Predictive Factors Associated With Acute Ocular Involvement in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

CHIE SOTOZONO, MAYUMI UETA, EIJI NAKATANI, AMANE KITAMI, HIDEAKI WATANABE, HIROHIKO SUEKI, MASAFUMI IIJIMA, MICHIKO AIHARA, ZENRO IKEZAWA, YUKOH AIHARA, YOKO KANO, TETSUO SHIOHARA, MIKIKO TOHYAMA, YUJI SHIRAKATA, HIDEAKI KANEDA, MASANORI FUKUSHIMA, SHIGERU KINOSHITA, AND KOJI HASHIMOTO, ON BEHALF OF THE JAPANESE RESEARCH COMMITTEE ON SEVERE CUTANEOUS ADVERSE REACTION

• PURPOSE: To suggest an objective score for grading the acute ocular severity of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and to determine predictive factors for severe acute ocular involvement such as ocular surface epithelial defect and/or pseudomembrane formation.

• DESIGN: Retrospective cohort study.

• METHODS: The medical records of SJS (n = 87) and TEN (n = 48) patients between 2005 and 2007 were reviewed. An acute ocular severity score was determined on a scale from 0 to 3 (none, mild, severe, and very severe) according to the existence of hyperemia, corneal or conjunctival epithelial defect, and pseudomembrane formation. The associations between the severe acute ocular involvement and factors such as patient age, exposed drugs, systemic severity, and the prevalence of ocular sequelae were examined.

• RESULTS: The number of cases with score grade 0, 1, 2, and 3 was 19 (21.8%), 31 (35.6%), 22 (25.3%), and 15 (17.2%) in 87 SJS cases and 12 (25.0%), 11 (22.9%), 17 (35.4%), and 8 (16.7%) in 48 TEN cases. Multivariate logistic regression analysis revealed that patient age (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.96–0.99; $P = .007$) and nonsteroidal anti-inflammatory drugs NSAIDs or cold remedies (OR, 2.58; 95% CI, 1.26–5.29; $P = .010$) were predictive factors for severe acute ocular involvement. The prevalence of visual disturbance and eye dryness increased according to the increase of acute ocular severity ($P = .001$ and $P = .007$ in SJS; $P = .007$ and $P = .014$ in TEN, respectively).

• CONCLUSIONS: At the onset of SJS/TEN, strict attention should be paid to ocular involvement in young patients and in patients exposed to NSAIDs or cold remedies. (Am J Ophthalmol 2015;160(2):228–237. © 2015 by Elsevier Inc. All rights reserved.)

STEVENS-JOHNSON SYNDROME (SJS) AND ITS MORE severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory disorders of the skin and mucous membranes that predispose patients to life-threatening complications such as sepsis, respiratory dysfunction, and multiple organ failure.[1–4] Both diseases are rare, yet can affect anyone, regardless of age, and usually as a consequence of adverse drug reactions. A variety of drugs including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiepileptic medications (ie, many if not most of the popularly used over-the-counter drugs) have been reported to cause severe drug reactions and induce SJS or TEN.[5,6] Ocular surface inflammation develops rapidly at the acute stage of the disease, and acute conjunctivitis occur prior to, or simultaneously with, skin eruptions.[7] Extensive inflammation of the ocular surface is often accompanied by corneal and/or conjunctival epithelial defects. Common signs after the acute stage include persistent epithelial defects, ulceration, and perforation, ultimately developing into corneal, conjunctival, and eyelid cicatricial changes such as neovascularization, opacification, keratinization, and symblepharon.[7,8] Visual impairment and severe dryness of the eye continue lifelong as ocular sequelae.[7,8] Although we previously reported both surgical[9–14] and nonsurgical[15] therapeutic methods to treat chronic-stage SJS/TEN, it remains impossible to restore the ocular surface to its normal healthy state (ie, that of before disease onset).

In a previous report from Power and associates,[16] the authors categorized acute ocular severity into the grades of mild, severe, or very severe. In that grading system, mild

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From the Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan (C.S., M.U., S.K.); the Department of Dermatology, Showa University School of Medicine, Tokyo, Japan (A.K., H.W., H.S., M.I.); the Department of Dermatology, Yokohama City University Medical Center, Yokohama, Japan (M.A., Z.I.); the Department of Pediatrics, Yokohama City University Medical Center, Yokohama, Japan (Y.A.), the Department of Dermatology, Kyorin University School of Medicine, Tokyo, Japan (Y.K., T.S.); the Department of Dermatology, Ehime University Graduate School of Medicine, Matsuyama, Japan (M.T., Y.S., K.H.); and the Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Japan (E.N., H.K., M.F.).

Inquiries to Chie Sotozono, Department of Ophthalmology, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Hirokoji-agaru, Kawaramachi-dori, Kamigyo-ku, Kyoto 602-0841, Japan; e-mail: csotozon@koto.kpu-m.ac.jp

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involvement was defined as mild conjunctival injection, lid edema, and/or chemosis; moderate involvement consisted of membrane formation, corneal epithelial loss of more than 30%, corneal ulceration, and/or corneal infiltrates; and severe involvement consisted of fornix shortening, symblepharon formation, and/or visual loss. Considering the fact that SJS and TEN are characterized by epidermal necrosis with detachment and erosion of the mucous membranes,[2,17] corneal or conjunctival epithelial defects are prominent disease-related factors at the onset. In addition, it is reported that extreme inflammation develops on the ocular surface accompanying pseudomembrane formation at the acute stage.[16,18,19] Thus, we hypothesized that a simple grading system based on the presence of conjunctivitis, corneal or conjunctival epithelial defect, and pseudomembrane formation might be appropriate to evaluate acute ocular severity of SJS/TEN.

Owing to the high mortality rate of patients with SJS and TEN (1%～5% and 20%～30%, respectively), investigations of these diseases have been intensively focused on systemic severity and general treatment.[6,20–22] Unfortunately, even in the large-scale survey of the severe adverse drug reactions conducted in Europe,[4,21–23] the ocular involvement was not explored. Moreover, the predictive features of ocular involvement at the acute stage of SJS/TEN remain unclear.

The aim of this study was to construct a simpler and more practical score for grading the acute ocular severity of SJS and TEN, as well as to determine predictive factors having severe or very severe (as opposed to none or mild) acute ocular involvement in SJS/TEN patients based on a Japanese nationwide retrospective study of SJS and TEN patients in which both dermatologists and ophthalmologists participated.[24] Furthermore, correlation between the severe acute ocular involvement and the prevalence of ocular sequelae (visual disturbance and dryness of the eye) was examined.

METHODS

THIS STUDY WAS APPROVED BY THE ETHICS COMMITTEE and Institutional Review Board of Kyoto Prefectural University of Medicine, Kyoto, Japan (RBMR-E-215), and was carried out in accordance with the tenets set forth in the Declaration of Helsinki.

• **PATIENTS:** In order to investigate ocular involvement in SJS/TEN patients as a first step, we retrospectively reviewed SJS and TEN patients who were diagnosed in the period from January 2005 to December 2007, with the medical records of those patients being obtained from dermatologists.[24]

• **DATA COLLECTION:** To identify SJS and TEN patients, a questionnaire was first sent to dermatologists at 607 medical institutions, and dermatologists from 212 medical institutions responded. Secondly, case report forms (CRFs) were sent to dermatologists. Based on the medical records in each institution, patients matching the diagnostic criteria for SJS and TEN, which was made by the Japanese Ministry of Health, Labour and Welfare in 2005 (Table 1) (diagnostic criteria and systemic severity index score for Stevens-Johnson syndrome available at http://www.nanbyou.or.jp/entry/3680, accessed April 21, 2015), were determined. The CRF was structured as follows: (1) diagnostic criteria,

TABLE 1. Diagnostic Criteria for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis by Japanese Ministry of Health, Labour and Welfare (2005)

	Diagnostic Criteria
Stevens-Johnson syndrome	
Clinical entity	A severe mucocutaneous disorder characterized by erythema, epidermal detachment, and enanthema accompanied by high fever
Essential criteria (required)	1. Severe hyperemic and/or hemorrhagic mucocutaneous lesions 2. Epidermal detachment involving <10% of the total body surface area 3. High-grade fever (≥38.0 °C) in the absence of antipyretic therapy
Supportive findings	1. Flat, atypical target lesions 2. Bilateral acute keratoconjunctivitis accompanied by ocular surface epithelial defect and/or pseudomembrane formation 3. Histologic evidence of epidermal necrosis
Toxic epidermal necrolysis	
Clinical entity	A severe mucocutaneous disorder characterized by extensive erythema, epidermal detachment (including blisters and erosions), and enanthema accompanied by high fever. The extent of epidermal detachment is ≥10% of the total body surface area
Essential criteria (required)	1. Epidermal detachment involving >10% of the total body surface area 2. Exclusion of staphylococcal scalded skin syndrome 3. High-grade fever (≥38.0 °C) in the absence of antipyretic therapy
Supportive findings	1. Generalized macular or diffuse erythema 2. Enanthema including bilateral acute keratoconjunctivitis accompanied by ocular surface epithelial defect and/or pseudomembrane formation 3. Histologic evidence of marked epidermal necrosis