of skin lesions, latest dressings are being developed and utilized to promote faster healing, sepsis control, as well as to reduce the destructive inflammatory component of SJS/TEN. Nano Crystalline Silver (NCS) is one of the dressing component with an excellent antibacterial properties, together with the potency of reducing the excessive inflammatory component of the disease.[27,28] Based on the previous reports, the dressing seems to be effective in this series of patients in terms of sepsis control and initiating the "tipping point" to stop the epidermal cleavage and start up re-epithelialisation. Applicate with biological skin substitutes, NCS may function as an effective substance for healing promotion, pain control and contractures prevention in a potentially destructive disease progression. When this is achievable with the application of appropriate local dressing, rather than systemic immunomodulator drugs with many complicating problems both for patient and disease, this could be a very logical choice to make.[26]

Biologic skin covers

Some experts were utilizing biologic skin covers following epidermal stripping procedures (autologous epidermal sheets, cultured human allogeneic or cadaveric allografts). Novel dressings are being studied: Apligraft®, Biobrane®, and TransCyte® (human newborn fibroblasts cultured on the nylon mesh of Biobrane®).

A controlled right–left comparative and randomised study indicates that frozen cultured human allogeneic epidermal sheets can shorten by 44% the healing period of partial-thickness burns.[29] Apligraft®, claimed as an equivalent of living skin, was applied in 38 patients over meshed split-thickness autografts while the control site was treated only with split-thickness autograft. The result reveals that Apligraf®-treated sites were having better results to control sites in 58% and worse in 16%. Vascularity and pigmentation were better significantly.[30]

Biobrane® reduced healing period without increasing the infection risk in a study involving 89 children with <25% burns. Furthermore, in a trial involving 20 children, Biobrane® was superior to topical 1% silver sulfadiazine in terms of reduction of pain, requirements for analgesics, wound healing period and length of hospitalization.[31]

TransCyte® is made of newborn human fibroblasts which are cultured on nylon mesh of Biobrane®. In a study involving 14 patients, areas treated with TransCyte® were healed faster (11 versus 18 days) and having less hypertrophic

scars compared to sites treated with silver sulfadiazine.[32] In a randomized controlled trials involving 600 second-degree burns patients, the use of topical recombinant bovine basic fibroblast growth factor allowed a more rapid formation of granulation tissue as well as epidermal regeneration when compared with placebo.[25]

Skin topical steroid

Topical corticosteroids serves as the primary therapy for most variety of skin inflammatory disorder. In particular, topical corticosteroids are most beneficial for treatment of superficial skin inflammation, which occurred either in the epidermis, upper dermis, or dermal-epidermal junction. In such condition, application of topical steroid might even be better than systemic corticosteroids therapy. Currently, there still has not any publication on studies of topical steroid use such as clobetasol propionate in management of skin lesion of SJS-TEN.[34]

Similar to systemic corticosteroids, topical corticosteroids may also cause systemic adverse effects, namely steroid induced diabetes, hypothalamic-pituitary axis suppression, and iatrogenic Cushing's syndrome. Research has indicated that systemic absorption leading to topical steroids related adverse effects was higher during application to mucous membranes (such as the oral cavity) as well as non-intact skin.[35] Other than suppression of hypothalamic pituitary axis, the use of topical corticosteroid may also potentially increase the risk of local and systemic infection. The occurrence of underlying comorbidities which may increase risk of infection should also be taken into consideration, including diabetes and immunosuppression.[34]

In order to minimize the potential complications from topical corticosteroid therapy as well as to facilitate early identification of potential risk, some steps are required:

First step is to minimize and limit the area to be treated with topical steroid to 10 % of total body surface area between the treatment and control areas. Skin integrity and body surface area are two important factors, influencing systemic absorption of topical medications. In SJS/ TEN, a massive damage to the skin structure as well as impaired skin barrier function occurred, leading to a much higher absorption rate of topical medications compared to application on intact skin. Second step is to shorten the duration of treatment, followed with systematic daily evaluations to identify any alterations in skin appearance which indicate worsening of disease or local infection.[34]

Topical treatment with Clobetasol will enhance the survival rate of epidermal keratinocyte through TNF signaling suppression and keratinocyte apoptosis inhibition, leading to a shorter duration of disease course and minimized re-epithelialization period. Furthermore, it was predicted that the genomic analysis from specimens of skin biopsy will demonstrate differential pro-apoptotic genes expression, prior and following steroid therapy.[34] Further investigations are still required to assess safety as well as efficacy, as basis to future large controlled trials of topical corticosteroids and other immunosuppressive agents for the treatment of SJS and TEN.

Sunscreens

Avoidance of sunlight exposure is advisable for several months following the healing process of SJS / TEN, due to the adverse effect of ultraviolet in worsening the hyperpigmentation sequelae. The use of sunblocks as protective agent against sunlight is recommended. Laser treatment may be given to minimize alteration of skin pigmentation as well as to improve cosmetic appeal.[1]

Oral and nasal care

Oral and nasal crusts are removed by wet compress twice a day. Oral erosions is sprayed or mouth-washed with antiseptics (chlorhexidine) several times a day.[16] The use of mild ointments (such as white petroleum or dexpanthenol ointment) are also recommended for treating mucosal lesions of the oral cavity and lips.[36]

Ophthalmologic care

Involvement of ocular organs frequently occurred in SJS and TEN and may result in severe complications and blindness. The degree of severity in acute ocular involvement does not necessarily predict the risk of late complications. The diagnosis of TEN, when compared to SJS does not necessarily correlated to a more severe ocular involvement nor increasing rate of late ocular complications. Specialized care, even in mild cases should always be taken into account. Late complications may be prevented through prompt and proper intervention during acute ocular involvement.[22]

All SJS/ TEN patients should always have their eyes examined daily by an ophthalmologist, with or without apparent acute ocular involvement. Ocular treatment may integrate ophthalmic preservative-free emollients, antiseptic eye drops, and/or vitamin A. Eye drops, physiologic saline, or antibiotics (e.g., fluoroquinolone or bacitracin) when necessary, are instilled every 2 hours. Latest studies suggests that ophthalmic topical steroids use (administration of 0.1% fluorometholone ointment repeated every 1-2 hours in 1-2 weeks duration) given together with amniotic membranes can aid in visual acuity preservation as well as protection

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against scarring.[37] Daily examination by an ophthalmologist is essential for early detection and prevention of ocular sequelae. Development of synaechia may be treated by disrupting the lesion with a blunt instrument. It is advisable to use gas-permeable scleral contact lenses in order to decrease discomfort and photophobia; these lenses may enhance visual acuity and promote healing of defect in corneal epithelium for half of the patients.[38]

Ophthalmic topical antibiotics

The ophthalmologic treatment of acute SJS/TEN should be aimed on prophylaxis of infection and adhesion, as well as to minimize the destructive inflammation.[1] A study by Yip et al revealed that severe dry eyes as particular late ocular complications were correlated with the use of topical antibiotics. This has not been mentioned in the previous studies. During acute stage of the disease, chloramphenicol eye drops are at times prescribed. The use of this treatment was often empirical in order to prevent secondary bacterial infections. The topical antibacterial can also be given as a combination of eye drop containing chloramphenicol and dexamethasone 0.1%. Sometimes tetracycline ointment is also given in combination with the two formulations mentioned above. Patients receiving therapy with topical corticosteroids and topical lubricants were also most likely to get additional topical antibiotics.[18]

Other author considers that prudent utilization of topical antibiotics for prophylactic purpose is advisable. The use of 0.5 % moxifloxacin (e.g. Vigamox®) for this purpose is excellent, owing to its bactericidal properties. It is effective to overcome most of the common skin pathogens, it may also achieve long term high concentrations on the cornea, as a single drop can maintain at least 6 hours of high concentrations in the tear film following application.[43] Furthermore, 20 minutes after application, moxifloxacin at a single dose can achieve 6-14 times higher conjunctival drug concentrations compared to other fluoroquinolone drops.[44] Those contributing factors should allow minimum dose application for an effective prophylaxis of infection.

A possible reasoning to explain severe symptoms of dry eye in correlation with topical antibiotic use could result from toxicity from preservatives in topical antibiotics to the accessory tear glands. Preservatives are substances intended to either prevent the growth or to destroy microorganisms. All clinical, experimental as well as ex vivo researchers suggest that allergic, toxic or inflammatory reactions are most likely to occur from preservatives in topical eyedrops rather than other additives such as stabilizing agents.[39] Among the preservatives as additives in the eye drops mentioned above are Thiomersal and Phenylmercuric nitrate. Those are ophthalmic preservatives of the mercurial chemical class. Previous studies both in vivo as well as ex vivo have indicate their ability in causing ocular damage such as acute as well as delayed ocular hypersensitivity, also stromal and endothelial cell edema.[40]

An alternative reasoning is direct toxicity from the topical antibiotic to the accessory tear glands.[41] Conjunctival tissue inflammations and polypharmacy both may result in tear gland damage which leads to the sequelae of dry eyes. The careful use and meticulously planned frequency of topical antibiotics as well as other topical treatments instillation would thus become important for all cases of SJS or TEN. Empirically administered topical antibiotics are not recommended if there are no clinical signs of concommitant ocular infection.[18]

Keeping the hygiene of the ophthalmic region is advisable and carries no harmful risk. Vigorous ophthalmic rinse daily with sterile saline will cleanse ocular surface and lid margins from any inflammatory debris and in addition, will reduce ocular surface infection risk.[42]

Ophthalmic topical cyclosporine

Topical cyclosporine use as a possible medication for SJS/TEN, aimed to reduce the intensity of inflammation on the ocular surface has been indicated. However, currently there have not yet any existing studies to support this treatment. Theoretically, systemic and topical ophthalmic use of cyclosporine may serve as excellent candidates as an immunosuppressant agent owing to its capability to selectively suppress T-cell immunity by IL-2 expression inhibition as well as prevention of proliferation and activation of T lymphocytes. [45]

There has been a large range of indication in inflammatory as well as immune-mediated ocular surface diseases to be treated with topical ophthalmic cyclosporine, particularly for severe allergic keratoconjunctivitis, dry eye disease, also for corneal transplant surgery. TEN is on the extreme edge of this immune-mediated ocular surface diseases spectrum, where the use of ophthalmic cyclosporine may serve as a potential medication for management of TEN in the acute phase in order to limit the destructive inflammation.[46]

Furthermore, twice per day use of topical moxifloxacin 0.5%, cyclosporine 0.5% (Restasis®, Allergan®), and dexamethasone 0.1% drops have shown good result for treatment of eye involvement of SJS. These drops were applied 2 hours apart, sequentially, in the morning and then repeated in the evening. At midday, a third drop of moxifloxacin may also be applied, following the recommendation of three times daily antibiotic application for treatment of bacterial conjunctivitis. The use of

tobramycin and dexamethasone combination ointment (Tobradex®, Alcon®) may be applied at night to the eyelid margins and eyelashes. Educating the nursing staff for proper application of the medications is very important. Topical antibiotic and antiinflammatory medications combination observed over the past few years in dozens cases of SJS/TEN demonstrate no case of infectious complications. The purpose has been to create a balance between theoretical benefit and possible harm from overmedication of an already fragile ocular surface.[42]

Shammas et al had previously report the use of topical ophthalmic cyclosporine for the acute stage of SJS and TEN in 8 patients. Despite the demonstrated good result in preservation of visual acuity and intact ocular surface in 12 patients, the role of cyclosporine remained unclear, as it had been used in combination with amniotic membrane coverage of the entire ocular surface.[47] In conclusion, the use of topical ophthalmic cyclosporine for ocular manifestation of TEN may have beneficial effects for prevention of ophthalmic complications. Further studies with larger series are required in order to draw a more definitive conclusion.

Ophthalmic topical corticosteroid

Systemic corticosteroids apparently fail to reduce ocular inflammation. On the other hand, support for topical corticosteroids as therapeutic measure in ocular manifestations of TEN came from numerous studies in the ophthalmology literature.[42,48,49] The ocular sequelae of SJS and TEN shares the same destructive pathologic process as with the cutaneous manifestation of the disease, with ocular surface desquamation which leads to pseudomembranous or membranous conjunctivitis.[49] Other ocular sequelaes include symblepharon (bulbar and palpebral conjunctivae adhesions), and corneal limbal stem cells destruction leading to vascularization and corneal epithelium destruction.[18,42] Corneal conjunctivalization may result in corneal opacification and severe visual loss.[50]

Direct ophthalmologic high-dose topical steroids application has demonstrate the ability to reduce disease duration as well as to improve visual outcomes for patients with TEN.[48] Sotozono et al observed 64 TEN patients for the visual outcomes. Thirty-three patients were treated with topical ocular steroids during the acute phase of the disease while 31 patients were not. The result of 20/200 vision or better occured to over 74 % of patients treated with topical steroid, compared with just 21 % of the patients who were not treated with steroids. Patients with 20/20 vision or better was also significantly increased in the topical steroid group (41 %) compared to the untreated group (21 %). The most important note is, patients without steroid treatment were statistically significant (P <0.00001) or much more likely to have worse than 20/2,000 vision (41 % versus 21 %).[48]

Symblepharon ring

Symblepharon still possibly developing despite all the proper measures applied. An ophthalmologist must perform a daily examination of the fornices. After application of topical anesthetic, early symblepharon formation is to be assessed by sweeping the fornices with a round-tipped muscle hook or scleral depressor. Symblepharon rings are very effective for symblepharon prevention.[42]

Amniotic membrane

Currently, there has been many reports which demonstrate the effectively of early grafting with cryopreserved amniotic membrane for acute phase of SJS/TEN to reduce the destructive ocular inflammation. Amniotic membrane consists of a one layer epithelial cells which is attached to a thick basement membrane and an avascular stroma. It is the innermost layer of the fetal membranes developing from the placenta. Despite the remains unknown exact mechanism, amniotic membrane demonstrates an excellent antiinflammatory as well as antiscarring effects. Application of amniotic membrane had shown successful results for reducing inflammation and promoting epithelial healing in various settings, namely acute chemical burns and corneal ulceration.[47]

Opthalmologic follow up are required be done to search for any sign and symptoms of sicca syndrome, keratitis and corneal lesion. Artificial tears and lubricants may be prescribed when necessary. Corneal inflammation lesion in its most severe form may persist to several months or years leading to a severe loss of visual acuity. Grafting using autolog cell from contralateral limbus or oral mucosa which carries stem cell, is a new approach with promising result.[1]

Genital care

Genital involvement may consist of erosive and ulcerative vaginitis, vulvar bullae formation and vaginal adhesion. The formation of extensive scar which will impair genital function may occur after the recovery of genital mucosa ulceration. Necrotizing part of vagina and vulva may develop into adhesion. However, symptomatic vaginal obstruction due to SJS/TEN rarely happened. Metaplastic changes on endometrial and cervical epithelium in the vaginal wall once reported, resulting in dyspareunia and post coital bleeding.[51]

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Regular genital examinations are required to monitor any involvement of the genital mucosa. Genital erosions in females or urethral erosions in both sexes may result in adhesions or strictures, where appropriate placement of wet dressings or sitz baths (immersing buttock to upper half of the thigh with water) may generally avoid these complications.[1,22]

Other proposed strategies to prevent adhesion and metaplastic changes of the genital area consist of the use of intravaginal topical steroid, vaginal molds and menstrual prevention with hormonal control method during the period of SJS/TEN.[51]

CONCLUSION

SJS/ TEN frequently lead to late sequeale which includes skin, ocular, oral, and genital involvement. These sequelaes are often severe and chonic. Thus, may cause significant decrease in quality of life of SJS/TEN survivors. It is therefore most important to detect them early in order to manage them adequately. To date, we still have an impression that the specific sequelae of SJS – TEN are often late diagnosed and insufficiently treated. Hence, we focused on prevention of such sequelae. Finally, we want to emphasize that for mucosal involvement in particular, such as ocular, genital and oral involvement, a careful topical treatment have to be taken into special consideration in order to prevent severe late sequelae.

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