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Acute Management of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis to Minimize Ocular Sequels

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Although relatively rare, Stevens-Johnson Syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), exhibits significant levels of mortality and morbidity relative to all other severe drug-induced blistering disorders. At the acute stage, the management algorithm for SJS/TEN involves exclusion of infectious agents, identification and prompt withdrawal of the suspected drug, and institution of treatment tailored individually according to the cause, type, and stage of the complications (reviewed in ¹). Because the primary objective is to save the patient's life, the majority of medical attention is devoted to acute treatment of widespread skin blisters and failing vital organs. Thus, consulting ophthalmologists have not held an active role in instituting effective measures to ameliorate the condition of SJS/TEN despite potentially blinding complications.

In addition to SJS/TEN's detrimental effects on the skin, an overwhelming majority of suffering patients also develop ocular surface inflammation and ulceration at an acute stage. For some SJS/TEN patients, ocular morbidity and visual loss can be caused during hospitalization by limbal stem cell deficiency following large corneal epithelial defects affecting the limbus. However, a significant number of patients still retain clear corneas and normal vision upon discharge, but gradually develop corneal blindness at the chronic stage because of cicatricial complications of the conjunctiva, fornix, tarsus, or lid margin after prolonged ulceration and inflammation of the ocular surface (² and refs cited therein).

There are various methods of management of SJS/TEN at the acute stage. Some believe that T-cell mediated immunologic responses are the cause of SJS/TEN and have consequentially administered high-dose glucocorticoids, cyclophosphamide, or cyclosporine as a means of arresting the progression of skin lesions. However, these drugs are of unproven benefit at the acute stage and clearly deleterious at the chronic stage (reviewed in ³). The use of systemic glucocorticoids is especially controversial; it is no longer recommended by many, but continues to be instituted by others (³ and refs cited therein). In 1999, Fritsch and Ruiz-Maldonado³ advocated in *Fitzpatrick's Dermatology in General Medicine* the use of a relatively high dose (e.g., 100 mg/day) of methylprednisolone, but cautioned its use to be limited to a short period of time only at the acute stage under the assumption that such a short-term high dose of steroid therapy can curb disease progression.

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In this Issue of *American Journal of Ophthalmology*, Araki and colleagues⁴ from Kyoto, Japan, administered an intravenous pulse therapy of a much higher dose (i.e., 500 or 1000 mg/day) of methylprednisolone for 3 to 4 days starting within 4 days from onset of the disease. This short-term, intense, steroid therapy resulted in dramatic improvement of skin eruptions in 5 patients with SJS or TEN. Although ocular inflammation still increased for several days, the above therapy, together with topical 0.1% betamethasone over 5 times daily for at least 2 weeks, also resulted in disappearance of pseudomembrane and regeneration of corneal and conjunctival epithelia within 6 weeks. As a result, all eyes retained clear corneas and 20/20 vision without evidence of limbal stem cell deficiency at the chronic stage.

Although their proposed therapy can be incorporated as a new strategy to reduce ocular morbidity and blindness associated with SJS/TEN, one needs to consider the following two issues:

The first issue is the obvious concern that a systemic high dose of glucocorticoids may heighten the risk of inciting (existing) infections in the wake of managing patients with life-threatening diseases. Such a concern, frequently raised by those who oppose this regimen, is partly derived from a nosologic confusion between erythema multiforme (EM) and SJS/TEN as a continuum. The fact that EM is known to have a high underlying infectious etiology does not bode well with hasty initiation of the steroid therapy. Nevertheless, at the acute stage it is feasible to differentiate EM clinically from SJS/TEN simply based on the type of skin lesions and their predominant body distribution as proposed by Bastuji-Garin et al⁵ in 1993. In so doing, EM differs from SJS/TEN with respect to clinical course, prognosis, cause and treatment (reviewed in ⁶). Indeed, subsequent clinical characterization⁷, clinicopathological correlation⁸, and a large international case-control epidemiological survey⁹ have substantiated that EM, defined by typical targets or raised atypical targets with primary acral (i.e., extremities) distribution, is benign and self-limited, may recur, infrequently involves the eye, and is more related to infection (mainly but not exclusively *herpes simplex virus*). In contrast, SJS/TEN, defined by widespread small blisters arising from flat atypical targets or purpuric maculae with predominant trunk and head distribution, is ominous, tends not to recur, frequently involves the eye, and is more related to drugs. Therefore, weighing against the risk of likely ocular morbidity and blindness, it seems justified to contemplate the purported high-dose pulse steroid therapy as soon as the clinical diagnosis of SJS/TEN is established. This should ideally happen about one week after drug exposure or 4 days after ocular involvement, if the likelihood of EM is eliminated. It is assuring that Araki et al did not observe significant adverse effects due to administration of steroid in their study. As alluded, the safety margin can further be elevated by careful monitoring and exclusion of common viral and microbial infections through a concerted effort of several subspecialties via skin biopsies (also see below) and microbial cultures of the tissue and the blood.

The second issue lies in whether there is a better strategy that one may deploy to abort disease progression by specifically targeting the pathogenic basis that leads to skin blisters and relentless ocular surface inflammation. In contrast to EM, where there is more inflammatory (lichenoid) infiltrate, SJS/TEM is pathologically characterized by predominantly epidermal necrolysis with minimal inflammatory infiltrate in the dermal stroma⁸, in which macrophages and dendritic cells show strong immunoreactivity for tumor necrosis factor (TNF)- α expression¹⁰. Besides scant amounts of cytotoxic CD4+ T cells in the dermis and CD8+ T cells in the epidermis that might secrete Perforin and Granzyme B to invoke cell lysis (reviewed in ¹¹), TNF- α ¹² and the CD95 (Fas) receptor-ligand system have been implicated as prime mediators leading to keratinocyte apoptosis and consequentially to necrolysis. Therefore, besides intravenous infusion of human

immunoglobulins, which is presumed to block the Fas receptor, another attractive and novel therapy may be transplantation of cryopreserved amniotic membrane as a biological bandage over the entire ocular surface (reviewed in ¹³ and refs cited therein). This surgical procedure, when performed within two weeks from the onset of ocular involvement, rapidly suppresses inflammation and promotes epithelialization at the acute stage. As a result, it prevents cicatricial complications at the chronic stage. Such clinical efficacies are supported by experimental studies exhibiting amniotic membrane's anti-inflammatory action that is manifest by rapid elimination of polymorphonuclear neutrophils^{14;15}, mononuclear inflammatory cells¹⁶, or macrophages¹⁷ via facilitation of cellular apoptosis. They are also supported by downregulation of T-helper cytokines secreted by activated lymphocytes¹⁸, and downregulation of several pro-inflammatory cytokines such as TNF- α secreted by activated macrophages¹⁹.

Further clinical studies with a larger sample size are warranted to help determine the pros and cons of these new therapies that can be delivered at the acute stage. In addition to research into the underlying destructive pathogenic mechanism, explaining how rapid diffuse necrolysis (apoptosis) develops in the epidermis and mucosal epithelia, these new therapies will undoubtedly propel ophthalmologists into an active and integral role for the acute management of SJS/TEN to halt potentially blinding sequels of this most devastating ocular surface disease.

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