Special Article

SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation

Katie D. White, MD, PhD[a], Riichiro Abe, MD, PhD[b], Michael Ardern-Jones, DPhil, FRCP[c], Thomas Beachkofsky, MD[d], Charles Bouchard, MD, MA[e], Bruce Carleton, PharmD[f,g], James Chodosh, MD, MPH[h], Ricardo Cibotti, PhD[i], Robert Davis, MD, MPH[j], Joshua C. Denny, MD, MS[a], Roni P. Dodiuk-Gad, MD[k,l], Elizabeth N. Ergen, MD[m], Jennifer L. Goldman, MD, MS[n], James H. Holmes IV, MD, FACS[o,p], Shuen-lu Hung, PhD[q], Mario E. Lacouture, MD[r], Rannakoe J. Lehloenya, MBChB, FCDerm (SA)[s], Simon Mallal, MBBS[a,t], Teri A. Manolio, MD, PhD[u,v], Robert G. Micheletti, MD[w], Caroline M. Mitchell, MD, MPH[x], Maja Mockenhaupt, MD[y], David A. Ostrov, PhD[z], Rebecca Pavlos, PhD[t], Munir Pirmohamed, MB ChB (Hons), PhD[aa], Elena Pope, MD, MSc, FRCPC[bb,cc], Alec Redwood, PhD[t], Misha Rosenbach, MD[w], Michael D. Rosenblum, MD, PhD[dd], Jean-Claude Roujeau, MD[ee], Arturo P. Saavedra, MD, PhD, MBA[x], Hajirah N. Saeed, MD[h], Jeffery P. Struewing, MD[u], Hirohiko Sueki, MD[ff], Chonlaphat Sukasem, BPharm, PhD[gg], Cynthia Sung, PhD, FCP[hh,ii], Jason A. Trubiano, MD[jj,kk], Jessica Weintraub, PharmD, BCPS[ll], Lisa M. Wheatley, MD, MPH[mm], Kristina B. Williams, RN, BSN[a], Brandon Worley, MD, MSc[nn], Wen-Hung Chung, MD, PhD[oo], Neil H. Shear, MD[a], and Elizabeth J. Phillips, MD[a,t]

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Learning objectives:

1. To identify current knowledge gaps in the clinical management of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

2. To identify key research questions and gaps pertinent to SJS/TEN.

3. To discuss advances in knowledge of the genetic and mechanistic basis of SJS/TEN and their translational outputs such as pharmacogenomic screening.

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E. J. Phillips has received research support from the National Health and Medical Research Council Australia, the NIH, and ACH2 Australia; receives royalties from UpToDate; has received consultancy fees from Biocryst, Aicuris, Xcovery, and Medicines for Malaria (MMV); and is codirector of the company holding the patent for HLA-B*57:01 testing for abacavir hypersensitivity reaction. The rest of the authors declare that they have no relevant conflicts of interest. M. Schatz disclosed no relevant financial relationships.

This article is a summary of a meeting that was held on March 2, 2017. You may view the presentations from the meeting and earn additional CME credit at http://www.jaci-inpractice.org/sjs-ten-2017.

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a life-threatening, immunologically mediated, and usually drug-induced disease with a high burden to individuals, their families, and society with an annual incidence of 1 to 5 per 1,000,000. To effect significant reduction in short- and long-term morbidity and mortality, and advance clinical care and research, coordination of multiple medical, surgical, behavioral, and basic scientific disciplines is required. On March 2, 2017, an investigator-driven meeting was held immediately before the American Academy of Dermatology Annual meeting for the central purpose of assembling, for the first time in the United States, clinicians and scientists from multiple disciplines involved in SJS/TEN clinical care and basic science research. As a product of this meeting, this article summarizes the current state of knowledge and expert opinion related to SJS/TEN covering a broad spectrum of topics including epidemiology and

[a]Vanderbilt University Medical Center, Nashville, Tenn
[b]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan
[c]University of Southampton, Southampton, United Kingdom
[d]Wilford Hall Ambulatory Surgical Center, Lackland Air Force Base, San Antonio, Texas
[e]Loyola University Medical Center, Chicago, Ill
[f]University of British Columbia, Vancouver, British Columbia, Canada
[g]B.C. Children's Hospital, British Columbia, Vancouver, British Columbia, Canada
[h]Massachusetts Eye and Ear, Harvard Medical School, Boston, Mass
[i]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Md
[j]University of Tennessee Health Sciences, Memphis, Tenn
[k]Emek Medical Center, Technion-Institute of Technology, Afula, Israel
[l]Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[m]University of Alabama at Birmingham, Birmingham, Ala
[n]Children's Mercy Hospital Kansas City, Kansas City, Mo
[o]Wake Forest Baptist Medical Center, Winston-Salem, NC
[p]Wake Forest University School of Medicine, Winston-Salem, NC
[q]National Yang-Ming University, Taipei, Taiwan
[r]Memorial Sloan Kettering Cancer Center, New York, NY
[s]University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[t]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western Australia, Australia
[u]National Human Genome Research Institute, National Institutes of Health, Bethesda, Md
[v]F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Md
[w]University of Pennsylvania, Philadelphia, Pa
[x]Massachusetts General Hospital, Boston, Mass
[y]Medical Center and Medical Faculty—University of Freiburg, Freiburg, Germany
[z]University of Florida, Gainesville, Fla
[aa]University of Liverpool, Liverpool, United Kingdom
[bb]University of Toronto, Toronto, Ontario, Canada
[cc]Hospital for Sick Children, Toronto, Ontario, Canada
[dd]University of California, San Francisco, Calif
[ee]University Paris-Est-Créteil, Créteil, France
[ff]Showa University School of Medicine, Tokyo, Japan
[gg]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[hh]Duke-NUS Medical School, Singapore, Singapore
[ii]Health Sciences Authority, Singapore, Singapore
[jj]Austin Health, Heidelberg, Victoria, Australia
[kk]University of Melbourne, Melbourne, Victoria, Australia
[ll]US Food and Drug Administration, Silver Spring, Md
[mm]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md
[nn]University of Ottawa, Ottawa, Ontario, Canada
[oo]Chang Gung Memorial Hospital, Taipei, Taiwan

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Abbreviations used
ADR- Adverse drug reaction
AMT- Amniotic membrane transplantation
BSA- Body surface area
CPNDS- Canadian Pharmacogenomics Network for Drug Safety
DIHS- Drug-induced hypersensitivity syndrome
DRESS- Drug reaction with eosinophilia and systemic symptoms
DSC- Drug safety communication
EMM- Erythema multiforme majus
EHR- Electronic health record
FAERS- Food and Drug Administration Adverse Event Reporting System
FDA- Food and Drug Administration
GBFDE- Generalized bullous fixed drug eruption
HAS- Health Sciences Authority
HCP- Healthcare professional
HIV- Human immunodeficiency virus
HLA- Human leukocyte antigen
ICD- International Classification of Diseases
IM-ADR- Immunologically mediated adverse drug reaction
ITCH- International Consortium on Drug Hypersensitivity
IVIG- Intravenous immunoglobulin
MIRM- Mycoplasma-induced rash and mucositis
NATIENS- North American Therapeutics in Epidermal Necrolysis Syndrome
NK- Natural killer
NPV- Negative predictive value
NSAID- Nonsteroidal anti-inflammatory drug
OR- Odds ratio
PBMC- Peripheral blood mononuclear cells
PD-1- Programmed cell death protein 1
PMC- Postmarketing commitments
PMR- Postmarketing requirements
PMTCT- Prevention of mother-to-child HIV transmission
PPV- Positive predictive value
PTSD- Posttraumatic stress disorder
REMS- Risk evaluation and mitigation strategies
SCAR- Severe cutaneous adverse reaction
SCORTEN- Severity of illness score for TEN
SDH- Society of Dermatology Hospitalists
SJS/TEN- Stevens-Johnson syndrome/toxic epidermal necrolysis
TB- Tuberculosis
TCR- T-cell receptor
TEN- Toxic epidermal necrolysis
TNF- Tumor necrosis factor
Treg- Regulatory T

pharmacogenomic networks; clinical management and complications; special populations such as pediatrics, the elderly, and pregnant women; regulatory issues and the electronic health record; new agents that cause SJS/TEN; pharmacogenomics and immunopathogenesis; and the patient perspective. Goals include the maintenance of a durable and productive multidisciplinary network that will significantly further scientific progress and translation into prevention, early diagnosis, and management of SJS/TEN. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:38-69)

Key words: *Stevens-Johnson; Toxic epidermal necrolysis; HLA; Networks; Pharmacogenomics; Pharmacovigilance; Electronic health record; T cells; Granulysin*

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the severest in the spectrum of immunologically mediated adverse drug reactions (IM-ADRs) that are considered to be primarily T-cell—mediated. SJS/TEN is characterized by a painful blistering skin rash that is often associated with multiorgan involvement, commonly fever, hematologic abnormalities, and ophthalmologic and genitourinary involvement. Early dermatologic findings may include erythematous or dusky colored macules that evolve to become fluid-filled bullae and/or denuded skin. Involved nonblistered skin often sloughs with direct lateral pressure (Nikolsky sign) and demonstrates interface dermatitis with necrotic

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Corresponding author: Elizabeth J. Phillips, MD, FIDSA, FAAAAI, Vanderbilt University Medical Center, 1161-21st Avenue South, A-2200 Medical Center North, Nashville, TN 37232. E-mail: elizabeth.j.phillips@vanderbilt.edu.

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keratinocytes and epidermal separation on histopathologic examination (Table I). SJS and TEN are thought to be the same disease across a spectrum of severity defined by the percentage of skin detachment related to the body surface area (BSA) comprising SJS (<10%), SJS/TEN overlap (10%-30%), and TEN (>30%) (Table I). The mortality associated with TEN in the setting of aggressive supportive care at experienced centers is approximately 30%; however, in the elderly and immunocompromised populations this can exceed 50%. The short-term morbidity associated with SJS/TEN is well recognized and includes sepsis, respiratory complications, gastrointestinal and genital tract mucositis, and eye disease. However, long-term morbidity is also considerable and includes vision loss, urogynecological complications, chronic respiratory disease, depression and posttraumatic stress, disfigured painful skin, restricted therapeutic choices, and shortened life span. Over the last 10 to 15 years, there have been significant advances in our understanding of the immunogenomics of IM-ADRs.[2] For SJS/TEN this has included several strong associations from Southeast Asia between HLA class I alleles and drug-associated SJS/TEN including HLA-B*15:02 and carbamazepine SJS/TEN and HLA-B*58:01 and allopurinol SJS/TEN. This has led not only to successful HLA-B*15:02 screening programs in Taiwan, Singapore, and other parts of Southeast Asia that have almost eliminated carbamazepine-associated SJS/TEN, but also furthered our understanding of the immunopathogenesis of SJS/TEN. Despite this progress there are still a large number of clinical and research gaps. A few highlights of these gaps include the lack of (1) an evidence-based approach to guide therapeutic interventions above aggressive supportive care in acute SJS/TEN, (2) predictive biomarkers for early diagnosis and prognosis, (3) genetic predictors for most drugs that cause SJS/TEN, and (4) an explanation for why only a small proportion (<10%) of those carrying an HLA risk allele will develop SJS/TEN following drug exposure.[2]

To explore gaps and unmet needs for further research into the epidemiology, pathogenesis, treatment, and prevention of SJS/TEN, the National Human Genome Research Institute, along with the Food and Drug Administration and 5 other National Institutes of Health institutes and centers (the National Center for Advancing Translational Sciences, the National Institute on Drug Abuse, the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis, Musculoskeletal and Skin Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases), brought together 30 international experts in severe cutaneous adverse reactions, pharmacogenomics, and related fields for a 2015 workshop titled "Research directions in genetic predispositions to SJS/TEN.".[3,4] This 2-day workshop reviewed the current state of knowledge of surveillance, pathogenesis, and treatment of SJS/TEN, examined the role of genomics in the etiology, treatment, and eradication of preventable cases of SJS/TEN, and identified gaps, unmet needs, and priorities for future research to work toward the global elimination of genetically mediated SJS/TEN. A primary conclusion of this meeting was that although there have been great research strides in SJS/TEN with compelling examples of implementation of personalized medicine, there is continued need to broaden these discoveries for translation and implementation across diverse populations and causative drugs. Overarching and facilitative research goals were set and 3 high priority areas were identified and targeted: clinical care, pharmacovigilance and epidemiology, and basic research. An important outcome of the meeting was recognition of the need, because of the overall rarity and diverse epidemiology of SJS/TEN, to develop a large global collaborative network and a supportive funding infrastructure to further all aspects of SJS/TEN research.

An ongoing dialogue among an SJS/TEN working group comprising members from academia and government followed this meeting and has led to new initiatives that have included the establishment of an SJS/TEN phenotyping group that published a standardized case report form for SJS/TEN,[5] a subgroup evaluating SJS/TEN causality assessment tools, and a national survey of dermatologists, burn surgeons, and ophthalmologists who care for patients with SJS/TEN that identified knowledge gaps, priorities, unmet needs, and unresolved controversies in SJS/TEN clinical care and research. More than 50% of survey respondents were interested in the opportunity for further engagement in all aspects of SJS/TEN research.[6]

The fundamental clinical, epidemiological, and basic research questions identified in the 2015 National Institutes of Health workshop served as a catalyst for further efforts toward organized collaboration. To engage a broad constituency of stakeholders in this effort, a meeting "Stevens-Johnson-syndrome/Toxic epidermal necrolysis 2017: Building Multidisciplinary Networks to Drive Science and Translation" was held on March 2, 2017. This meeting had representation across allergy-immunology, dermatology, ophthalmology, burns surgery, gynecology, clinical pharmacology, basic science (immunobiology, genetics), epidemiology, informatics, regulatory science, patients and their families, and government and included 142 participants from 6 continents (Figure 1). A major goal of this meeting was to bring together established and new investigators to create a durable network of SJS/TEN clinicians and scientists to discuss and prioritize achievable short- and long-term research objectives. This meeting was charged with presentation of the most current and cutting-edge research relevant to SJS/TEN, provision of mentorship for new investigators of disparate backgrounds to become future leaders in SJS/TEN, and, importantly, to provide a multidisciplinary and interactive forum where the most controversial areas of SJS/TEN clinical care and research could be discussed. The meeting highlighted key areas amenable to network building and clinical translation. Representatives from 3 National Institutes of Health institutes—the National Human Genome Research Institute, the National Institute of Allergy and Infectious Diseases, and the National Institute of Arthritis, Musculoskeletal and Skin Diseases—provided updates on funding mechanisms relevant to SJS/TEN with a focus on newer R01/R21 funding related to serious IM-ADRs.[7,8]

This article is a summary of the proceedings of the meeting that includes the new and evolving science, key controversies, outputs of the meeting, and proposed future directions.

GLOBAL EPIDEMIOLOGY AND PHARMACOGENOMICS NETWORKS*

Key Points:

- SJS/TEN is a life-threatening mainly drug-induced disease with considerable short- and long-term morbidity and

* Bruce Carleton, PharmD; Robert G. Micheletti, MD; Maja Mockenhaupt, MD; Munir Pirmohamed, MBChB (Hons), PhD; Jean-Claude Roujeau, MD; Hirohiko Sueki, MD; Chonlaphat Sukasem, BPharm, PhD; Jason A. Trubiano, MD; Brandon Worley, MD, MSc

TABLE I. Phenotypic characteristics of SJS/TEN and severe cutaneous syndromes

Characteristic	SJS/TEN	EMM	GBFDE
Target lesions	Flat, atypical target lesions present	Typical or raised atypical target lesions	No
Blisters and erosions	Yes <10%: SJS; 10%-30%: SJS/TEN overlap; >30%: TEN	Yes, in the center of targets	Yes
Distribution	Widespread	Mainly limbs or acral	Localized
Well-demarcated, erythematous patches (≥5 cm)	No	No	Yes
Erosions of mucosa (eye/lip/genital)	Yes	Yes	Yes or no
Recurrent history	Rare	Occasional	Common
Prognosis	Mortality depends on risk factors (SCORTEN[1])	Favorable	Generally favorable but associated with higher morality with >20% BSA involvement and in elderly
Etiology	Usually drug-induced	Suspected infection not drug	Usually drug-induced

EMM, Erythema multiforme majus; *GBFDE*, generalized bullous fixed drug eruption.
SCORTEN: Age < 40 y (0), >40 y (+1); Associated malignancy: no (0), yes (+1); Heart rate (beats/min): <120 (0), >120 (+1); serum blood urea nitrogen (mg/dL): <28 (0), >28 (+1); detached or compromised body surface: <10% (0), >10% (+1); Serum bicarbonate (mEq/L): >20 (0), <20 (+1); Serum glucose (mg/dL): <252 (0), >252 (+1).

FIGURE 1. Participants representing 14 countries from 6 medical subspecialties, SJS/TEN advocacy groups, the US government, and the SJS/TEN research community gathered in Orlando, Florida, on March 2, 2017, for the inaugural *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation meeting*. Thirty predoctoral and postdoctoral trainees attended and presented original research at this meeting. **A**, Subspeciality distribution of participants. **B**, Global distribution of participants. *PGx*, Pharmacogenomics.

mortality that poses a burden to health care systems and families disproportionate to its prevalence.
- The rarity of SJS/TEN has created challenges for the generation of evidence-based treatment.
- Collaborative pharmacogenomic studies have been successful in determining HLA associations in SJS/TEN and provide the promise for more associations to be delineated in the future.
- The development of networks that include an SJS/TEN phenotype adjudication committee as well as centralized biological sample collection and repositories would provide a platform to study pathogenesis and predictors.

A number of collaborative networks exist that study the epidemiology and pharmacogenomics of SJS/TEN across genetically diverse populations, seek to discover pathogenic mechanisms and other mediators of disease risk, and allow for the development of clinical trials to evaluate therapeutic interventions. Session one of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured representatives from some of these international collaborative networks. The strength of these networks lies in the rigorous definitions for clinical diagnosis, causality assessment at the individual case level, estimation of risk factors for each severe cutaneous adverse reaction (SCAR) entity, and centralized collection of samples to facilitate investigation of the mechanisms and search for new therapeutic options.

The Society of Dermatology Hospitalists SJS/TEN Study Group (United States)

The Society of Dermatology Hospitalists (SDH) is a US-based organization dedicated to the care of complex dermatological patients in the inpatient setting. In an effort to describe the SJS/TEN experience of dermatology hospitalists in the United States and explore ongoing management controversies in SJS/TEN, the SDH retrospectively collected information on the disease course, management, and outcomes of patients treated for SJS/TEN at member institutions. As a collaborative research effort of 18 tertiary care centers, the SDH has

compiled a database of 405 US SJS/TEN cases between 2000 and 2015, with most patients treated from 2010 onward. Medications were the most common cause of SJS/TEN in this cohort, accounting for 91.3% of cases and trimethoprim/sulfamethoxazole was most often implicated (26.0%). Sixty-six percent of patients met criteria for TEN (>30% BSA denuded) or SJS/TEN overlap (10%-30% BSA denuded) at the time of admission. The severity of illness score for TEN (SCORTEN)[1] predicted mortality for the cohort at the time of admission to be 20.0%. Sixty-seven percent of patients were managed in a specialized burn or intensive care unit and 70% received pharmacotherapeutic intervention in addition to supportive care, most commonly corticosteroids, intravenous immunoglobulin (IVIG), or both steroids and IVIG. Only 4 patients in this cohort received cyclosporine and 1 patient received the TNF-α inhibitor etanercept. Actual mortality of patients in the cohort was 13.7%, for a standardized mortality ratio of 0.69 (95% CI, 0.57-0.78). The improved survival of patients in this cohort compared with SCORTEN-predicted mortality is notable and likely multifactorial. Preliminary analyses showed an overall lack of consensus regarding the management of SJS/TEN and no clear evidence of benefit from any particular pharmacotherapeutic intervention compared with supportive care alone. Additional work to account for relevant confounding factors and choice of pharmacotherapy is ongoing. Future work of the SDH will include evaluation of the updated SCORTEN algorithm to predict SJS/TEN mortality, longitudinal analyses of SJS/TEN survivors to determine sequelae and quality of life following recovery, and a prospective SJS/TEN cohort study and, ultimately, randomized controlled trial.

The North American Therapeutics in Epidermal Necrolysis Syndrome Trial Network (North America)

Composed of 24 academic institutions and burn centers in the United States and Canada, the North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) Trial Network brings together expertise in burn surgery, dermatology, eye, and mucosal complications and leaders in immunogenetic science to create the feasibility for a multicenter, translational clinical trial comparing cyclosporine, etanercept, and supportive care.[6] The NATIENS Trial Network's mission is to enhance the quality and standardization of care for patients with SJS/TEN through accelerating scientific discovery. The NATIENS Trial Network also includes 3 scientific centers with expertise in immunogenetics, next-generation genomic sequencing, cellular immunology, and pharmacokinetics. A double-blind randomized controlled trial assessing standardized supportive care and immunomodulatory therapeutics in SJS/TEN is planned to begin in 2019 and will be the first to rigorously study SJS/TEN in a multicenter setting. Its members have developed tools for standardized assessment of skin involvement and reepithelialization to measure response to therapy, a comprehensive supportive care protocol, and immunogenetic and cellular analyses to study the underlying pathophysiology. Outcomes from the NATIENS Trial Network's clinical trial will include a rigorous and objective assessment of a standardized supportive care model and immunomodulatory therapies in acute SJS/TEN, longitudinal patient follow-up for standardized assessment of short- and long-term sequelae, systemic and tissue-specific genetic and immunologic analyses to define pathogenic mechanisms and provide mechanistic support for immunomodulatory therapies in acute disease, as well as the infrastructure and clinical and scientific partnerships for the future study of unexplored therapeutic targets and markers of SJS/TEN risk in North American populations.

The Canadian Pharmacogenomics Network for Drug Safety

The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) consists of more than 65 multidisciplinary expert collaborators from 26 pediatric and adult academic health centers in Canada that recruit patients via active surveillance and collect genomic samples and clinical information on drug outcomes. Currently, the CPNDS active surveillance clinical database includes detailed clinical information for various drugs from more than 9,313 adverse drug reaction cases and 84,082 drug-exposure—matched controls. More patients are recruited networkwide each day. The CPNDS has used this methodology to study the pharmacogenomics of several severe adverse drug reactions (ADRs) and was the first to confirm the role of *HLA* markers for carbamazepine-related skin reactions in children.[9] The CPNDS is actively addressing the problem of these severe reactions by using diverse approaches such as (1) *discovery/replication through collaboration.* This approach is used to confirm previously identified pharmacogenomic biomarkers as well as identify novel genomic variation associated with these reactions, which, given the rarity of SJS/TEN, requires collaboration between international consortia. Further collaboration with the EpiPGX Consortium (Europe) has led to the identification of more than 80 cases of severe cutaneous ADRs associated with anticonvulsants. A genomewide assessment of these cases using both genotyping arrays and exome sequencing is in process. Collaborations with additional international consortia are underway. (2) *Knowledge translation and commercialization.* A key outcome is translation of pharmacogenomics into clinical practice. The CPNDS has published clinical practice guidelines for carbamazepine-related ADRs[10] and is currently working with the Clinical Pharmacogenetics Implementation Consortium to update relevant guidelines and develop commercial pediatric pharmacogenomic panels that will include ADR pharmacogenomic markers (for more information, please visit https://cpicpgx.org/).

The International Consortium on Drug Hypersensitivity network

The International Consortium on Drug Hypersensitivity (ITCH) network, coordinated in Liverpool, UK, and funded by the International Serious Adverse Event Consortium, was established for the recruitment of patients with SCAR and now includes 1,500 precisely phenotyped cases from 12 countries with associated genetic data.[11] Analyses using the ITCH cohort have concentrated on identifying drug-specific genetic predisposing factors and genetic factors predisposing to SJS/TEN irrespective of drug etiology. Genomewide association studies from 1,260 SCAR cases in the ITCH cohort rely on careful quality control procedures that include controlling for population stratification, imputation using the latest releases of genomic data, and validation of imputed genetic variants, where appropriate.

The ITCH database includes 177 SJS/TEN cases that are derived from Caucasian patients from 3 ethnic groups: Spanish, Italian, and Northern European. Analysis of all 177 SJS/TEN cases identified an HLA-B allele that is associated with SJS/TEN

irrespective of drug. This HLA-B allele is present at 0.02% of the general Caucasian population (n = 9,237 not exposed to drug) but is found at 100-fold higher frequency among SJS/TEN cases (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). Interestingly, this association seems to be largely limited to Italian patients. Replication in Italian patients will be challenging given the rarity of SJS/TEN and new patients will need to be recruited for this analysis.

Drug-specific analysis in the ITCH cohort has also led to replication of HLA allele associations that have been previously identified in other populations. For instance, in 13 European patients with allopurinol-induced SCAR of whom 9 had SJS, HLA-B*58:01 was identified at a genomewide significance level with an odds ratio of 36. Although the association of HLA-B*58:01 with SJS was just below genomewide significance in this population, the odds ratio was higher at 45 (M. Pirmohamed, MBChB, PhD, unpublished data, March 2017). This is consistent with previous data that suggest that HLA-B*58:01 is present in approximately 60% of allopurinol patients of European ancestry with SJS/TEN.

The ITCH network also includes African recruitment sites. Work in this cohort has identified the association of HLA-C*04:01 carriage and SJS/TEN secondary to the antiretroviral drug nevirapine. Further analysis of the interaction of HLA-C*04:01 with the *endoplasmic reticulum aminopeptidase* genes that influence peptide processing showed that *endoplasmic reticulum aminopeptidase 2* may have a potentially protective effect.[12]

The RegiSCAR Network and sample repository

The RegiSCAR project was born out of experience with multiple epidemiological studies on SCAR that have been undertaken in Europe during the past 3 decades. Early studies included large retrospective case compilations performed in the 1980s and published in the early 1990s, followed by a large case-control study that provided the best available evidence for drug causality at the time (SCAR study).[13-15] In parallel, a population-based registry on SJS/TEN was started in Germany to assess disease incidence and demography, using the same criteria for case validation and ascertaining medication history.[16] Later, a second case-control surveillance (EuroSCAR study, 1997-2001) was undertaken that could confirm results on drug risk of the previous study and provide new data on recently marketed drugs.[17-20] These studies were followed by a multinational registry (RegiSCAR study) that was founded to systematically collect biological samples of patients with SCAR and patients were followed longitudinally after hospital discharge.[20-23] These studies required that investigators establish and maintain a network of hospitals and departments likely to treat SCAR, determine precise definitions of clinical entities (phenotypes), and determine methods for systematic case ascertainment, standardized case validation, and data management and statistical analysis. Case ascertainment was done by trained investigators (health care professionals) using a standardized questionnaire in direct conversation with the patient and in cases of severe illness, the patient's relatives, treating physicians, family physician, and medical records.

The RegiSCAR project is a registry of SCAR cases in several European and non-European countries that combines a protocol for systematic blood sampling and centralized biobanking of PBMCs, plasma, and DNA and cohort studies investigating outcome, sequelae, and treatment.[20,21] Earlier studies focused on SJS/TEN, whereas RegiSCAR includes a broader spectrum of reactions including drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and generalized bullous fixed drug eruption (GBFDE). Continuous surveillance of SJS/TEN in this cohort shows that approximately 67% of strictly validated cases had a probable or very probable drug cause as determined by the algorithm for assessment of drug causality in epidermal necrolysis score (Table II ; M. Mockenhaupt, MD, unpublished data, March 2017), 20% were secondary to a possible drug cause, and 13% were unlikely or not at all drug-induced. Genetic studies of SJS/TEN in European cases in the RegiSCAR cohort have led to the identification of risk alleles differing from other ethnic groups and genomewide association study analysis demonstrated that the HLA region on chromosome 6 is of major importance.[22,23] A RegiSCAR cohort study of several hundred patients with SJS/TEN revealed that the vast majority of survivors are left with sequelae persisting over months and years.

Thai-SCAR and the Southeast Asian Pharmacogenomics Research Network

In Thailand and other parts of Southeast Asia drugs that commonly cause SCAR have been marketed since 1980, an era of less socioeconomic development and limited clinical research capacity in the region, and this resulted in a lack of pharmacovigilance and an increase in SCAR incidence during this time frame. In 1984, Thailand developed Thai VigiBase, a database and spontaneous reporting system for SJS/TEN and other serious ADRs administered by the Thailand Food and Drug Administration. Thai VigiBase receives approximately 50,000 reports each year of which approximately 20% are serious immune-mediated ADRs and 70.4% of these cases are SJS/TEN. Using this resource, multiple predictive genomic markers that may be used to identify patients at elevated risk for the most common drug-specific SJS/TEN in the Thai population were discovered by the international collaborative research team. For example, HLA-B*15:02 and HLA-B*58:01 are common alleles among Southeast Asian populations and are strongly associated with carbamazepine- and allopurinol-induced SJS/TEN, respectively.[26-30] In Thailand, the Ramathibodi Hospital in Bangkok has effectively incorporated pharmacogenomics practice into health care settings through the use of preprescription genetic testing that has been reimbursed by the Thai universal health coverage scheme since 2014 (cost per test equates to 985.7 Thai baht or ~US $30 per patient). As a result of the proactive approach, the incidence of SJS/TEN has decreased sharply and the country is now working to eradicate SJS/TEN and the associated morbidity and mortality (Figure 2). Thailand and other Southeast Asian countries have further organized a collaborative approach to overcoming genetically mediated SJS/TEN by forming the Southeast Asian Pharmacogenomic Network that includes 10 nations and approximately 560 million Southeast Asians. The mission of this network is for these countries to work together to collaborate on sustainable pharmacogenomic research among regions with similar genetic backgrounds that will lead to further discovery and clinical translation. There is a critical need to identify and determine the population frequencies of genetic variants and implement

TABLE II. The algorithm for assessment of drug causality in epidermal necrolysis score (ALDEN)

Criterion	Values	Rules to apply	Score
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 d	−3 to 3
	Compatible +2	From 29 to 56 d	
	Likely +1	From 1 to 4 d	
	Unlikely −1	>56 d	
	Excluded −3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 2 to 4 d Likely: +1: from 5 to 56 d	
Drug present in the body on the index day	Definite 0	Drug continued up to the index day or stopped at a time point less than 5 times the elimination half-life* before the index day	−3 to 0
	Doubtful −1	Drug stopped at a time point before the index day by more than 5 times the elimination half-life* but liver or kidney function alterations or suspected drug interactions† are present	
	Excluded −3	Drug stopped at a time point before the index day by more than 5 times the elimination half-life,* without liver or kidney function alterations or suspected drug interactions†	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	−2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar‡ drug or other reaction with the same drug	
	Positive unspecific: 1	Other reaction after use of similar‡ drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative −2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	−2 or 0
	Negative −2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case-control studies§	−1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies§	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected −1	No evidence of association from previous epidemiology study with sufficient number of exposed controls‡	
		Intermediate score = total of all previous criteria	−11 to 10
Other cause	Possible −1	Rank all drugs from highest to lowest in intermediate score	−1
		If at least 1 has an intermediate score of >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	
Final score −12 to 10			

NSAID, Nonsteroidal anti-inflammatory drug.
<0, Very unlikely; 0-1, unlikely; 2-3, possible; 4-5, probable; >6, very probable.
This table is reprinted with permission from Sassolas et al.[24] The legend has been modified from the original text.
*Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks and in Sassolas et al[24]), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance.
†Suspected interaction was considered when more than 5 drugs were present in a patient's body at the same time.
‡Similar drug = same ATC (anatomical therapeutic chemical) code up to the fourth level (chemical subgroups[25]); see Sassolas et al[24] for methods.
§See Mockenhaupt et al[18] for definitions of "high risk," "lower risk," and "no evidence of association." "High-risk" drugs include sulfamethoxazole-trimethoprim, sulfonamide anti-infectives, allopurinol, carbamazepine, phenytoin, phenobarbital, oxicam-NSAIDs. "Lower risk" drugs include acetic acid NSAIDs, macrolides, quinolones, cephalosporins, tetracyclines, aminopenicillins. Drugs with "no evidence of association" with SJS/TEN include beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide diuretics, furosemide, propionic acid NSAIDs, sulfonylurea antidiabetics, insulin.

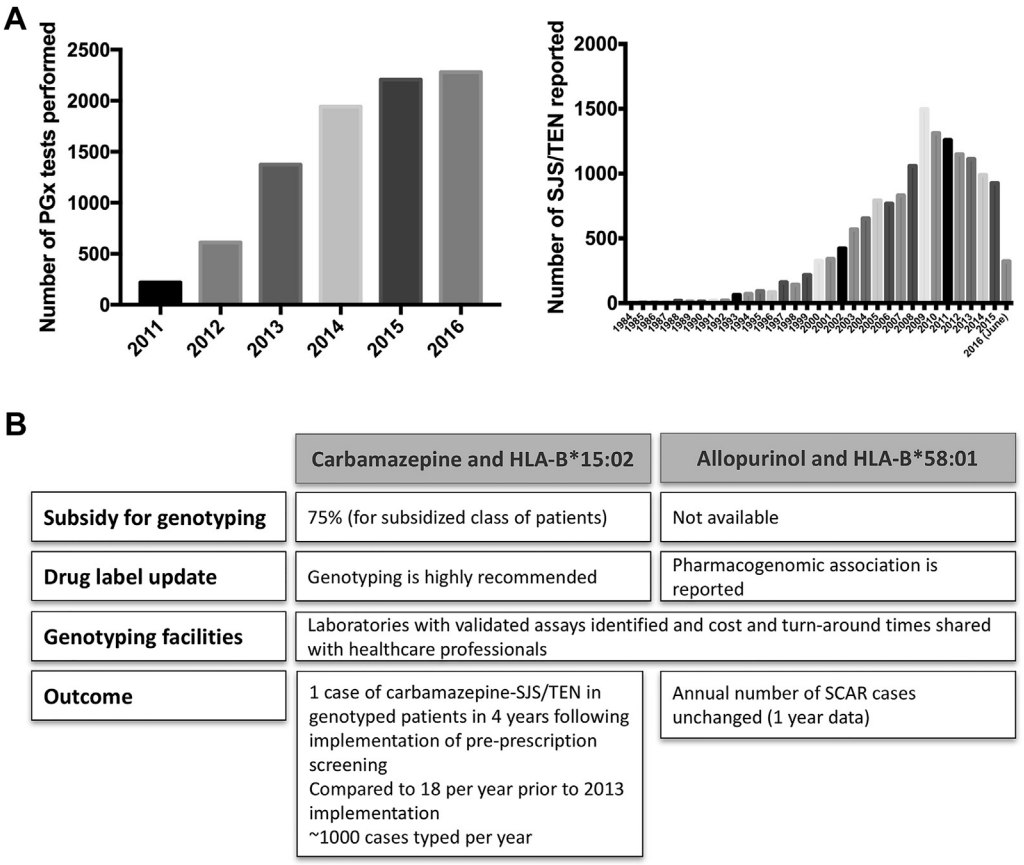

FIGURE 2. Pharmacogenomic testing to prevent SJS/TEN in Thailand and Singapore. **A**, Thai VigiBase and implementation. Following the incorporation of pharmacogenomics testing at Ramathibodi Hospital in Bangkok, Thailand, the number of pharmacogenomics tests performed rose from fewer than 500 in 2011 to more than 2,000 in 2015. Concurrently, with financial reimbursement supplied by the Thai universal health coverage scheme from 2014 onward, the number of reported cases of SJS/TEN collected through Thai-VigiBase fell, demonstrating the efficacy of genetic testing to prevent SJS/TEN in this population. **B**, Pharmacovigilance in Singapore. Carbamazepine and allopurinol are 2 of the most common causes of SCARs in Singapore and the risk alleles associated with carbamazepine- and allopurinol-SCARs (HLA-B*15:02 and HLA-B*58:01, respectively) occur at high frequency in the Singapore population. In 2013, the primary regulatory body in Singapore, the HSA, in conjunction with the Ministry of Health recommended HLA-B*15:02 genotyping before initiation of carbamazepine as standard of care for new patients of Asian ancestry. Following this recommendation, only 1 case of carbamazepine-associated SJS/TEN in 4 years has been reported, a marked reduction in incidence from the pretesting baseline of approximately 18 cases per year. For allopurinol, because of the low (2%) PPV of HLA-B*58:01 testing and lower efficacy or higher cost of alternative medications, genotyping was not recommended for routine standard of care for patients with chronic gout initiating drug therapy, although testing facilities were identified so that physicians have the option to conduct genotyping for high-risk patients such as those with renal impairment. *PGx*, Pharmacogenomics.

knowledge of genetic variation in pharmacogenomics in Thailand and other Southeast Asian populations to construct prescribing guidelines that will further facilitate SJS/TEN prevention.

The Japanese Research Committee on Severe Cutaneous Adverse Reactions

To date, no epidemiologic data of SJS/TEN have been reported in Japan, a population of 120 million. In Japan, drug-related adverse events are adjudicated by the Ministry of Health, Labor, and Welfare and patient medical costs are partially covered without revealing the localization of legal responsibility by the Japanese Post Marketing Adverse Event Relief System.[31] To investigate the epidemiology of SJS/TEN, the Japanese Research Committee on Severe Cutaneous Adverse Reactions collected a total of 370 cases (258 cases of SJS and 112 cases of TEN) using registration forms obtained from 2005 to 2007. The incidence of SJS/TEN per million per year is similar to that in other countries (3.1 for SJS, 1.3 for TEN, and 4.4 for SJS/TEN combined), with a relative SJS-to-TEN ratio of 2.3:1. Incidence was highest among Japanese individuals in the seventh decade of life (23.3% of all SJS cases, 19.8% of all TEN cases occurring among persons ages 60-69 years), and there was no obvious sex bias observed. The mortality rates for SJS and TEN were 3% and 19%, respectively. The rates of mortality and short- or long-term sequelae were significantly higher for TEN than for SJS (mortality $P = 4.39 \times 10^{-7}$; sequelae $P = 1.04 \times 10^{-8}$,

chi-square test). The most frequently suspected agents were antibiotics (16.3% for SJS and 19.5% for TEN), nonsteroidal anti-inflammatory drugs (14.6% for SJS and 16.8% for TEN), and anticonvulsants (14% for SJS and 9.9% for TEN). The period from the start of anticonvulsant treatment to the onset of the rash was significantly longer than that of antibiotics or nonsteroidal anti-inflammatory drugs (onset of 70%-80% of cases was 4 weeks for anticonvulsants and 2 weeks for antibiotics and nonsteroidal anti-inflammatory drugs). Eye involvement was documented in 26% of SJS cases and 77% of patients with TEN, and mucous membrane involvement was significantly more frequent in TEN than in SJS.[32]

Variants in pharmacogenes associated with carbamazepine and allopurinol SJS/TEN in the Japanese population were also examined in this study. HLA-B*15:02, the risk allele most commonly associated with carbamazepine-SCAR in South East Asians, was not identified among 61 patients with SCAR, whereas HLA-B*15:11, which, along with HLA-B*15:02, belongs to the B75 serotype, was recognized in 4 of 14 patients with carbamazepine-SCAR.[33] In contrast and in keeping with previously published data from Japanese and Europeans, HLA-A*31:01 was present in 45 of 77 patients with carbamazepine-induced SCAR, including 21 of 36 patients with drug reaction and eosinophilia and systemic symptoms and 5 of 6 patients with SJS/TEN, relative to 54 of 420 carbamazepine-tolerant controls (odds ratio [OR], 10.8; $P = 3.64 \times 10^{-15}$).[34] Regarding allopurinol, HLA-B*58:01 was found in 10 of 18 patients with SCAR (OR, 62.8; $P = 5.39 \times 10^{-12}$).

SPECIAL POPULATIONS AND CONSIDERATIONS*

Key Points:

- SJS/TEN survivors frequently suffer from psychological complications and decreased health-related quality of life. Prompt recognition and treatment is needed to address the psychological sequelae of SJS/TEN.
- Drugs that are commonly suspected to cause SJS/TEN in children are similar to causative drugs in adults although non−drug-related diseases that mimic SJS/TEN such as erythema multiforme majus (EMM) are common, making diagnosis challenging. SJS/TEN mortality is low in children compared with adults.
- The risk of developing SJS/TEN and particularly drug-related SJS/TEN is significantly higher among the elderly and short- and long-term morbidity and mortality are higher as compared with younger adults.
- Pregnant women and especially HIV and/or HIV-TB coinfected pregnant women are at risk to receive drugs that more commonly cause SJS/TEN. Available data demonstrate that maternal SJS/TEN does not transmit to the fetus. However, maternal SJS/TEN is associated with higher than expected intrauterine death and sequelae may affect future reproductive capacity.

Session 2 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* focused on SJS/TEN in special populations including survivors, the young, the elderly, pregnant females, and individuals with infectious comorbidities.

Psychological complications and quality of life in SJS/TEN

Long-term psychological sequelae, posttraumatic stress disorder (PTSD), and fear of taking drugs in the future are important morbidities associated with SJS/TEN.[35-37] Two studies that explored patients' perspectives of surviving SJS/TEN found that ADRs had a persisting impact on survivors' lives physically and psychologically long after the event.[38,39] Survivors of drug reaction with eosinophilia and systemic symptoms were found to suffer from psychological symptoms of anxiety, depression, and PTSD.[40]

A recent study characterized the psychological complications and health-related quality of life of SJS/TEN survivors treated at a tertiary care burn center.[37] The Toronto study was conducted between 1995 and 2015 and included 17 adults (≥18 years) with biopsy-proven SJS/TEN at a mean of 51.6 ± 74.7 months (median, 9 months; range, 1-228 months) following acute disease who were capable of participating in follow-up and answering questionnaires. Participants were assessed by validated emotional and health-related quality-of-life questionnaires.[41-46] Participants were also evaluated by a health-related quality-of-life questionnaire specially designed for this study and by a medical interview conducted with a structured detailed questionnaire. Eleven out of 17 (65%) were found to have symptoms of PTSD (Impact of Events Scale-Revised, mean = 22.4 ± 19.9) and 5 (29%) met the criteria for PTSD. Twelve (71%) had psychological distress (General Health Questionnaire, mean total score = 4.6 ± 4.2) and 11 (65%) had symptoms of a psychiatric clinical disorder (Hospital Anxiety and Depression Scale, mean total score = 14.5 ± 8.4). History of past psychiatric disorder was not significantly associated with scores in the psychological assessment questionnaires. The dermatology quality-of-life index indicated a moderate to extremely large effect on the lives of 9 (53%) participants (mean total score, 6.9 ± 7.6). Skindex-29 indicated a mild to severe effect on health-related quality of life in 10 (59%) participants (mean, 24.6 ± 21.5). Participants rated their general health at a mean of 66.2/100 ± 18.1 (EuroQol five-dimensional questionnaire Visual analogue scale).[37] Fourteen out of 17 (82%) participants reported that SJS/TEN decreased their current quality of life, 12 (71%) reported that SJS/TEN influenced their current emotional status, and only 29% were employed following SJS/TEN. Participants wrote statements in the open text area, expressing their perspectives: "I have difficulty coping with stress and anxiety," "My emotions are out of whack. It is so easy to be introverted but that makes me depressed, so I keep a journal to record my thoughts and emotions," "The first years of my recovery were very agonizing and very depressing." Despite most survivors having psychological complications, only 4 were assessed by a mental health professional during the period following SJS/TEN.[37]

The high burden of psychological sequelae and impact of SJS/TEN on health-related quality of life suggest that all patients and their families should be offered psychological support during hospitalization, before discharge, and throughout follow-up, and should be offered contact with a support group. Several

* Roni P. Dodiuk-Gad, MD; Jennifer L. Goldman, MD, MS; Rannakoe J. Lehloenya, MBChB, FCDerm(SA); Maja Mockenhaupt, MD; Elena Pope, MD, MSc, FRCPC; Arturo P. Saavedra, MD, PhD, MBA

support groups have been established in different countries (see Box I).

SJS/TEN in children

Estimating the true incidence of SJS/TEN is hampered by the fact that non−drug-related diseases such as EMM may be confused with SJS/TEN, particularly in children. The skin lesions in EMM are often targetoid in appearance with central dusky or blistering skin surrounded by erythematous inflammation and an outer ring of pale edematous skin (Table I).[47] In children a high percentage of SJS/TEN may be non−drug-related and infectious causes are associated in up to 30%. *Mycoplasma pneumoniae* and herpes simplex virus have been associated with EMM in children. In the case of *Mycoplasma pneumoniae*, a distinct syndrome called *Mycoplasma*-induced rash and mucositis (MIRM) has recently been defined.[48-50]MIRM, which may represent an atypical form of EMM, can result in severe mucosal involvement. MIRM differs from typical SJS/TEN because of sparse cutaneous involvement. In addition, Mycoplasma-associated disease tends to affect younger patients and is not commonly associated with long-term complications. However, recurrence of mucosal and skin lesions has been observed.

Drugs that are commonly suspected to cause SJS/TEN in children are similar to drugs in adults and include sulfa antimicrobials and aromatic anticonvulsants (phenobarbital, carbamazepine, phenytoin, and lamotrigine).[51,52] Overall mortality is lower in children with SJS/TEN compared with adults,[53] suggesting that algorithms used in adults to predict SJS/TEN mortality are not applicable to children and the existing models that predict outcomes need to be modified or redesigned for pediatric patients.[54]

Children with SJS/TEN require high-acuity hospital care, and up to 50% have long-term sequelae including blindness, which can occur many years after the initial acute SJS/TEN episode. Ophthalmologic disease may impact children less frequently and preferentially affect those children with more severe disease: 100% of children with TEN had evidence of ocular involvement.[55] Ophthalmologic conditions were more common among children with concurrent infectious diseases than among children with noninfectious diseases, with the highest proportion seen among those with MIRM.[56] Because both short- and long-term ophthalmologic complications can occur in children with SJS/TEN, involvement of a pediatric ophthalmologist should occur early upon diagnosis. In children, recurrence of SJS is well reported, occurring in up to 20% of cases.[51]

In summary, compared with adults, children have lower rates of mortality, but their survival comes with high rates of long-term complications. Further work is needed to define SJS/TEN in children and determine the most optimal treatment strategies.

SJS/TEN in the elderly

The incidence of drug-associated SJS/TEN in patients older than 64 years is twice as high when compared with that in patients aged 20 to 64 years (9.4 per 10^6 vs 4.6 per 10^6 person-years).[57] Whether this is due to polypharmacy or other age-associated factors is unclear. Older adults also appear to be at a greater risk of a cutaneous disease similar to SJS or TEN, referred to as GBFDE. The skin lesions seen in GBFDE appear very similar to those of SJS/TEN, consisting of large erythematous, often violaceous patches with overlying fluid-filled bullae, but GBFDE is typically considered less severe than SJS/TEN because constitutional symptoms are absent and lesions are well demarcated and usually limited to the skin without mucosal involvement (Table I).[58] Despite its more benign presentation, GBFDE when associated with BSA involvement of more than 20% can be associated with mortality rates of more than 20%, which highlights the significance of cutaneous reactions in older adults.[58]

Advanced age is also a predictor of SJS/TEN mortality. Age more than 40 years is an independent risk factor for death in adults with SJS/TEN and mortality rates as high as 70% have been described in those older than 65 years.[1] Underlying diseases (eg, severe kidney or liver disease and malignancy) are also associated with higher rates of mortality from 90 days to 1 year following the SJS/TEN presentation.[21] Complications such as multiorgan failure, nosocomial infections, and septicemia may lead to death, even following initial healing of skin lesions. Sekula et al[21] found that 25% of patients with a serious comorbidity or who were older than 70 years who survived the first 3 months following a SJS/TEN diagnosis died during the subsequent 9 months.

As the older population continues to grow globally, the number of geriatric patients who develop SJS/TEN will also likely continue to increase. Given the paucity of data on therapeutic approaches to treat SJS/TEN in the geriatric population and the high rate of associated mortality among this group, further studies are needed to determine optimal treatment strategies and decrease the risk of death in both the short-term and long-term following a SJS/TEN diagnosis.

SJS/TEN in pregnancy and in HIV-infected pregnant women

SJS/TEN during pregnancy has potential consequences for both the mother and the fetus. There is limited epidemiological data on SJS/TEN in pregnant women and existing evidence is derived mainly from case reports. A review of published literature up to 2010 identified only 36 cases of SJS/TEN in pregnant women. The authors concluded that SJS/TEN mortality in pregnant women is lower than expected and this finding was likely attributable to younger age and lower SCORTEN among pregnant patients compared with other SJS/TEN cohorts.[59] Certain antiretroviral drugs are strongly associated with SJS/TEN and other IM-ADRs in certain genetic backgrounds (ie, nevirapine/HLA-C*04:01 SJS/TEN and abacavir/HLA-B*57:01 hypersensitivity syndrome).[60-64]

In the developing world, nevirapine is used to treat HIV-infected pregnant women. Studies that have examined mother-to-child transmission of HIV have documented cases of maternal SJS/TEN[59,65,66] and nevirapine has been identified as a causative drug in multiple cases (Figure 3).[67-69] However, since 2012, nevirapine has been replaced with efavirenz as the nonnucleoside reverse transcriptase inhibitor of choice for the prevention of mother-to-child HIV transmission (PMTCT) in South Africa. Between January 2013 and December 2015, the incidence rate of SJS/TEN in the same population dropped to 0 cases per year compared with 3.4 cases per year for the preceding 7 years.[68,69] Although an earlier case-control study of antiretroviral-associated SCAR suggested that pregnancy was independently associated with SCAR after controlling for nevirapine exposure,[68] these new data suggest that nevirapine might be associated with a higher incidence of SJS/TEN in

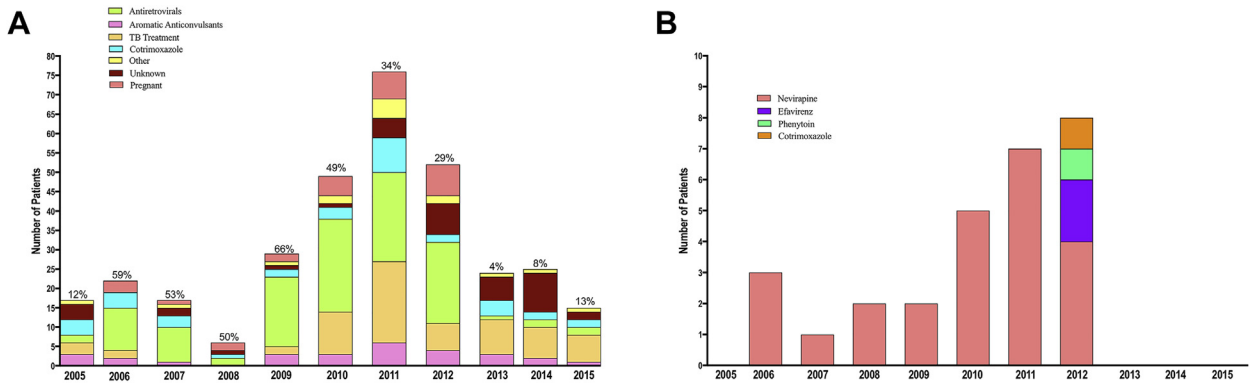

FIGURE 3. Epidemiology of SJS/TEN in special populations. **A**, All cases of SJS/TEN seen at Groote Schuur Hospital in South Africa between 2005 and 2015 showing the proportion of offending drugs. The proportion attributable to nevirapine for that year is shown as a percentage. **B**, All cases of pregnant women with SJS/TEN seen at Groote Schuur Hospital between 2005 and 2015 showing the proportion of offending drugs.

pregnancy but that pregnancy does not itself seem to predispose to SJS/TEN.[69] In a case series of HIV-infected women, no maternal deaths from SJS/TEN were seen during pregnancy, a finding that supports the findings by Struck et al that SJS/TEN mortality in pregnant women is lower than expected.[1,59,68-71]

Despite the observation that pregnant women with SJS/TEN have lower than expected mortality, fetal outcomes are worse, with higher than expected intrauterine death. Five of the 36 cases (14%) published by Struck et al delivered stillbirths and in a separate series of HIV-infected pregnant women this was 11%, higher than expected.[59,68,71] It remains uncertain whether maternal TEN, the more severe form of the disease, is associated with poorer fetal outcomes. Rarely, SJS/TEN can affect the fetus and there are 2 published cases of fetal SJS/TEN, one concurrently affecting the mother and the fetus and the other the fetus alone.[72,73] It may be difficult to differentiate between SJS/TEN and fetal maceration because maceration-associated desquamation starts within 6 hours of intrauterine death.[74] However, the finding of irregular purpuric macules in the case presented by Rodriguez et al[72] supported a diagnosis of SJS/TEN. The case published by Sweetnam et al[73] healed with keloidal scarring, an unusual feature in SJS/TEN in the absence of secondary infection, immobility, sustained pressure, or delayed reepithelialization.[75] Despite the extensive use of nevirapine in PMTCT, there are disproportionately few cases, if any, of neonatal SJS/TEN.[65] We can safely conclude that SJS/TEN rarely, if at all, affects newborns. In the context of PMTCT in HIV-infected mothers with SJS/TEN, concerns regarding the interruption of an antiretroviral causative drug and the potential risk of neonatal HIV infection have been evaluated in only a few instances. Most published reports on SJS/TEN in pregnant women, including those designed for PMTCT, do not address the risk of maternal HIV transmission to the fetus.[65,66] Reassuringly, in 12 children who had received PMTCT and were born to mothers with SJS/TEN during pregnancy, all were found to be HIV uninfected at 6 weeks following delivery.[68]

Consideration for the method of delivery in the current and subsequent pregnancies is important because long-term sequelae of genital mucositis in SJS/TEN, including structural changes secondary to adhesions, stenosis, hematocolpos, adenosis, and endometriosis, may impact future reproductive health and modes of delivery.[75] Both vaginal and cesarian section deliveries have been reported in the setting of past and current SJS/TEN.[59,68] The extent to which vaginal delivery is contraindicated is difficult to establish because of the rarity of SJS/TEN in pregnancy, the lack of a standardized case definition for genital disease, incomplete reporting of vaginal complications, and breadth and variability of indication for cesarian section based on hospital practice.[59,68] Awareness of sequelae and preventive strategies in acute SJS/TEN should reduce the incidence of vaginal fibrosis and consequently the number of cesarian sections performed.[68]

CLINICAL MANAGEMENT*

Key Points:

- Cessation of the implicated drug and intensive supportive care with early multidisciplinary involvement is key to the management of SJS/TEN.
- Up to 77% of patients with SJS/TEN have genitourinary involvement in the acute phase and of these up to 25% go on to have some form of chronic complications. Early genitourinary examination and acute management are likely to be key in avoiding chronic complications.
- Ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist if there is suspicion of SJS/TEN. Early interventions such as amniotic membrane transplantation (AMT) have been key to preventing long-term ocular morbidity. For patients who survive the acute phase, ocular complications are the most common and debilitating chronic sequelae and blindness can occur decades after the acute episode, which necessitates lifelong follow-up.

* Michael Ardern-Jones, DPhil (PhD), FRCP (MD); Thomas Beachkofsky, MD; Charles Bouchard, MD, MA; James Chodosh, MD, MPH; Roni P. Dodiuk-Gad, MD; James H. Holmes IV, MD, FACS; Rannakoe J. Lehloenya, MBChB, FCDerm; Caroline M. Mitchell, MD, MPH; Misha Rosenbach, MD; Jean-Claude Roujeau, MD; Hajirah N. Saeed, MD; Neil H. Shear, MD

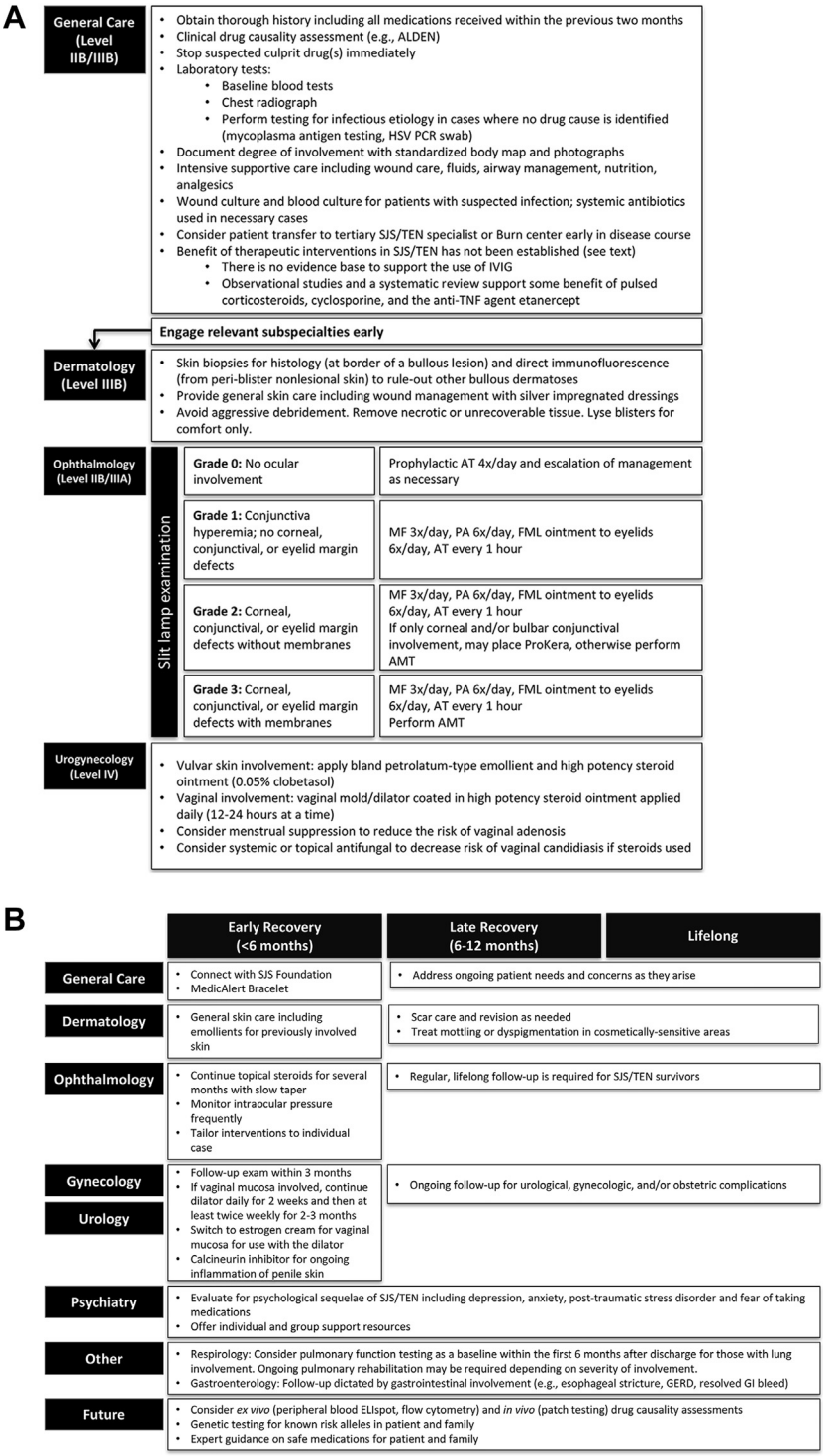

FIGURE 4. Suggested multidisciplinary approach to the management of (**A**) acute- and (**B**) recovery-phase SJS/TEN. Key points highlighted include the necessity to (1) recognize and stop the offending medication quickly, (2) provide care for SJS/TEN in a tertiary critical care center (most often a burn center), (3) consider all organ systems involved in SJS/TEN and consult relevant subspecialists early in the disease course, and (4) provide posthospital and long-term follow-up for patients to manage complications of SJS/TEN. *ALDEN*, Algorithm for assessment of drug causality in epidermal necrolysis; *AT*, artificial tears; *FML*, fluorometholone 0.1% ophthalmic ointment; *GERD*, gastroesophageal reflux disease; *GI*, gastrointestinal; *HSV*, herpes simplex virus; *MF*, moxifloxacin 0.5% ophthalmic solution; *PA*, prednisolone acetate 1% ophthalmic solution.

- Although IVIG has been widely applied, there is no evidence base to support its use.
- Improved evidence-based data to support specific clinical management and therapeutic intervention remains a priority need for SJS/TEN.

Although characterized by predominant epidermal and mucous membrane involvement, SJS/TEN is a multisystem disease. Session 3 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* featured discussion and expert recommendations from clinicians in dermatology, burn surgery and critical care medicine, ophthalmology, and gynecology. The state of current practices in the clinical management of SJS/TEN, unmet clinical research needs, and future directions were discussed (Figure 4).

Management and clinical guidelines

SJS/TEN causes both acute and chronic complications across a diverse group of patient populations.[76] Although early intervention is considered key to minimizing short- and long-term sequelae, international consensus and treatment guidelines for the management of SJS/TEN are lacking. A comprehensive, systematic review of the management of SJS/TEN in adults was undertaken in the United Kingdom in 2016 and included accreditation from the British Association of Dermatologists, the British Association of Plastic, Reconstructive and Aesthetic Surgeons, and the National Institutes for Health and Care Excellence.[77,78] The most important initial step in the management of SJS/TEN is to immediately discontinue any potential culprit drug (Figure 4). In many cases, the culprit drug is obvious from the exposure timeline, but in some cases, several or no culprits may be apparent. Where many possible culprits exist, all suspected drugs need to be stopped and, if needed, a structurally disparate alternative therapy with low risk for cross-reactivity with the culprit drug should be initiated. Any drug that has been tolerated for more than 3 months can safely be continued. The algorithm for assessment of drug causality in epidermal necrolysis causality score (Table II), particularly designed and validated for SJS/TEN, is an important tool to help aid in the causality assessment of potential culprit drugs.[24] Other drug causality assessments have also recently been developed.[79] In the cases where no drug is suspected, then infection may be implicated and screening tests are indicated (eg, Mycoplasma PCR, Herpes simplex swab PCR, and Enterovirus PCR). Furthermore, it is important to consider that other dermatoses such as linear IgA disease, staphylococcal scalded skin syndrome, GBFDE, pemphigus vulgaris and other autoimmune bullous diseases, and graft-versus-host disease can sometimes be difficult to distinguish from SJS/TEN by clinical appearance. Therefore, skin biopsy for routine histology and direct immunofluorescence is an important tool. Despite the urgency of the acute care for SJS/TEN, immediate consideration of postrecovery morbidities such as those involving the eyes and genitourinary mucosa is critical. This requires early input from the relevant specialties (Figure 4).

Optimal therapeutic intervention in SJS/TEN is controversial. Since the first report of a small case series showing response to IVIG, interest in the role of this therapy has been maintained. Recent surveys confirm that many physicians who treat SJS/TEN continue to support its use.[6,80,81] One systematic analysis of the published literature of IVIG in SJS/TEN included 17 case series from different countries where comparison with supportive care alone could be made. Although the number of publications showing benefit was greater than those showing no benefit, comparison of the total number of patients reported demonstrated no benefit of IVIG.[19,80,82-96] In addition, methodological concerns exist because of evidence of duplicated cases, variable dosing, and combined treatment with corticosteroids in many of the published case series. Thus, the benefit of treatment of SJS/TEN with IVIG is uncertain. Although review of the literature shows no evidence of harm, overall, there is no convincing evidence of benefit.[77,78]

Treatment of SJS/TEN with corticosteroids (eg, prednisolone, methylprednisolone, and dexamethasone) versus supportive care was also examined systematically. Only 3 studies out of 10 showed benefit of this treatment and the number of cases treated in studies where no benefit was seen was again higher than in those showing benefit (273 vs 78).[19,89,97-104] One small case series not included in this review suggested that pulsed dexamethasone given at a dose of 1.5 mg/kg for 3 days was helpful when given near the time of disease onset.[100] The weight of this evidence is small in comparison to the larger systematic review. However, methodological criticisms highlighting poor case validation and variable dosing suggest that some caution in data interpretation is required. A separate recent meta-analysis of observational studies for immunomodulating therapies of SJS/TEN (including IVIG, pulsed dose corticosteroids, and cyclosporine) showed that corticosteroids were associated with a survival benefit in 3 different analyses (aggregated study data: OR, 0.5; 95% CI, 0.3-1.01; individual patient data unstratified: OR, 0.7; 95% CI, 0.5-0.97; individual patient data stratified: OR, 0.8; 95% CI, 0.4-1.3). Despite low patient numbers, cyclosporine was associated with a promising significant result in the feasible unstratified individual patient data analysis (OR, 0.1; 95% CI, 0.0-0.4). IVIG was not beneficial in this meta-analysis.[105]

The published evidence of cyclosporine treatment of SJS/TEN showed evidence of a therapeutic benefit in case series and an open-label phase II trial.[106-111] No deaths were reported in the trial and the arrest of disease progression as well as reepithelialization was hastened. The meta-analysis above[105] also showed both study and patient-level benefit. However, the overall sample sizes reported are low, represent single-center experiences, or lack control groups. Lack of case validation in the reported case series should create caution against overinterpreting the data. G-CSF and anti-TNF receptor antagonists also have some reasonable evidence to suggest further examination of these therapies for SJS/TEN but as yet, experience remains limited with these treatments.[112-115] A recent phase II randomized controlled trial showed benefit in mortality of the anti-TNF agent etanercept over steroids (relative risk reduction, 50% vs 20%) and reduction of time to reepithelialization in the etanercept group.[115] Thalidomide, which was trialed in the late-1990s because of its anti-TNF activity, is the only treatment to have undergone a placebo-controlled randomized controlled trial. This study, however, was stopped early because thalidomide was associated with higher day 2 plasma TNF concentrations and increased mortality.[116]

For all therapeutic interventions to date, the inevitable delay between the onset of the rash and interventional treatment caused by the time taken for transfer to specialist centers means

that early intervention has yet to be thoroughly examined. Cyclosporine and etanercept have shown benefit in their respective trials when initiated up to approximately 5 days after the onset of skin signs of disease.

Ocular involvement and management

Acute ocular involvement in SJS/TEN occurs in up to 100% of patients and ranges from conjunctival hyperemia to near-total sloughing of the ocular surface and eyelid margins.[117-120] Acute pathology can result in chronic complications including corneal epithelial stem cell deficiency and eyelid margin keratinization, which, in turn, lead to corneal neovascularization and opacity, persistent corneal epithelial defects, severe dry eye, and ultimately blindness. Blindness can also occur in the acute phase as a result of corneal perforation, largely a result of inadequate care. There is incomplete correlation between the severity of SJS/TEN illness and ocular complications and the degree of ocular involvement in SJS/TEN is highly variable.[118,119,121-123] Furthermore, the immunopathogenesis of how SJS/TEN affects the eye, which is an immune-privileged site, is also largely unknown. Literature from specific populations has supported potential associations between specific HLA class I alleles and ocular involvement.[124-128]

The single best predictor of chronic corneal complications is acute eyelid margin involvement. Acute eyelid margin deepithelialization and ulceration leads to eventual eyelid margin keratinization, which causes corneal disease through various mechanisms and a window of opportunity exists in the acute phase to mitigate the severity of eyelid margin disease through the use of AMT.[129-132] Early treatment is the key to management and this reduces the risk of blindness. Dissemination of this message is urgently needed because in the United States alone, only 66% of burn intensive care units routinely consult ophthalmology on patients with SJS/TEN during their hospital stay.[6]

The critical period for ophthalmological care is within 7 days of disease onset, beyond which a crucial window of opportunity for ocular intervention is lost, and irreversible damage can occur. Further challenges and constraints on this time window exist because of delays in diagnosis and hence delayed transfer of patients to an appropriate care environment. Further delays may be incurred by aspects of clinical management such as waiting for skin biopsy results or for clinical signs to fully manifest. Importantly, ocular disease often precedes skin involvement and patients should be evaluated by an ophthalmologist even if there is any suspicion of SJS/TEN, while awaiting confirmation.

The ocular examination consists of examining the eyelid skin, eyelid margin, conjunctiva, and cornea, assessing for epithelial sloughing, defects, ulceration, and inflammation. The acute care involves the use of lubrication with artificial tears and ointments, topical antibiotics for infection prophylaxis, topical corticosteroids to control inflammation, and AMT in moderate to severe ocular disease to decrease inflammation, speed healing, and prevent keratinization.[120] The exact mechanism by which AMT improves outcomes is unknown. Treatment regimens depend on the severity of disease and can be found in Figure 4, *A*. Adjunct therapies are used on a case-by-case basis and include the use of bandage and scleral contact lenses for persistent epithelial defects of the cornea. Follow-up in the acute phase depends on the severity of ocular involvement, but at the very least, patients should be seen 24 to 48 hours after initial ophthalmologic examination because ocular involvement can progress quickly over time. Once acute disease has stabilized, follow-up can be tailored to the individual.

There is no defined protocol for the management of chronic ocular disease after hospital discharge, with few prospective studies and no randomized clinical studies. The consensus from experts in the field is that patients should be maintained on topical corticosteroids for several months, tapering slowly while monitoring the intraocular pressure. Close follow-up by an ophthalmologist is essential because new ocular signs can manifest over time, which also have limited windows during which interventions can be sight saving. These interventions include punctal occlusion, retinoic acid ointment to the eyelid margin, specialized scleral contact lenses, and oral mucous membrane grafting to the eyelids. End-stage disease may require a keratoprosthesis/artificial cornea for visual rehabilitation. A role for topical cyclosporine for the treatment of chronic dry eye following SJS/TEN may be limited by patient intolerance for the drug formulation.[133] Patients with SJS/TEN should be followed by an ophthalmologist for life because worsening symptoms and vision loss can occur decades after disease onset.

Genitourinary disease

The acute genitourinary manifestations of SJS/TEN in females include erosions and ulcerations of the vulva and vagina. These acute manifestations occur in up to 77% of patients and can lead to chronic complications in the form of vulvar adhesions and vaginal stenosis, resulting in hematocolpos, dyspareunia, chronic pain and bleeding, and difficulty conceiving.[68,134] Data are limited, but it is thought that urogynecological complications are common, and that they occur in up to 77% of female patients with SJS/TEN of which 9% to 25% of survivors go on to have chronic complications.[135,136] An additional complication is vaginal adenosis, where stratified squamous epithelium is replaced with columnar glandular epithelium.[137] Adenosis can increase the risk of vaginal malignancy. To prevent the complications above, all female patients should have a gynecologic examination at the time of admission for suspected SJS/TEN and should be followed closely in the early stages of SJS/TEN because mucosal disease can develop and spread rapidly. Any vulvar pathology should prompt an evaluation by a gynecologist for possible vaginal involvement.

Special patient categories in this respect include pediatric and pregnant patients. For the former, cooperation with examinations and treatments can be difficult and they may be deemed invasive. For the latter, decisions about mode and timing of delivery can be complicated by the presence of vaginal or vulvar erosions, abdominal skin pathology, or vaginal stenosis. In younger patients, evaluation may need to be done under sedation or anesthesia. General anesthesia may be difficult to accomplish in the acute phase when the patient is too unstable to be taken to the operating room. These determinations should be made on a case-by-case basis, taking patient cooperation and hospital resources into account. The goal of treatment in the acute phase is to decrease inflammation and prevent the development of adhesions. The following treatment recommendations are not all-inclusive and have not been proven through clinical trials but serve as a foundation for treatment as our understanding and study of gynecologic pathology in SJS/TEN grows.

Vulvar skin involvement can be treated with a bland petrolatum-type emollient. A high-potency steroid ointment, such as 0.05% clobetasol, can also be used to decrease inflammation and discomfort. If increased irritation occurs with such products, emollients alone should be used. Consider decreasing the frequency of steroid use after initial treatment.[138] Vaginal disease should be treated with twice-daily use of a soft, small vaginal mold/dilator or a tampon/roll of gauze covered with a nonlubricated condom. The device should be coated in high-potency steroid ointment before it is applied. This intervention is to provide anti-inflammatory treatment to the mucosa and to physically separate the mucosa to prevent adhesions, rather than to dilate the vagina, and the device should just be large enough to accomplish these ends. The vaginal mold can be left in place for 12 to 24 hours at a time, but should be removed at least once daily for cleaning of the device with soap and water and for application of additional anti-inflammatory medication. Even for those patients without visible disease, prophylactic treatment as above should be considered for several hours a day.

Patients uncomfortable with using a vaginal dilator/mold, particularly pediatric patients, can apply medication twice daily with a vaginal applicator. Even for virginal and/or pediatric patients, use of a small mold or a condom-covered tampon should be encouraged if the patient is emotionally and physically comfortable with the regimen. Other general considerations include menstrual suppression to reduce discomfort and to possibly decrease the risk of vaginal adenosis. Systemic and/or topical antifungal medication may be considered to decrease the risk of vaginal candidiasis in the setting of vaginal steroid use. The medication on the dilator can be changed to, or alternated with, estrogen cream to help promote healing of the vaginal mucosa. Lidocaine 5% ointment can also be used at the vaginal introitus, once open sores have healed, to reduce discomfort with the use of vaginal dilators. In pregnant women, usual obstetric care should continue and decisions about delivery made in consultation with the obstetrical team.

As with complications associated with SJS/TEN, outpatient follow-up after discharge from the hospital is essential. All patients should be scheduled for follow-up with a gynecologist within 3 months of discharge. Patients who had active vaginal disease in the acute phase should continue to use a dilator at least 2 times a week for 2 to 3 months after discharge.

Additional acute and recovery management of respiratory and gastrointestinal complications in SJS/TEN may be required as outlined in Figure 4. Although limited data suggest that urologic manifestations are common in SJS/TEN, aside from acute supportive measures and catheterization, there is limited research in this area and currently no clear guidelines or expert consensus on the management of acute urethral involvement or long-term urethral complications.[139] This represents an important area of future work in the field.

Clinical management summary

Rapid withdrawal of the culprit drug and intensive supportive care from a multidisciplinary team is the central priority in the management of acute SJS/TEN. There is no conclusive evidence that IVIG or corticosteroids are harmful or beneficial in the context of SJS/TEN. Smaller studies have shown some benefit, but the weight of evidence does not currently support their use. It may be that initiation of therapy close to the time of skin signs is needed with loss of efficacy within a few days. Although accumulating evidence exists for the use of cyclosporine and other immunomodulatory therapies such as etanercept from small studies and now phase II trials, sufficient experience with these treatments to recommend their use is lacking. In addition, it is currently unknown whether patients would present early enough at most centers for these treatments to be beneficial. Regardless of therapeutic intervention, there should be efforts to move toward a harmonized strategy of aggressive supportive care. Multidisciplinary collaboration is required in the acute care setting and in follow-up to identify and manage potential chronic sequelae early.

PHARMACOVIGILANCE AND THE ELECTRONIC HEALTH RECORD*

Key Points:

- The Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a database of spontaneous adverse event reports, is the primary tool used by the FDA to detect safety signals of SJS/TEN in the postmarketing setting.
- The Singapore Health Sciences Authority (HSA) has evaluated 2 common (~15%-20% carriage) HLA allele-drug pairs associated with SJS/TEN:
  - Genotyping for HLA-B*15:02 for new users of carbamazepine in patients of Southeast Asian descent/ethnicity became a diagnostic standard in 2013 and widespread screening has reduced the number of associated cases of SJS/TEN from approximately 18 per year to 1 case in the 4 years since implementation.
  - Genotyping for HLA-B*58:01 for new users of allopurinol was not mandated because of lower efficacy or higher costs of alternative gout medications. However, clinicians were notified of a laboratory where testing was available.
- Mining electronic health records (EHRs) can reliably identify common disease phenotypes for genomic studies. Rare drug adverse events have also been successfully studied using this technique.
  - 12% of general medicine patients in a large EHR were exposed to 1 of 5 SJS/TEN-associated drugs. Combining this information with genetic data could be used to prevent SJS/TEN in persons at high risk.

Session 4 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* centered on pharmacosurveillance mechanisms and sources of large data sets and bioinformatic methods for the detection and validation of SJS/TEN cases and predictors of risk.

Regulatory science and pharmacosurveillance: US Food and Drug Administration

The FDA's Division of Pharmacovigilance uses a number of tools and processes for the detection and evaluation of safety signals for SJS/TEN.[140] The FAERS is the primary tool used in the postmarketing setting (Figure 5). FAERS is a database of spontaneous adverse event reports that supports FDA's postmarketing surveillance program for drugs and therapeutic

* Robert Davis, MD, MPH; Joshua C. Denny, MD, MS; Jeffery P. Struewing, MD; Cynthia Sung, PhD; Jessica Weintraub, PharmD, BCPS

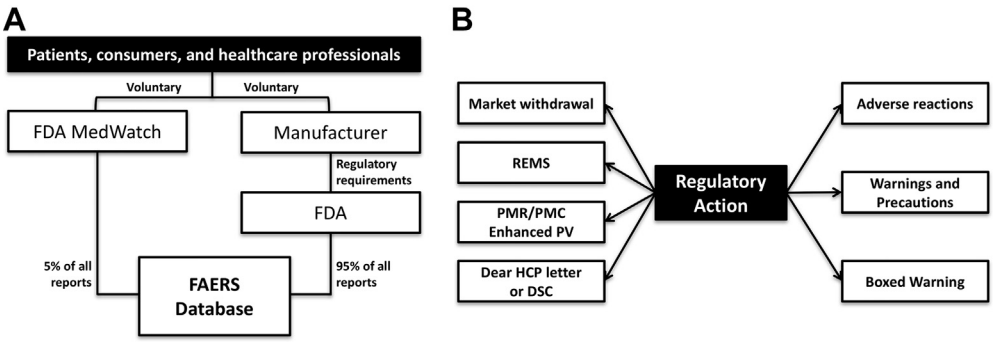

FIGURE 5. Regulatory mechanisms in the United States. **A**, The FAERS is a spontaneous adverse event reporting database that is the primary tool used for the detection of safety signals by the FDA. Reports are generated on a voluntary basis by patients, consumers, and health care providers. Reports may be submitted to the FAERS either directly by the consumer through the FDA MedWatch event reporting system or by drug manufacturers as determined by regulatory requirements. **B**, When a safety signal is identified, there are a number of possible regulatory actions that may be issued by the FDA. Regulatory actions highlighted in blue represent options for drug label modifications to reflect the adverse event. Drug-associated SJS/TEN is most often reported in the *Warnings and Precautions* section but may also appear as a *Boxed Warning* or in the *Postmarketing Experience* section of the drug label. Other potential regulatory actions are highlighted in green. These include (1) manufacturer issuance of a Dear Healthcare Professional (HCP) letter or a Drug Safety Communication (DSC), (2) use of postmarketing requirements (PMRs) or postmarketing commitments (PMCs) to further evaluate the event, (3) use of risk evaluation and mitigation strategies (REMS) to manage risk while enabling continued access to the drug, and (4) drug withdrawal. *DSC*, Drug safety communication; *FAERS*, Food and Drug Administration adverse event reporting system; *HCP*, healthcare professional; *PMC*, postmarketing commitments; *PMR*, postmarketing requirements; *PV*, pharmacovigilance; *REMS*, risk evaluation and mitigation strategies.

biologics. The data files, which are updated quarterly, can be downloaded from the FDA's Web site,[141] and individual case safety reports can be requested by submitting a Freedom of Information Act request. Adverse event reports can be submitted to the FDA from the Web site, or through MedWatcher, a free mobile application. Case reports for SJS/TEN should include patient characteristics such as age, sex, medical history, and all descriptors of the event including diagnostic information and the time to onset of symptoms from initiation of drug therapy to onset of disease should also be included. A comprehensive list of drugs including concomitant and recently discontinued products, including over-the-counter products and supplements, and time of initiation should also be included. The specific action taken for the suspect and concomitant products (continuation, discontinuation) should be reported. The reporter contact information should be included and if significant additional information becomes available after a report has been submitted, a follow-up report should be considered.

Adverse events that are reported to a drug manufacturer are required to be submitted to the FDA within 15 days of receipt if they are serious and unexpected by regulatory definition. Relevant to SJS/TEN, serious adverse events are defined as those that result in death, are life-threatening, result in initial or prolonged hospitalization, are associated with persistent or significant disability or incapacity, congenital anomalies, or other serious events. Expectedness is based on what currently appears in the FDA-approved labeling for that product. Events that are serious and expected as well as nonserious events can be submitted to the FDA on a quarterly basis for the first 3 years after product approval, and then annually.

Health care professionals review incoming FAERS reports. These safety reviewers receive a list of incoming reports for SJS, TEN, and other selected serious adverse events to ensure that those reports are prioritized. They use case definitions and causality assessment tailored to spontaneous reports to evaluate potential safety signals. Examples of regulatory actions that may be taken when a safety signal is identified include (1) updating the product labeling, (2) issuing a Drug Safety Communication, (3) postmarketing requirements or commitments to evaluate the event, (4) implementing risk evaluation and mitigation strategies to manage serious risks while enabling patients to have continued access to the product, or (5) market withdrawal (Figure 5).

In addition to FAERS, safety reviewers use VigiBase, a global database of adverse event reports maintained by the World Health Organization-Uppsala Monitoring Centre. Data mining in FAERS and VigiBase can be used to identify events that are disproportionately reported for a drug. Reports for the event are then reviewed to determine whether there is a potential safety signal. The medical literature is another important data stream because some published cases may not have been previously reported to regulatory authorities or manufacturers. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance database is another useful resource. It uses trained abstractors to collect data on adverse drug events diagnosed and treated in a nationally representative sample of emergency departments.

Postmarketing pharmacoepidemiology studies using prospective data collection, such as registries, can be useful in providing specific patient information, such as genetic information and ethnicity. Important limitations include underascertainment of cases and the need for large numbers of enrolled patients to identify rare events. Pharmacoepidemiology studies involving retrospective data collection, for example, from large administrative databases, have the advantage of providing large numbers of patients with

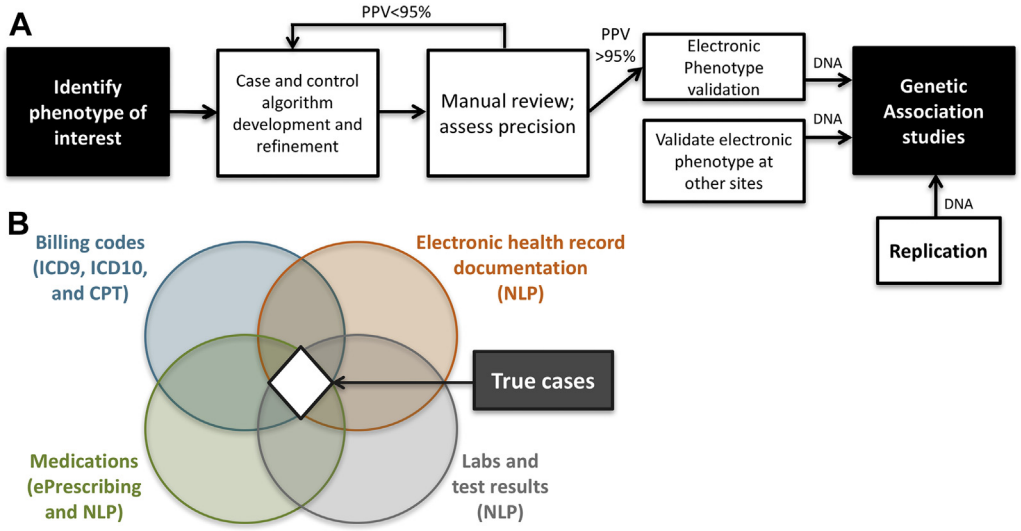

FIGURE 6. Use of EHR data to identify rare disease cases and for the discovery of genetic associations. **A**, For a phenotype of interest, an iterative algorithm incorporating multiple aspects of patient data is developed and validated to identify cases in the medical record. The predictive algorithm is deployed at the test site and replicated across additional sites. Identification of allelic variants associated with the phenotype of interest is achieved using genetic analysis of biobanked DNA linked to the research EHR. **B**, A predictive algorithm with high PPV relies on the incorporation of multiple forms of patient data including billing codes, medication history, clinic notes, and laboratory and test results. *CPT*, Current Procedural Terminology; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *NLP*, Natural language processing.

longitudinal follow-up in "real-world" settings, but cases may not be captured by billing codes alone and there may be incomplete capture of certain information such as ethnicity.

Finally, Sentinel is an active surveillance system sponsored by the FDA that uses administrative and claims data. The Active Risk Identification and Analysis System is a component of Sentinel comprising predefined analytic tools that enable rapid querying of the database.[142] Although evaluating SJS/TEN in Sentinel would be challenging at this time, research is ongoing.

In summary, FAERS is the primary tool used by the Division of Pharmacovigilance for the detection of safety signals for SJS/TEN and submission of high-quality reports by health care providers is essential. Supplementary tools include VigiBase, data mining, the medical literature, National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance, pharmacoepidemiologic studies, and Sentinel/Active Risk Identification and Analysis.

Finding rare diseases such as SJS/TEN in the EHR

EHR data have proven to be an effective and efficient resource for studying common diseases and drug response phenotypes (eg, drug efficacy or adverse drug responses). The genetic basis for hundreds of diseases has been uncovered, including replicating many known, expected genetic associations.[143,144] However, finding these diseases in the EHR is not a trivial effort. EHRs represent a longitudinal record of diseases with records generated for various purposes along the course of illness.[145,146] Thus, they can contain inaccurate data.[147] Accurate disease phenotypes typically require some combination of multiple types of EHR data including billing codes, laboratory data, medications prescribed to the patient, and narrative data such as in clinical reports (Figure 6).[145] Algorithms leveraging scores, Boolean logic, natural language processing, and machine learning approaches typically produce reliable algorithms.[148] These algorithms typically are usually developed with clinical experts working in concert with biomedical informaticians. Several example algorithms were presented, including autoimmune hypothyroidism[149] (as an example of one of many disease phenotypes) and 2 drug adverse events phenotypes, angiotensin-converting enzyme inhibitor—associated cough[150] and heparin-induced thrombocytopenia,[151] for which significant novel genetic associations were discovered using EHR data. The latter example demonstrates the potential for using EHRs for rare drug adverse events, such as SJS/TEN.

In a recent study of 12 research units and managed care organizations in the United States covering almost 60 million lives, electronic medical record databases were used to identify potential cases of SJS/TEN using *International Classification of Diseases* (*ICD*), *Ninth Revision* codes. Medical records were abstracted and standardized criteria applied by board-certified dermatologists to adjudicate diagnoses. Multivariate models were developed to identify factors independently associated with validated SJS/TEN case status. The likelihood of case status increased with the length of hospitalization and with the use of new *ICD* codes specific to SJS/TEN. The positive predictive value (PPV) of *International Classification of Diseases, Ninth Revision* codes 695.12 to 695.15 was 50% among hospitalized cases. Among patients hospitalized for 3 or more days, the PPV of these codes was even higher, and ranged from 57% to 92%. These results suggest that case finding using EHR data can be carried out using a combination of search codes and search terms.[152]

At Vanderbilt, manual chart reviews were used to investigate the potential identification of SJS/TEN in the EHR (Figure 6) including before 2008 when specific SJS/TEN billing codes, an important part of most algorithms, did not exist. Preliminary data suggest that SJS/TEN-specific *ICD* codes have a PPV of around 29%. Use of drug-specific *ICD* codes in combination with SJS/TEN or the more general erythema multiforme codes improve performance, increasing

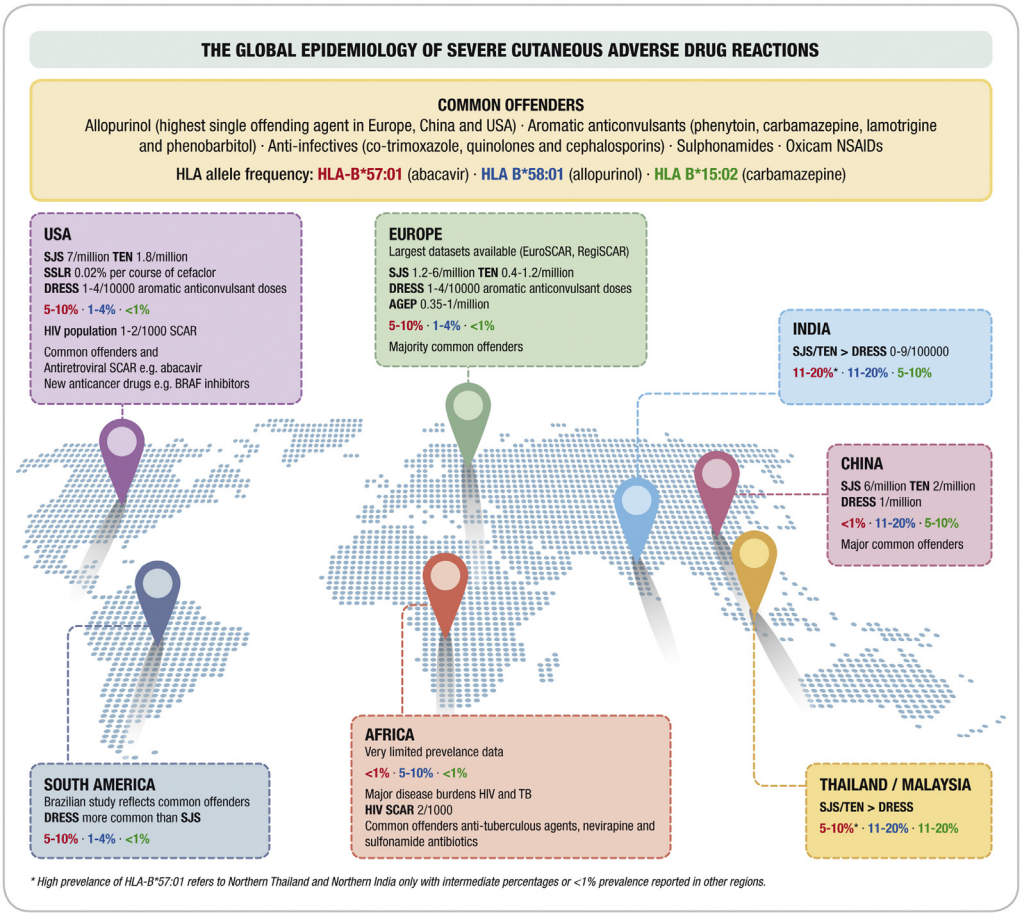

FIGURE 7. Global epidemiology of SJS/TEN and frequency of known risk HLA alleles. Incidence of SJS/TEN and other SCARs is represented for populations around the globe. Known common HLA risk allele frequencies are shown and color-coded to match the associated drug. *AGEP*, Acute generalized exanthematous pustulosis; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *SSLR*, serum-sickness like reaction. Reproduced with permission from Peter et al.[166]

the PPV to 38% and maintaining a 99.8% negative predictive value for phenytoin-related SJS/TEN. Given the rarity and severity of SJS/TEN, EHR-based algorithms designed to find SJS should focus on being able to identify most cases (ie, with a high senisitivity and high negative predictive value) with reasonable PPV. Another challenge in finding SJS/TEN cases in the EHR is confirming the phenotype because it can be difficult to verify the true diagnosis and clinical details of the cases if clinical details such as BSA involved, presence of mucosal involvement, pathology results, pictures, and other materials that are faxed into the EHR in a PDF format are not accessible by automated search methods. Many cases called "SJS" or "TEN" by treating physicians may not be SJS/TEN. The presence of a high-risk drug given in the appropriate time frame significantly increases the probability of a case identified through the EHR being SJS/TEN. In addition to difficulties finding true cases of SJS/TEN in the EHR, it is challenging to ascertain drug causality particularly if multiple drugs were started in a short time frame.

To estimate the potential number of individuals at risk, prescribing records of nearly one hundred thousand individuals at Vanderbilt University Medical Center "medical home" patients were analyzed for exposure to 5 drugs associated with severe delayed hypersensitivity syndromes including but not limited to SJS/TEN with known genomic predictors (allopurinol, lamotrigine, phenytoin, carbamazepine, and abacavir). Twelve percent of patients took at least 1 of these 5 medications, all of which except abacavir are known to be associated with SJS/TEN, and 6% took more than 1 drug. These numbers demonstrate the potential for prospective genotyping programs to potentially avert SJS/TEN events for these medications.

Regulatory perspective on pharmacogenomic screening for SJS/TEN in Singapore: Experience with implementation and cost-effectiveness

The experience of the drug regulatory authority of Singapore, the HSA, illustrates some of the benefits and challenges of implementing genetic screening to reduce the incidence of SJS/TEN. Two genetic associations with drug-induced SJS/TEN are relevant to this experience: HLA-B*15:02 with carbamazepine and HLA-B*58:01 with allopurinol. DNA collection of SJS/TEN cases and drug-tolerant controls confirmed strong genetic associations in the Singapore population (for carbamazepine: OR, 181; 95% CI, 8.7-3785; for allopurinol: OR, 100; 95% CI, 3.5-2820). Given the population frequency of these alleles

TABLE III. Adverse drug reactions with well-defined HLA associations

Drug ADR	HLA Allele	Allele frequency and carriage rate*	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
Abacavir Hypersensitivity syndrome[27,61-64]	B*57:01	*Allele frequency (%):* 1.6-7.1 European Caucasoid <3 Sub-Sahara African <3 Southeast Asian 0.3-2.4 African American 1-4 Thai	8% (3% true HSR and 2%-7% false-positive diagnosis)	960	100% for patch test confirmed	55%	13	Yes
		Carriage rate (%): 1.4-11.2 European Caucasoid* <1 Sub-Sahara African 0-2 Southeast Asian 0-2 African American						
Allopurinol SJS/TEN and DRESS/ DIHS[23,27,28,164,167,168]	B*58:01	*Allele frequency (%):* 0.5-6 European Caucasoid 2-8 Sub-Sahara African 0.5-17 Southeast Asian 2.6-6.4 African American 6-8.4 Thai	1/250-1/1,000	580	100% (Han Chinese)	3% (Han Chinese)†	250	Not in wide use (see section " Regulatory Perspective on Pharmacogenomic Screening for SJS/TEN in Singapore: Experience With Implementation and Cost-effectiveness")
		Carriage rate (%): 0-6.7 European Caucasoid 5.5-14 Sub-Sahara African 2-22 Southeast Asian >5.3 African American						
Carbamazepine SJS/TEN[27,163,165,169-171]	B*15:02	*Allele frequency (%):* <1 European Caucasoid <3 Sub-Sahara African 1-36 Southeast Asia <0.2 African American 8 Thai	<1-6/1,000	>1000	100% in Southeast Asian (with other B75 serotype)	2%-8%†	1,000	Yes
		Carriage rate (%): <1.2 European Caucasoid Up to 34 Southeast Asia						
Oxcarbazepine SJS/TEN[172]	B*15:02	*As above*		27.9	99.9% (Han Chinese)	0.73% (Han Chinese)		No
Carbamazepine DRESS/DIHS[173,174]	A*31:01	*Allele frequency (%):* 1-6 European Caucasoid <2 Sub-Sahara African 0.5-6 Southeast Asian <1 African American 7%-12% Japanese Up to 9.2% European Caucasoid* 5.5% Korean	0.05%	57.6	99.9%	0.89%	3,334	Not in wide use

(continued)

TABLE III. *(Continued)*

Drug ADR	HLA Allele	Allele frequency and carriage rate*	Disease prevalence	OR	NPV	PPV	NNT to prevent "1"	HLA screening
		Carriage rate (%): Up to 6 European Caucasoid <1 Sub-Sahara African	0.05%	23	99.9%	0.59%	5,000	Not in wide use
Dapsone DRESS/DIHS[175]	B*13:01	*Allele frequency (%):* <2 European Caucasoid 1-28 Southeast Asian 0 African American 28 Papuans/Australian Aboriginals 1.5 Japanese 2-4 Thai	1%–4% (Han Chinese)	20	99.8%	7.8%	84	Not in wide use
		Carriage rate (%): Up to 3.8 European Caucasoid 2-52 Southeast Asian						
Flucloxacillin DILI[176]	B*57:01	*As above*	8.5/100,000	81	99.99%	0.12%	13,819	No

DIHS, Drug-induced hypersensitivity syndrome; *DILI*, drug-induced liver injury; *DRESS*, drug reaction with eosinophilia and systemic symptoms; *HSR*, hypersensitivity reaction; *NNT*, number needed to treat; *NPV*, negative predictive value.
*Allele frequencies and carriage rates were obtained from allelefrequencies.net.[177] Allele frequency describes the total number of copies of the allele in the relevant population. Allele carriage rate refers to the percentage of individuals who have the allele in the population including both homozygous and heterozygous carriers. For carbamazepine-induced SJS/TEN and abacavir hypersensitivity, there is no current evidence to suggest a gene-dose effect (ie, homozygosity or heterozygosity for an HLA risk allele) appear equally associated with risk of SJS/TEN.
†Although the NPV has been 100% for both HLA-B*15:02 and carbamazepine and HLA-B*58:01 and allopurinol SJS/TEN across Southeast Asian population, there has been variability in the PPV (2%-8% for Southeast Asians for carbamazepine and 2% for allopurinol SJS/TEN in Singapore).

(14.9% for HLA-B*15:02 and 18.5% for HLA-B*58:01), specificity and sensitivity of the tests,[153,154] and incidence of the reaction, the PPV of the genetic tests in Singapore is approximately 6% for HLA-B*15:02 and approximately 2% for HLA-B*58:01. Both tests have nearly a 100% negative predictive value across Southeast Asian populations.

Patients testing positive for HLA-B*15:02 have a number of alternative drugs to treat epilepsy or neuropathic pain. Cost-effectiveness analyses conducted from a health-systems perspective showed that genotyping for HLA-B*15:02 for new users of carbamazepine falls below a commonly used incremental cost-effectiveness ratio of US $50,000 per quality-adjusted life-year.[155] Before implementation, discussion sessions with clinicians and stakeholders highlighted 2 key concerns: genotyping test costs and turnaround time. Centralization of testing achieved a 40% to 50% cost reduction to US $146 and a turnaround time of 3 days. In April 2013, the Singapore Ministry of Health and the HSA issued a joint Dear Health Care Professional Letter stating that genotyping for HLA-B*15:02 would be the standard of care before prescribing carbamazepine to new users with a 75% subsidy to low-income patients for the HLA-B*15:02 test.[156] Orders for the HLA-B*15:02 test have since reached a steady rate of 250 tests per quarter. In the 3 years after the Dear Health Care Professional Letter, there were no reported cases of carbamazepine-induced SJS/TEN in genotyped patients in Singapore. In the fourth year, HSA received 1 report of SJS in a HLA-B*15:02−negative patient. Overall, genotyping has led to a significant reduction of carbamazepine-SJS/TEN from the historical incidence of 18 cases per year obtained from voluntary reporting. Similar national health policy programs for genotype reimbursement have been in place in Taiwan since 2010 and in Hong Kong since 2008 and have successfully reduced HLA-B*15:02−associated carbamazepine SJS/TEN in both settings.[157,158]

The case for HLA-B*58:01 genotyping for allopurinol has been more challenging because of limited options for the treatment of chronic gout. At 2% PPV, many HLA-B*58:01−positive patients would be given second-line or more expensive gout drugs. A similar cost-effectiveness analysis as done for carbamazepine was done for HLA-B*58:01 in the setting of new users of allopurinol and included an option for an enhanced safety monitoring program. At a test cost below US $90, genotyping would become cost-effective if test-positive patients are given probenecid and nonresponders are switched to allopurinol with an enhanced safety program. An enhanced safety program for all patients with gout without genotyping would become cost-effective at a program cost of less than US $39 per patient.[159] In March 2016, the Singapore Ministry of Health and the HSA issued another Dear Health Care Professional Letter stating that routine genotyping for HLA-B*58:01 was not required as standard of care but could be considered for patients who have other preexisting risk factors such as renal impairment.[160] Information on the availability of an HLA-B*58:01 genotyping test at a similar price as the HLA-B*15:02 test was communicated. Additional measures to mitigate the risk are publication of clinician and consumer guides for earlier recognition of different types of severe cutaneous adverse reactions, design of a low-cost safety program, and targeted genotyping for a higher risk subgroup of patients with gout.[160,161]

In summary, systems-wide implementation of genotyping requires weighing a multiplicity of factors: from the strength of

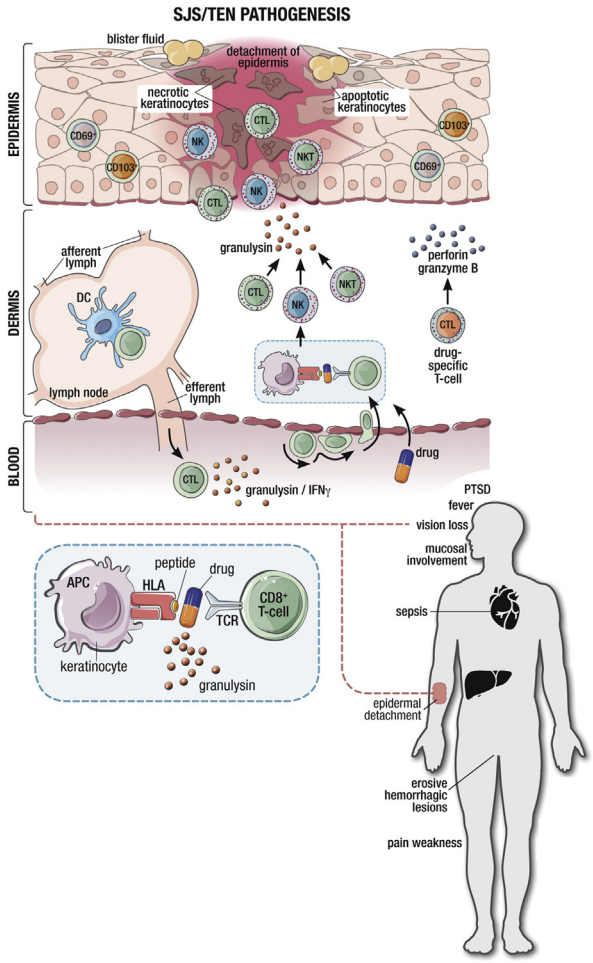

FIGURE 8. Proposed model of SJS/TEN immunopathogenesis. SJS/TEN affects the epidermis following interaction of pathogenic immune effector cells with drug-modified epitopes presented by HLA on the surface of keratinocytes. Cytotoxic CD8+ T cells, NK cells, and NK T cells that recognize HLA-drug epitopes produce cytolytic proteins such as granulysin and other mediators of inflammation. The result is widespread keratinocyte death, the formation of fluid-filled bullae containing immune cells, and, ultimately, epidermal necrosis and sloughing.

the genetic association and prevalence of the allele in the population to the PPV and availability of alternative drugs or treatment plans for test-positive patients.[161]

SJS/TEN PREVENTION, PREDICTION, AND PATHOGENESIS: WHAT'S NEW AND WHAT'S NEXT*

Key Points:

- HLA-associated SCARs including SJS/TEN have provided models for T-cell–mediated ADRs and a roadmap for assessment and implementation of pharmacogenomic screening that can be applied in clinical use for the prevention of drug hypersensitivity. Despite strong HLA associations, PPVs remain relatively low and many other factors contribute to the development of disease and present opportunities for further research into mechanism and pathogenesis.
- SJS/TEN and other cutaneous reactions secondary to immune checkpoint inhibitors of cytotoxic T-lymphocyte–associated protein 4 and programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 during treatment of cancer are increasing as the use of these agents rises. The severity of adverse cutaneous reactions to immunotherapies correlates with improved cancer outcomes and survival, suggesting that patients most likely to benefit are also those most likely to develop toxicity. This provides potentially important clues to the immunopathogenesis of these reactions and underscores the need to manage these toxicities so that patients can benefit from anticancer therapies. In addition, gene expression analyses have shown similarities between lichenoid rash associated with immune checkpoint inhibitors and SJS/TEN to noncancer agents.
- In SJS/TEN there is currently much focus on effector memory $CD8^+$ T-cell responses. However, suppressor immune responses, such as those conferred by regulatory T (Treg) cells, play a key role in the maintenance of immune homeostasis in the skin and are notably diminished early in the course of SJS/TEN. Augmenting regulatory immune responses might provide alternative or complementary treatment modalities for SJS/TEN.
- Blister fluid cells from the skin lesions in patients with SJS/TEN are characterized by the infiltration of $CD8^+$ T cells, natural

TABLE IV. Frequencies of immune subsets in blister fluid obtained from patients with acute SJS/TEN

Surface CD expression	Case 1	Case 2	Case 3	Case 4	Case 5
CD3+	46%	70%	33%	68%	61%
CD4+	4%	0%	0%	9%	0%
CD8+	42%	70%	33%	59%	61%
CD20+	0%	0%	0%	0%	0%
CD56+	48%	70%	100%	100%	72%
CD3+, CD56− (T cells)	42%	30%	0%	0%	30%
CD3−, CD56+ (NK cells)	44%	30%	66%	32%	41%
CD3+, CD56+ (NK T cells)	4%	44%	33%	68%	31%
CD4+, CD56+	0%	0%	0%	9%	0%
CD8+, CD56+ (NKT cells)	4%	44%	33%	59%	31%

Unpublished data (Hung S.-I., PhD, March 2017), and Chung et al.[180]

TABLE V. Rapid immunochromographic test for granulysin

Syndrome	Blister fluid granulysin concentration
SJS/TEN	High: 100 ng/mL
Bullous fixed drug eruption	High: 100 ng/mL
Bullous erythema multiforme	Moderate: 50 ng/mL
Hand-foot-and-mouth disease bullae	Low: 10-20 ng/mL
Chemotherapy hemorrhagic bullae	Low: 10-20 ng/mL
Pemphigus	Negative: <5 ng/mL
Bullous pemphigoid	Negative: <5 ng/mL
Acute generalized exanthematous pustulosis	Negative: <5 ng/mL

Chung et al,[180] Su et al,[186] and unpublished data (Chung W.-H., MD, PhD, March 2017).

* Riichiro Abe, MD, PhD; Wen-Hung Chung, MD, PhD; Shuen-Iu Hung, PhD; Mario E. Lacouture, MD; David A. Ostrov, PhD; Rebecca Pavlos, PhD; Alec Redwood, PhD; Michael D. Rosenblum, MD, PhD; Katie D. White, MD, PhD

TABLE VI. Cutaneous adverse events and SJS/TEN associated with immune checkpoint inhibitors

Drug name	Target	Indication	Severe rash (%)	SJS/TEN reported[194,195]
Ipilimumab	CTLA-4	Melanoma	2.4	Yes
Nivolumab	PD-1	Melanoma, NSCLC, RCC, HL, HNSCC, UC, CRC	1.2	Yes
Ipilimumab + nivolumab	CTLA-4+ PD-1	Melanoma	5.0%	Yes
Pembrolizumab	PD-1	Melanoma, NSCLC, HNSCC, HL, dMMR tumors	1.7%	Yes
Atezolizumab	PD-L1	Bladder cancer, NSCLC	1.3%	No
Avelumab	PD-L1	Merkel cell carcinoma	0%	Yes

CRC, Colorectal cancer; *dMMR*, defective mismatch repair; *CTLA-4*, cytotoxic T-lymphocyte–associated protein 4; *HL*, Hodgkin lymphoma; *HNSCC*, head and neck squamous cell carcinoma; *PD-L1*, programmed cell death protein ligand 1; *NSCLC*, non–small cell lung cancer; *RCC*, renal cell carcinoma; *UC*, urothelial carcinoma.

killer (NK) cells, and NK T cells. A public T-cell receptor (TCR) αβ clonotype has been found in blister fluid and PBMCs from Taiwanese patients with HLA-B*15:02–restricted carbamazepine SJS/TEN. Binding assays with this TCR recombinant protein support a pharmacological interaction with immune proteins model for carbamazepine SJS/TEN. The applicability of this model to other class I HLA-restricted drug-induced SJS/TEN is currently being explored.

- Virtual modeling predicts that carbamazepine binds to HLA-B*15:02 at a higher affinity in the absence of peptide and contacts both HLA and TCR.
- T-cell, NK cell, and NK T-cell–derived granulysin is a key mediator of tissue damage and disease in SJS/TEN. Serum granulysin levels, as well as IL-15, may prove useful as prognostic markers during acute SJS/TEN. Targeting granulysin as well as pathogenic T cells may provide additional therapeutic interventional strategies to join other biologics such as anti-TNF (etanercept) therapy.
- In some patients, a generalized exanthema develops following antibiotic treatment for gastrointestinal infection. It is hypothesized that the risk for cutaneous ADRs may be influenced by the gut microbiome or potentially other bacterial pathogens.

Understanding the immunopathogenesis of SJS/TEN is central to the development of pretherapy screening strategies and effective SJS/TEN treatment regimens. Critical to this is deciphering and linking the influences of host genetics and structural, biochemical, and functional interactions between drugs and/or pathogens and the immune system. Session 5 of *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* reviewed seminal advances in our understanding of the pharmacogenomics and immunology of SJS/TEN and other T-cell–mediated severe ADRs and ongoing basic and translational science research in this field.

SJS/TEN is an IM-ADR influenced by genes that affect pharmacokinetics, pharmacodynamics, and immune responses. Additional influences include comorbid disease such as renal impairment and external factors such as environmental exposures and viral infection.[162] Class I associations that have also provided key insights to IM-ADR pathogenesis include carbamazepine and HLA-B*15:02 in SJS/TEN and allopurinol and HLA-B*58:01 in SCARs.[163-165] Many other HLA associations with drugs that cause SCARs including SJS/TEN are documented and incidence varies across ADR phenotypes and across populations, reflecting risk allele carriage (Figure 7). However, for most drugs

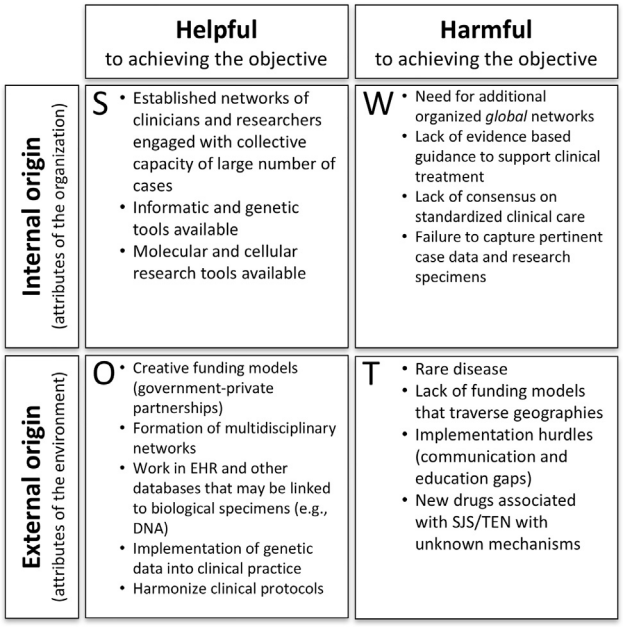

FIGURE 9. Strengths, weaknesses, opportunities, and threats (SWOT) analysis for SJS/TEN clinical management and research. Participants at *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* contributed to a SWOT analysis to define unmet needs in SJS/TEN clinical care and research and to identify approaches to address these needs.

that are implicated in SJS/TEN there remains no known HLA association, and for up to 20% of SJS/TEN cases no causative drug is identified.

Carriage of a given risk HLA allele is permissive but insufficient for the development of drug hypersensitivity as evidenced by the small percentage of individuals carrying the risk alleles who develop an ADR when exposed to the drug (Table III). Identifying additional factors that contribute to the development of ADRs will be important in understanding mechanisms of pathogenesis and also help guide pharmacogenomic screening in the future. Drug dose, metabolism, and clearance rate are known to be independent pharmacological factors in the development of SJS in some settings and may account for part of the PPV gap. For example, variants in the allele coding for the metabolic enzyme *CYP2C9*3* are significantly associated with phenytoin SCAR in Taiwan, Japan, Malaysia, and Thailand.[178,179] In

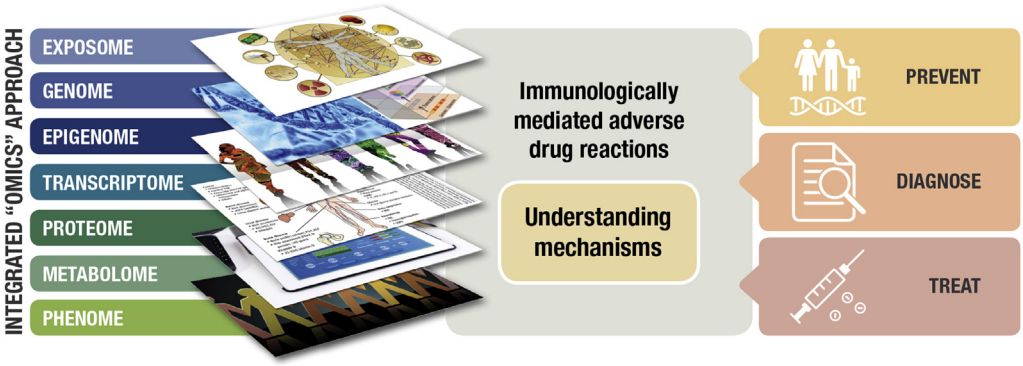

FIGURE 10. Integrated—omics approaches as part of personalized medicine in SJS/TEN. There exist multiple opportunities to apply personalized medicine approaches for the prevention and treatment of SJS/TEN. Part of these approaches will include integrated—omics platforms that link genetic, immunologic, ecologic, and other data within an individual patient to estimate risk of disease, facilitate precise and rapid diagnosis, inform prognosis and response to therapy, and predict which medications are safe for future use. Aggregation of these data may allow us to define the general principals of immunopathogenesis and genetics that may be applied more broadly to larger populations.

addition to HLA and metabolic-based genetic factors, potential roles for risk-enhancing TCR clonotypes, tissue-specific memory T-cell subsets, NK cells, and NK T cells are under investigation. Finally, the nature of HLA and peptide alterations following drug exposure as determined by genetic factors within the proteasome pathway and peptide processing machinery may potentially contribute to disease pathogenesis and are under study.

Studies showing a strong association between HLA class I alleles and drug-induced SJS/TEN disease support the concept that class I—restricted antigen-driven $CD8^+$ T cells are of fundamental importance in immunopathogenesis (Figure 8).[164,165] Hung et al have shown that cells recruited to the blisters in SJS/TEN are predominantly T cells, NK cells, and NK T cells, and that the percentage of each cell subset varies between patients (Table IV). Using blister fluid as a source of potentially pathogenic effector cells, T cells identified in blister fluid from individuals with SJS/TEN are characterized by a dominant clonotype(s), defined as a population of $CD8^+$ T cells that express the same TCR sequence. This suggests that T cells bearing this TCR are able to bind and be stimulated by peptides from the eliciting drug. These T cells also express granulysin and granzyme-B consistent with a cytotoxic T lymphocyte phenotype. Similar shared TCRs were not found in patients with allopurinol SCAR, although some evidence of clonal expansion within individual patients was seen in blister fluid.[181]

Surface plasmon resonance experiments have demonstrated that carbamazepine (and carbamazepine metabolites) are capable of binding directly to HLA-B*15:02 and residues important in the HLA-carbamazepine interaction have been mapped to the HLA peptide-binding groove using site-directed mutagenesis studies.[182,183] Ostrov et al[184] and Illing et al[185] previously solved the crystal structure of abacavir bound to HLA-B*57:01 that defined the altered peptide repertoire model for drug-HLA interaction. More recent work by Ostrov et al has focused on determining whether known HLA and drug structures can be used to predict which drug will bind a particular HLA protein. Modeling algorithms of drug-binding affinities predicted that abacavir would bind to HLA-B*57:01 with higher affinity in the presence of a self-peptide. This is consistent with known crystallagraphy data and represents proof-of-concept for this type of *in silico* approach to predicting drug-HLA interactions. Using this approach, carbamazepine binding was not predicted to bind a site within the antigen-binding cleft (under the peptide, as abacavir interacted with the F pocket of HLA-B*57:01). Based on the crystal structures of HLA-B*15:02, TCR complexes with HLA-B molecules and atomic models of HLA-B*15:02 complexed with peptides corresponding to HLA-B*15:02 elution studies and TCRαβ sequences of the shared TCR discovered in Taiwanese patients mentioned above, carbamazepine was predicted to bind complexes of peptide and HLA-B*15:02 in a TCR contact site located at the interface of the trimolecular HLA-B*15:02-peptide-TCR complex (D. Ostrov, PhD, unpublished data, March 2017).

Cytotoxic protein and cytokine mediators are important in SJS/TEN pathogenesis and have potentially important applications as diagnostic and predictive markers and therapeutic targets. Chung et al[180] discovered that the cytolytic protein granulysin, produced by $CD8^+$ T cells, NK cells, and NK T cells, is a primary mediator of keratinocyte cell death in SJS/TEN. Granulysin is found at high concentration in serum and blister fluid from patients with SJS/TEN and plasma levels correlate with disease severity and prognosis.[180,186] Chung et al have developed a rapid immunochromographic test to measure blister fluid granulysin concentration and this assay measured over multiple time points appears to distinguish SJS/TEN and bullous fixed drug eruption from other blistering skin diseases such as bullous erythema multiforme, bullous pemphigus, and viral infection (Table V). His group has also identified that systemic IL-15, a cytokine that activates NK cells and cytotoxic T cells, is also correlated with SJS/TEN severity and both IL-15 and granulysin may be used as prognostic markers during acute SJS/TEN.[186]

Chung et al have also conducted an open, prospective, randomized trial evaluating the efficacy of immunomodulatory therapies for the treatment of SJS/TEN. This study included 48 patients randomized to receive the TNF-α inhibitor etanercept and 45 patients to receive corticosteroid therapy. This study demonstrated that etanercept reduced time to reepithelialization

Box I. The SJS Foundation and Patient Perspectives

FIGURE 11A. Julie McCawley.

Julie McCawley. Jean and Julie McCawley, Katie Niemeyer, and the family of Angela Anderson attended *SJS/TEN 2017: Building Multidisciplinary Networks to Drive Science and Translation* on behalf of patients and families around the world who have been affected by SJS/TEN.

Julie McCawley, now aged 23 years, developed SJS/TEN at age 11 months and as a result suffers from severe sight impairment (Figure 11, *A*). In March of 1995, her mother, Jean, founded the Stevens-Johnson Syndrome Foundation (http://sjsupport.org), a grassroots nonprofit patient support and advocacy group that aims to bring public awareness to this devastating and life-threatening illness. In 1997, the SJS Foundation launched its first Web site that included an online chat room for patients and families affected by SJS. Their network quickly brought together numerous patients and families affected by SJS/TEN from around the world. In 1999, the SJS Foundation collaborated with physicians at Johns-Hopkins to create an SJS fact sheet that has now been distributed to more than 100,000 hospitals and pharmacies and to the general public through awareness campaigns. The SJS Foundation now supports a voluntary case registry, has championed the establishment of August as SJS Awareness month, actively supports SJS/TEN research, and maintains a Facebook page with more than 5,000 followers. Julie McCawley is now an elementary school teacher and creator of SJS Kids Support (www.freewebs.com/sjskidssupport), a Web site for children affected by SJS/TEN that explains the disease and its complications in accessible terminology with content focused on the concerns of young victims and of children with loved ones affected by SJS/TEN.

FIGURE 11B. Angela Anderson.

"Angela was unique. She was a trendsetter … one in a million. The disease that took her was one in a million. Even in death, she stood out from the crowd." —Eulogy for Angela Anderson (Figure 11, *B*). Paul Anderson shared the story of his daughter Angela's vibrant 22-year life and tragic 4-day hospitalization with SJS/TEN that ended in her death on December 28, 2015. In memory of Angela, he and his wife, Wanpen, and son, Tim, established the Angela Anderson SJS Research Fund to promote SJS/TEN research. The Anderson family recruited support from family, friends, and the general public through awareness events, media communications, and a GoFundMe campaign to raise $22,000 for SJS/TEN research. This is an especially significant contribution because it represents $1000 in research funding for each year of Angela's life. Angela's story has been reported in numerous media outlets, further raising community awareness of SJS/TEN. The Angela Anderson SJS Research Fund continues to receive donations to further research efforts and her family and friends continue to work tirelessly to disseminate her story as education for the public and medical communities.

and reduced mortality. This work and other early studies suggest the potential efficacy of etanercept as a therapeutic option for SJS/TEN and provide a mechanism to explain therapeutic responses with this drug.[112,115,187,188] Future work that may translate into targeted therapy is focused on developing and testing novel inhibitors to pathogenic mediators in SJS/TEN including an mAb targeting granulysin and an mAb targeting the TCR$\alpha\beta$ subunits to disrupt TCR signaling.[189,190] Another insight into the immunopathogenesis of SJS/TEN has come from studies demonstrating that interaction of annexin A1 with the formyl peptide receptor 1, expressed on the surface of keratinocytes obtained from patients with SJS/TEN but not present on control keratinocytes, is a key mediator of keratinocyte necroptosis in SJS/TEN.[191]

More recently Abe et al (R. Abe, MD, PhD, unpublished data, March 2017) have examined the role of the microbiome in the development of severe cutaneous ADRs. Using PBMCs obtained from patients who developed a generalized exanthema within 1 to 3 days after completing treatment for gastrointestinal bacterial infection, they have shown that $CD4^+$ cells express the activation marker CD154 following exposure to whole, killed bacteria. Cell culture supernatants from these experiments contain elevated levels of inflammatory cytokines compared with cultures derived from PBMCs obtained from normal donors. Abe et al are investigating the hypothesis that treatment of bacterial gastrointestinal infection generates bacterial products that stimulate an immune response. This raises the interesting possibility that the risk for cutaneous ADRs may be influenced by the microbiome and in particular bacterial pathogens in the gut.

FIGURE 11C. Katie Neimeyer with SJS/TEN survivor and PGA champion Gene Sauers.

Katie Niemeyer is a survivor of SJS/TEN as a teenager and now works as a certified nurse anesthetist, entrepreneur, mother, and philanthropist to promote SJS/TEN awareness and research (Figure 11, *C*). Left with chronic eye irritation that hindered her training as a distance runner, Katie created a high-performance wristband, Handana, to keep sweat from burning her already sensitive eyes. Handana was the first runner up in the 2015 Under Armour Future Show. Katie has donated proceeds from her business endeavors to supporting research in the treatment of acute and chronic SJS/TEN eye disease and established the Katie Niemeyer Research Fund at the Massachusetts Eye and Ear clinic. Katie is also the founding member of the SJ Syndrome of Texas (www.sjsyndrome.com) and frequently shares her story with health care and general audiences around the country to educate and inspire hope within and outside the SJS/TEN community.

These stories underscore major threats associated with SJS/TEN, a disease that (1) affects previously healthy individuals in an unpredictable manner in the absence of validated screening mechanisms, (2) is characterized by sequelae that are numerous, severe, and lifelong, (3) lacks highly specific diagnostic modalities that often results in delayed recognition of acute disease, and (4) in its severest form, moves quickly and with high mortality.

Severe cutaneous syndromes associated with novel cancer immunotherapeutics have provided significant insights into the potential immunopathogenesis of SJS/TEN. First approved for clinical use in 2011, the immune checkpoint inhibitors are a class of drugs that block inhibitory receptors such as PD-1 (nivolumab) and cytotoxic T-lymphocyte–associated protein 4 (ipilimumab) on the surface of T cells promoting T-cell activation and effector functions.[192] This class of therapy has shown tremendous efficacy in the treatment of certain cancers including stage IV melanoma, lymphoma, and cancers of the head and neck, lung, bladder, and kidney.[193] Cutaneous eruptions occur in approximately one-third of patients treated with checkpoint blockade (Table VI). Most often these eruptions are clinically benign, do not limit treatment, and respond to topical corticosteroids. A small proportion of patients receiving checkpoint inhibitor blockade develop SJS/TEN.[196-198] Importantly, the severity of the cutaneous ADR related to checkpoint inhibitor therapy correlates with improved tumor response and patient survival.[199,200] Similarities in gene expression profiling among the various phenotypes of cutaneous reactions associated with anti–PD-1/programmed cell death protein ligand 1 therapy that resemble those associated with SJS/TEN suggest that PD-1 may be important in specifically regulating epidermal integrity.[201] Lacouture et al[195] have shown that serum IL-6 is elevated in patients with early maculopapular rash secondary to checkpoint inhibitor therapy. Furthermore, they are investigating whether therapeutics that target T-cell activation pathways and inflammation, such as Janus kinase inhibitors and/or IL-6 inhibition, might provide benefit for the treatment of checkpoint inhibitor blockade-associated cutaneous reactions.

Another key in the immunopathogenesis of many immunologically mediated diseases including SJS/TEN is thought to be an imbalance of effector/autoreactive and regulatory immune responses. Extensive research supports the scientific premise that autoimmune disease reflects a disruption of this balance. Treg cells are defined as $CD4^+$ T cells that express the transcription factor FoxP3 that drives the suppressor phenotype. Tissue-resident Treg cells are highly abundant in the skin and gut tissues of mice and humans. Individuals who lack functional Treg-cell responses succumb at an early age to fulminant systemic autoimmune disease, highlighting the critical role these cells play in immune regulation.[202,203] Treg-cell suppressor function is mediated via various mechanisms including IL-10 secretion, surface expression of the inhibitory receptor cytotoxic T-lymphocyte–associated protein 4, and through IL-2 consumption by the high-affinity IL-2 receptor CD25. Rosenblum et al[204] have developed a murine model of cutaneous autoimmune disease that demonstrated that mice spontaneously suppress skin inflammatory responses over time despite ongoing antigen exposure but that depletion of Treg cells in these mice leads to prolonged disease and death. These data support a mechanistic role for Treg cells in maintaining immune homeostasis in the skin. Furthermore, it has been shown that (1) Treg cells are less abundant in skin from patients with SJS/TEN compared with erythema multiforme,[205] (2) that circulating Treg cells obtained from patients with SJS/TEN display impaired suppressor function,[206] (3) that Treg cells can prevent epidermal injury in animal TEN model systems,[207] and (4) that Treg-cell–mediated suppression decreases cytotoxic T-cell responses to drugs in *in vitro* systems.[208] Data from human trials have shown that therapies that augment Treg-cell function (including adoptive transfer of expanded autologous Treg cells and low-dose systemic IL-2) ameliorate alopecia areata, chronic graft-versus-host disease, and systemic lupus erythematosus.[209-212] As noted above, immunohistochemistry experiments have shown that Treg cells are present at significantly reduced numbers in skin from

patients with SJS/TEN compared with EMM and this can be used to differentiate these 2 disease phenotypes.[205] The use of strategies to boost regulatory immune responses in acute SJS/TEN is intriguing and warrants further study.

DISCUSSION AND FUTURE DIRECTIONS

SJS/TEN is a life-threatening disease that in adults is usually drug related and in children in particular, both SJS/TEN and its mimickers (Table I) can create unique diagnostic challenges in the absence of an apparent causative agent. The low incidence of SJS/TEN of 1 to 5 per 1,000,000 and high mortality rate have highlighted the need for research and clinical networks to drive research, translation, consensus guidelines, and evidence-based approaches. This 1-day meeting highlighted that there has been significant progress to strengthen SJS/TEN research efforts over the last decade. Harnessing strengths and opportunities and proactively addressing weaknesses and threats will be crucial to these research efforts moving forward (Figure 9). Key strengths have included the establishment of epidemiological and pharmacogenomic networks, the ability to use informatics tools to find SJS/TEN cases in the EHR, and access to genetic tools to analyze the data. With these research strengths has come the opportunity to establish and access DNA and cellular biobanks to facilitate further genetic and mechanistic discovery science. The preexisting networks also create a unique platform for the establishment of larger multidisciplinary networks where clinical protocols can be harmonized and therapeutic approaches studied. Addressing weaknesses and threats will be equally important. Lack of evidence-based treatment guidelines and consensus on standardized clinical care has been a hurdle to the creation of very large global networks to study treatment interventions. In addition, many studies have been strictly epidemiologically based and have not had the resources or infrastructure to collect and cryopreserve valuable research samples. Ultimately creative strategies will be needed to maximize and coordinate research efforts and may require creative funding mechanisms from multiple governments and other sources. It is also predicted that the patient-centered integrated -omics approaches that are part of the personalized medicine of the future will be key to not only understanding the mechanistic basis of SJS/TEN but also furthering preventive efforts and facilitating earlier diagnosis and treatment (Figure 10).

You may view the Abstracts presented at this meeting at: https://medsites.mc.vanderbilt.edu/sjsmeeting/home.

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A docking model of dapsone bound to HLA-B*13:01 explains the risk of dapsone hypersensitivity syndrome

Hideaki Watanabe[a,*], Yurie Watanabe[b], Yasuya Tashiro[a], Taisei Mushiroda[c], Takeshi Ozeki[c], Hideo Hashizume[d], Hirohiko Sueki[a], Toshinori Yamamoto[e], Naoko Utsunomiya-Tate[f], Hiroaki Gouda[b,**], Yoshio Kusakabe[b,f]

[a] Department of Dermatology, Showa University School of Medicine, Tokyo, Japan
[b] Department of Analytical and Physical Chemistry, Showa University School of Pharmacy, Tokyo, Japan
[c] RIKEN Center for Integrative Medical Sciences, Yokohama, Japan
[d] Department of Dermatology, Shimada Municipal Hospital, Shizuoka, Japan
[e] Showa University Medical Foundation, Showa University School of Pharmacy, Tokyo, Japan
[f] Laboratory of Chemistry, Faculty of Pharma Sciences, Teikyo University, Tokyo, Japan

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ABSTRACT

Background: Dapsone (4,4′-diaminodiphenylsulfone) has been widely used for the treatment of infections such as leprosy. Dapsone hypersensitivity syndrome (DHS) is a major side effect, developing in 0.5–3.6% of patients treated with dapsone, and its mortality rate is ~10%. Recently, human leukocyte antigen (HLA)-B*13:01 was identified as a marker of susceptibility to DHS.
Objectives: To investigate why HLA-B*13:01 is responsible for DHS from a structural point of view.
Methods: First, we used homology modeling to derive the three-dimensional structures of HLA-B*13:01 (associated with DHS) and HLA-B*13:02 (not so associated despite strong sequence identity [99%] with HLA-B*13:01). Next, we used molecular docking, molecular dynamic simulations, and the molecular mechanics Poisson-Boltzman surface area method, to investigate the interactions of dapsone with HLA-B*13:01 and 13:02.
Results: We found a crucial structural difference between HLA-B*13:01 and 13:02 in the F-pocket of the antigen-binding site. As Trp95 in the α-domain of HLA-B*13:02 is replaced with the less bulky Ile95 in HLA-B*13:01, we found an additional well-defined sub-pocket within the antigen-binding site of HLA-B*13:01. All three representative docking poses of dapsone against the antigen-binding site of HLA-B*13:01 used this unique sub-pocket, indicating its suitability for binding dapsone. However, HLA-B*13:02 does not seem to possess a binding pocket suitable for binding dapsone. Finally, a binding free energy calculation combined with a molecular dynamics simulation and the molecular mechanics Poisson-Boltzman surface area method indicated that the binding affinity of dapsone for HLA-B*13:01 would be much greater than that for HLA-B*13:02.
Conclusions: Our computational results suggest that dapsone would fit within the structure of the antigen-recognition site of HLA-B*13:01. This may change the self-peptides that bind to HLA-B*13:01, explaining why HLA-B*13:01 is a marker of DHS susceptibility.

Abbreviations: Dapsone, 4,4′-diaminodiphenylsulfone; DHS, dapsone hypersensitivity syndrome; HLA, human leukocyte antigen; 3D, three-dimensional; MD, molecular dynamics; MM-PBSA, molecular mechanics Poisson-Boltzman surface area; TEN, toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TCR, T cell receptor; OPLS, optimized potentials for liquid simulations; GAFF, general AMBER force field; TIP3P, transferable intermolecular potential 3P.

* Corresponding author at: Department of Dermatology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
** Corresponding author at: Department of Analytical and Physical Chemistry, Showa University School of Pharmacy, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan.
E-mail addresses: hwatanabe@med.showa-u.ac.jp (H. Watanabe), godah@pharm.showa-u.ac.jp (H. Gouda).

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1. Introduction

Dapsone (4,4′-diaminodiphenylsulfone; Fig. 1), which was first synthesized in 1908 [1], has been used widely for the treatment of infections such as leprosy [2] and inflammatory diseases, such as linear IgA dermatosis [3] and subcorneal pustular dermatosis [4]. Approximately 0.5–3.6% of patients treated with dapsone develop hypersensitivity to the drug, which was first described by Lowe and Smith in 1949 [5] and named "dapsone hypersensitivity syndrome" (DHS) in 1951 [6]. DHS is a serious adverse drug reaction, clinically defined by a severe skin eruption, fever, lymphadenopathy, hematological abnormalities, with eosinophilia and atypical lymphocytes, and internal organ involvement such as hepatitis after long-term administration of certain anticonvulsants [7,8]. This type of reaction is now recognized as a drug-induced hypersensitivity syndrome or a drug reaction with eosinophilia and systemic symptoms [9–11]. A recent systematic review of published epidemiologic studies reported a DHS mortality rate of 9.9% [12].

Recently, a human leukocyte antigen (HLA) class I allele, HLA-B*13:01, was identified as a marker of susceptibility to DHS [8,13]. To date, genetic factors have been shown to play important roles in several types of drug eruptions including DHS. For example, the HLA-B*15:02 allele was identified as an important predictor of risk for carbamazepine-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in a southeast Asian population [14]; in contrast, the HLA-A*31:01 allele was found in European [15] and Japanese populations [16]. Moreover, recent clinical testing for this allele revealed a decreased incidence of each of these disorders in a Taiwanese population [17]. Abacavir hypersensitivity syndrome has also been reported to be associated with the HLA-B*57:01 allele [18].

Illing et al. recently suggested that abacavir hypersensitivity syndrome could be explained by reference to the altered peptide repertoire model [18,19]. In the altered peptide repertoire model, the drug interacts with the antigen-binding cleft of a specific HLA allele and alters the self-peptides binding to the HLA molecule, resulting in a T cell response. In their X-ray crystallographic study, abacavir was found to bind specifically in the vicinity of the F-pocket of the antigen-binding cleft of the HLA-B*57:01 allele, which was identified as a marker of susceptibility to abacavir hypersensitivity syndrome. Their study motivated us to investigate the possibility of the altered peptide repertoire model for DHS in individuals possessing the HLA-B*13:01 allele. Thus, we performed computational analyses of dapsone/HLA-B*13:01 interactions using homology modeling, molecular docking, molecular dynamics (MD) simulation, and the molecular mechanics Poisson-Boltzman surface area (MM-PBSA) method in this investigation.

2. Materials and methods

2.1. Homology modeling of HLA-B*13:01 and 13:02

All calculations for homology modeling were conducted using the Schrödinger suite 2015-4 (Schrödinger, LLC, New York, NY, USA). An HLA molecule exists physiologically as a heterodimer, with an α-domain containing the antigen-binding site and a β-domain, also called β_2 microglobulin. HLA-B*13:01 and 13:02 differ in the α-domain amino acid sequence. The α-domain sequences of HLA-B*13:01 and 13:02 (Table 1) were obtained from the UniProtKB-Swiss-Prot database (accession number P30461). The amino acid sequence of the common β domain was based on accession number P61769. Next, BLAST searches of the Protein Data Bank (PDB) were performed, based on the α-domain sequences of HLA-B*13:01 and 13:02, and the top 10 ranking highly homologous structures were selected as templates for modeling homology using the Prime 4.2 program. In total, 10 homology models each were constructed for HLA-B*13:01 and 13:02. Finally, the resulting three-dimensional 3D structures of HLA-B*13:01 and 13:02 were minimized using the OPLS (Optimized Potentials for Liquid Simulations) version 3 force field incorporated in the Schrödinger suite version 2015-4. We used this field to calculate energies.

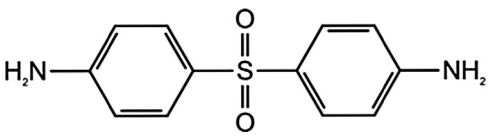

Fig. 1. Chemical structure of dapsone.

2.2. Molecular docking calculations for dapsone against HLA-B*13:01 and 13:02

Molecular docking calculations were also conducted using the Schrödinger suite 2015-4 (Schrödinger, LLC). An initial 3D structure of dapsone (Fig. 1) was generated using the Ligprep program, and conformational searches were performed using the Confgen program. In total, 15 conformers were generated. Then, molecular docking calculations of these conformers were performed against the antigen-binding sites of HLA-B*13:01 and 13:02 using the Glide 6.9 program (SP mode). To arrange the receptor grid, the center of the grid was set to a centroid (the geometric center) of two α-helices composing the cleft lip, and the grid box size was set to cover the whole of the cleft ($30 \times 30 \times 10$ Å^3). The scaling factor of van der Waals radii for the ligand was set to 0.80. Three poses were generated for each conformer. As a result, in total, 450 poses (15 (conformers) × 3 (number of generations) × 10 (number of homology models)) were obtained for each HLA allele. The poses generated were ranked according to the Glidescore. The top 50 complex models were superimposed on the α-domains of the HLA molecules and were clustered based on the atomic positional root-mean-square deviations (RMSDs) of dapsone to group similar docking poses. When the cut-off distance of the RMSDs was set to 2 Å, we obtained three representative poses for both HLA-B*13:01 and 13:02. These representative structures of dapsone in complex with HLA-B*13:01 and 13:02 were used as the initial structures in the following MD simulations.

2.3. Molecular dynamics simulations and binding free energy calculations

All MD simulations were performed using the AMBER14 simulation package [20]. The AMBER ff14SB force field and general AMBER force field (GAFF) [21] were used to estimate energies for amino acids and the ligand, respectively. The partial charges for dapsone were derived from the restraint electrostatic potential method using an ab initio calculation at the HF/6-31G* level [22]. Each representative structure of the dapsone–HLA-B*13:01 and dapsone–HLA-B*13:02 complexes was solvated in a truncated octahedron box of transferable intermolecular potential 3P (TIP3P) water molecules [23] with a margin of 8 Å in each dimension. TIP3P is a popular model for water simulations. In addition, Na^+ ions were added to neutralize the dapsone–HLA-B*13:01 and dapsone–HLA-B*13:02 complexes. Each system was equilibrated by a procedure described previously [24]. Finally, the production phase of the MD simulations of 20 ns length were carried out at constant pressure (1 atm) and temperature (300 K), under periodic boundary conditions, and using the particle-mesh Ewald treatment of electrostatics [25]. The SHAKE algorithm [26] was applied to all bonds involving hydrogen, and a time step of 2 fs was used. A 10-Å cutoff was used for van der Waals interactions. The binding free

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Table 1
α Domain sequence of HLA-B*13:01 (up) and HLA-B*13:02 (bottom).

HLA-B*13:01	1	G S H S M R Y F Y T A M S R P G R G E P R F I T V
HLA-B*13:02	1	G S H S M R Y F Y T A M S R P G R G E P R F I T V
HLA-B*13:01	26	G Y V D D T Q F V R F D S D A T S P R M A P R A P
HLA-B*13:02	26	G Y V D D T Q F V R F D S D A T S P R M A P R A P
HLA-B*13:01	51	W I E Q E G P E Y W D R E T Q I S K T N T Q T Y R
HLA-B*13:02	51	W I E Q E G P E Y W D R E T Q I S K T N T Q T Y R
HLA-B*13:01	76	E N L R T A L R Y Y N Q S E A G S H I I Q R M Y G
HLA-B*13:02	76	E N L R T A L R Y Y N Q S E A G S H T W Q T M Y G
HLA-B*13:01	101	C D L G P D G R L L R G H N Q L A Y D G K D Y I A
HLA-B*13:02	101	C D L G P D G R L L R G H N Q L A Y D G K D Y I A
HLA-B*13:01	126	L N E D L S S W T A A D T A A Q I T Q L K W E A A
HLA-B*13:02	126	L N E D L S S W T A A D T A A Q I T Q L K W E A A
HLA-B*13:01	151	R V A E Q L R A Y L E G E C V E W L R R Y L E N G
HLA-B*13:02	151	R V A E Q L R A Y L E G E C V E W L R R Y L E N G
HLA-B*13:01	176	K E T L Q R A D P P K T H V T H H P I S D H E A T
HLA-B*13:02	176	K E T L Q R A D P P K T H V T H H P I S D H E A T
HLA-B*13:01	201	L R C W A L G F Y P A E I T L T W Q R D G E D Q T
HLA-B*13:02	201	L R C W A L G F Y P A E I T L T W Q R D G E D Q T
HLA-B*13:01	226	Q D T E L V E T R P A G D R T F Q K W A A V V V P
HLA-B*13:02	226	Q D T E L V E T R P A G D R T F Q K W A A V V V P
HLA-B*13:01	251	S G E E Q R Y T C H V Q H E G L P K P L T L R W E
HLA-B*13:02	251	S G E E Q R Y T C H V Q H E G L P K P L T L R W E
HLA-B*13:01	276	P S S Q S T V P I V G I V A G L A V L A V V V I G
HLA-B*13:02	276	P S S Q S T V P I V G I V A G L A V L A V V V I G
HLA-B*13:01	301	A V V A A V M C R R K S S G G K G G S Y S Q A A C
HLA-B*13:02	301	A V V A A V M C R R K S S G G K G G S Y S Q A A C
HLA-B*13:01	326	S D S A Q G S D V S L T A
HLA-B*13:02	326	S D S A Q G S D V S L T A

*Residues different between HLA-B*13:01 and HLA-B*13:02 were shadowed.

energy (ΔG_{bind}) calculation was conducted using the MM-PBSA python script included within the AMBER14 package. The value of the relative dielectric constant (ε) of protein was set to 2 or 4, and that of the bulk solvent was set to 80. The MM-PBSA calculations were performed using 500 snapshots for each complex, which were extracted from the last 5 ns on the MD trajectory with an interval of 10 ps. Moreover, the hydrogen bond interactions between dapsone and HLA-B*13:01 were also examined using 500 snapshots. According to the definition of a hydrogen bond, the distance between heavy atoms was within 3.5 Å, and angle cut-off was >120°.

3. Results

3.1. Comparison of the amino acid sequences of the α-domains of HLA-B*13:01 versus 13:02

The amino acid sequences of the α-domains of HLA-B*13:01 and 13:02 are shown in Table 1. We found only three amino acid residues that differed between HLA-B*13:01 and 13:02 among 338 amino acids total. The different residues were $I^{94}I^{95}R^{97}$ in HLA-B*13:01 versus $T^{94}W^{95}T^{97}$ in HLA-B*13:02. These sequence differences are likely because HLA-B*13:01 is an important predictor of the risk of DHS, while HLA-B*13:02 is not. Because we were interested in how these three amino acid substitutions influence the 3D structures of HLA molecules, we examined the 3D structures of HLA-B*13:01 and 13:02, as described in the next section.

Table 2
Templates for homology modeling of HLA-B*13:01 and HLA-B*13:02.

HLA-B*13:01			HLA-B*13:02		
PDB ID	Protein name	Identity (%)	PDB ID	Protein name	Identity (%)
3DX7	HLA-B*44:03	96	3W39	HLA-B*52:01	95
1A1O	HLA-B*53:01	95	1E27	HLA-B*51:01	94
1SYV	HLA-B*44:05	95	1A1O	HLA-B*53:01	94
1M6O	HLA-B*44:02	95	3DX7	HLA-B*44:03	94
3W39	HLA-B*52:01	94	2BVP	HLA-B*57:03	93
2BVP	HLA-B*57:03	94	1SYV	HLA-B*44:05	94
1XH3	HLA-B*35:01	94	1XR9	HLA-B*15:01	94
3VRI	HLA-B*57:01	94	1M6O	HLA-B*44:02	94
1XR9	HLA-B*15:01	94	3VRI	HLA-B*57:01	93
4MJI	HLA-B*51:01	93	1XH3	HLA-B*35:01	93

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3.2. Comparison of the 3D structures of HLA-B*13:01 and HLA-B*13:02

Because the X-ray structures of HLA-B*13:01 and HLA-B*13:02 have not yet been reported, we used a homology modeling method to construct 3D structures of these HLA molecules. Initially, a BLAST search of the PDB was performed using the amino acid sequences of the α-domains of HLA-B*13:01 and 13:02 as queries to obtain template candidates for each HLA allele. As the PDB contains a number of coordinates for various HLA alleles, we found more than 10 crystal structures with >90% sequence identity with both HLA-B*13:01 and 13:02. Table 2 shows the 10 'best' highly homologous structures. These structures were used as templates for homology modeling; that is, a total of 10 structures each were generated for HLA-B*13:01 and 13:02. The generation of multiple

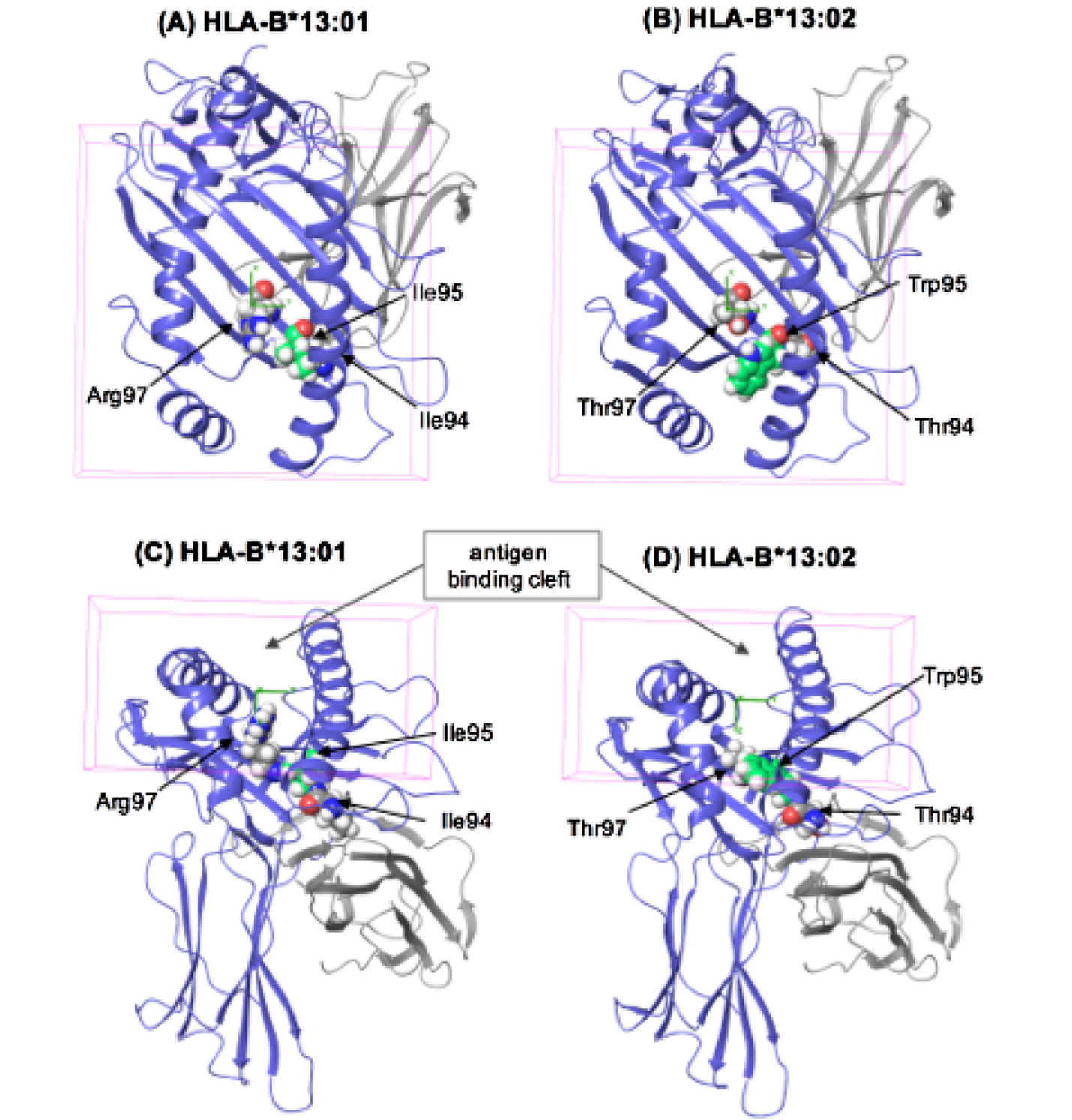

Fig. 2. Representative homology model structures of HLA-B*13:01 (A and C) and HLA-B*13:02 (B and D). The residue differences, $I^{94}I^{95}R^{97}$ (HLA-B*13:01) versus $T^{94}W^{95}T^{97}$ (HLA-B*13:02), are highlighted using sphere models. (B) and (D) are side views of (A) and (C), respectively. The template structures are PDB ID 3W39 for HLA-B*13:01 and 1XR9 for HLA-B*13:02. The grid box and the center used for molecular docking are shown in magenta and green, respectively.

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structures was intended to incorporate some degree of protein flexibility in the molecular docking calculations described in the following section. As all crystal structures in Table 2 were deposited as heterodimers, with one α-domain and one β-domain (β_2 microglobulin), the homology models were also generated as heterodimers. Because we were specifically interested in the structural differences between HLA-B*13:01 and 13:02, we focused our attention on the structures of the α-domain. Fig. 2 shows representative structures of HLA-B*13:01 and 13:02 in ribbon representations. The three amino acid differences between HLA-B*13:01 and HLA-B*13:02 ($I^{94}I^{95}R^{97}$ vs. $T^{94}W^{95}T^{97}$, respectively) are also indicated using sphere models. We found that all three of these amino acids are located in the antigen-binding site, which is a long and narrow cleft located between two α-helices, as shown in Fig. 2 and Supplementary Fig. 1. Thus, we considered that these three amino acid substitutions would cause structural differences in the antigen-binding sites between HLA-B*13:01 and 13:02. By comparing the molecular surface representation of antigen-binding sites (Fig. 3), we found that HLA-B*13:01 had an extra deep sub-pocket around the F-pocket of its antigen-binding site, which was not observed in HLA-B*13:02 (Supplementary Fig. 2). This seemed to be due to the amino acid difference at position 95: Ile95 in HLA-B*13:01 versus Trp95 in HLA-B*13:02. Because this amino acid is located at the bottom of the antigen-binding site, the less bulky Ile95 in HLA-B*13:01 could contribute to the formation of an extra sub-pocket. This unique sub-pocket in HLA-B*13:01 was created by several hydrophobic residues, including Ile95 (Fig. 3), and was observed in all 10 homology models of HLA-B*13:01. These results encouraged us to investigate the interactions of dapsone with HLA-B*13:01 and 13:02.

3.3. Molecular docking calculations

In total, 450 models each for dapsone–HLA-B*13:01 and dapsone–HLA-B*13:02 complexes were generated by molecular docking calculations and ranked according to the Glidescore. After superposition of the top 50 complex models on the α-domains of HLA molecules, their docking poses with dapsone were clustered by atom-positional RMSD to group similar poses. Using this procedure, we obtained three representative complex models for HLA-B*13:01 and 13:02 each. Fig. 4a shows three representative models of the dapsone–HLA-B*13:01 complex (models 1–3). In all three of these models, one of the two aniline groups of dapsone used the extra deep sub-pocket to bind to HLA-B*13:01. The only difference in the three poses was the orientation of the other exposed aniline group. The size of the extra sub-pocket appeared to be a good fit to accommodate the aniline group, suggesting that dapsone binds tightly to HLA-B*13:01 in this unique sub-pocket. Three representative models of the dapsone–HLA-B*13:02 complex (models 4–6) are shown in Fig. 4b. Dapsone appears to adhere to the bottom of the antigen-binding cleft of HLA-B*13:02, making fewer contacts with HLA-B*13:02, indicating that HLA-B*13:02 does not possess the extra pocket suitable for dapsone binding. These results suggested that dapsone binds to HLA-B*13:01 more tightly than to 13:02 (Fig. 4c, d, Supplementary 3). This was examined using binding free energy calculations combined with MD simulation and the MM-PBSA method in the following section. The side chains of the 94th residues (Ile94 of HLA-B*13:01 and Thr94 of HLA-B*13:02) were buried in the interior of the HLA molecules. The 97th residues (Arg97 of HLA-B*13:01 and Thr97 of HLA-B*13:02) neighbored the 116th residues (Leu116 in both HLA-B*13:01 and HLA-B*13:02), but in the direction opposite to that of the extra sub-pocket. Therefore, both residues 94 and 97 seem to not directly contribute to formation of the unique sub-pocket of HLA-B*13:01.

3.4. Binding free energy calculations

Each representative structure of the dapsone–HLA-B*13:01 (models 1–3) and dapsone–HLA-B*13:02 (models 4–6) complexes was subjected to MD simulations with explicit water molecules for further refinement and generation of an ensemble of solution structures. The MD simulation, for 20 ns, was performed for each representative structure, and the RMSD values relative to the initial structure were monitored along the entire MD trajectory. Supplementary Fig. 4 shows the RMSD values for the simulation of the dapsone–HLA-B*13:01 and dapsone–HLA-B*13:02 complexes. The RMSD values of all simulations almost reached a stable state after ~15 ns, nearly converging. In total, 500 snapshots with an interval of 10 ps from the last 5-ns trajectory were considered

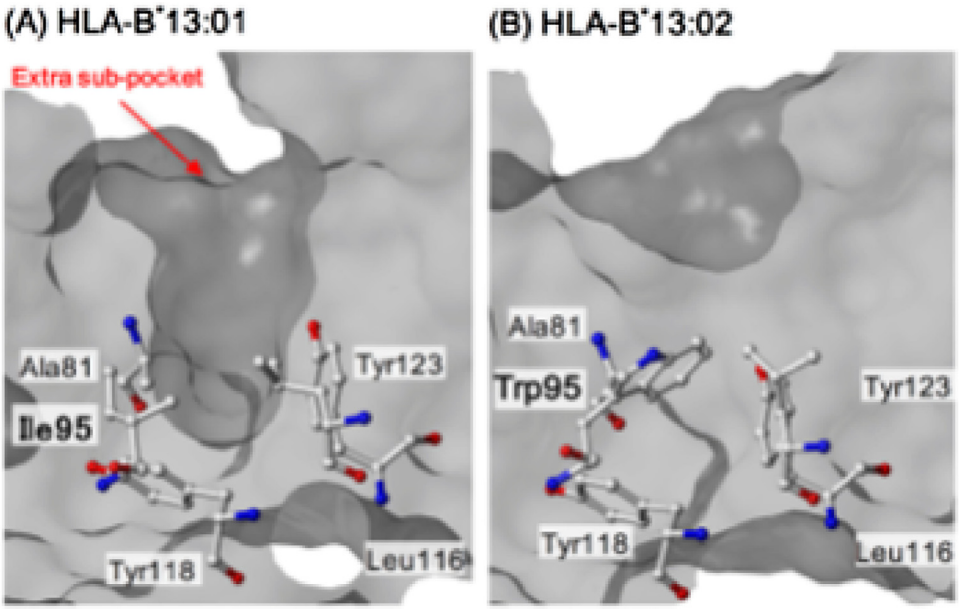

Fig. 3. Sectional views of the molecular surfaces around the F-pockets of representative homology model structures of HLA-B*13:01 (A) and HLA-B*13:02 (B).

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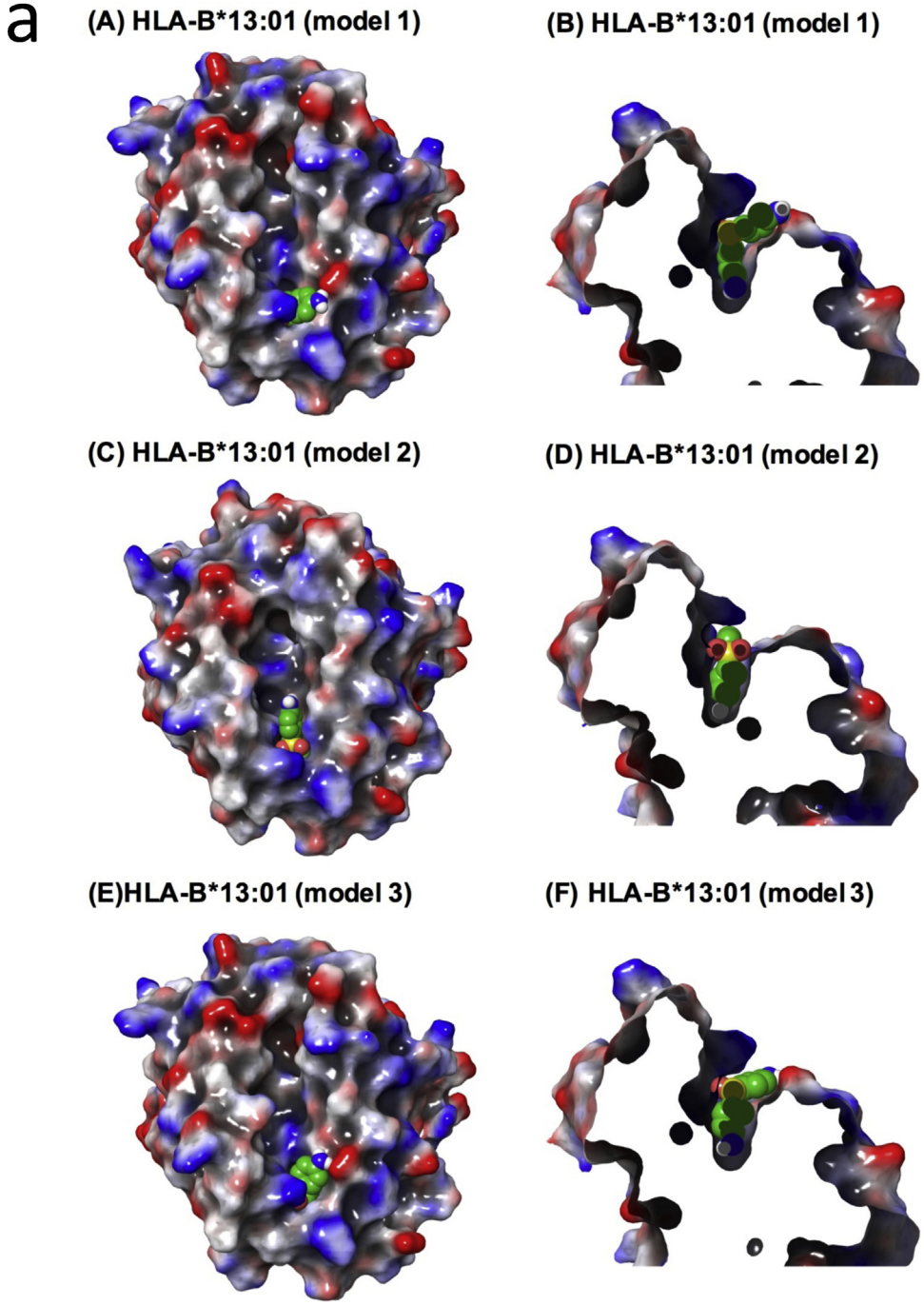

Fig. 4. (a) Representative binding models of the dapsone–HLA-B*13:01 complex obtained after docking and clustering calculations. (top) model 1, (middle) model 2, and (bottom) model 3. Right figures are a sectional view of left figures. Templates for HLA-B*13:01 structures were PDB ID 3W39 for models 1 and 3 and 1SYV for model 2. The molecular surfaces of the HLA molecules were colored by reference to the electrostatic potential. (b) Representative binding models of the dapsone–HLA-B*13:02 complex obtained after docking and clustering calculations. (top) model 4, (middle) model 5, and (bottom) model 6. Right figures are sectional view of left figures. Templates for HLA-B*13:02 structures were PDB ID: 1XR9 for model 4 and 5, and 3VRI for model 6. The molecular surfaces of the HLA molecules were colored by reference to the electrostatic potential. (c, d) Representative binding models before MD simulations for (c) dapsone–HLA-B*13:01 and (d) dapsone–HLA-B*13:02, based on observations of the stick representation of their HLA 3D homology models. Dapsone (green) inserts are deeper in HLA-B*13:01 than in HLA-B*13:02. The hydrogen bonds are shown by dashed lines.

for an ensemble of solution structures and used for the subsequent MM-PBSA calculation.

Table 3 shows the resulting ΔG_{bind} values for the dapsone–HLA-B*13:01 (models 1–3) and dapsone–HLA-B*13:02 (models 4–6) complexes by MM-PBSA methods. We found that all calculated ΔG_{bind} values were much greater for dapsone binding to HLA-B*13:01 (models 1–3) than to HLA-B*13:02 (models 4–6), regardless of the values of the dielectric constants for inside of protein. Additionally, the average ΔG_{bind} values of the HLA-B*13:01 complexes (−5.24 and −8.59 kcal/mol for $\varepsilon = 2$ and $\varepsilon = 4$, respectively) were much greater than those of the HLA-B*13:02 complexes (−1.67 and −4.93 kcal/mol for $\varepsilon = 2$ and $\varepsilon = 4$, respectively) by more than 3.5 kcal/mol. These results suggested that the binding affinity of dapsone to HLA-B*13:01 was much greater than that to HLA-B*13:02. Next, to investigate the interaction between HLA-B*13:01 and dapsone in more detail, hydrogen bonding

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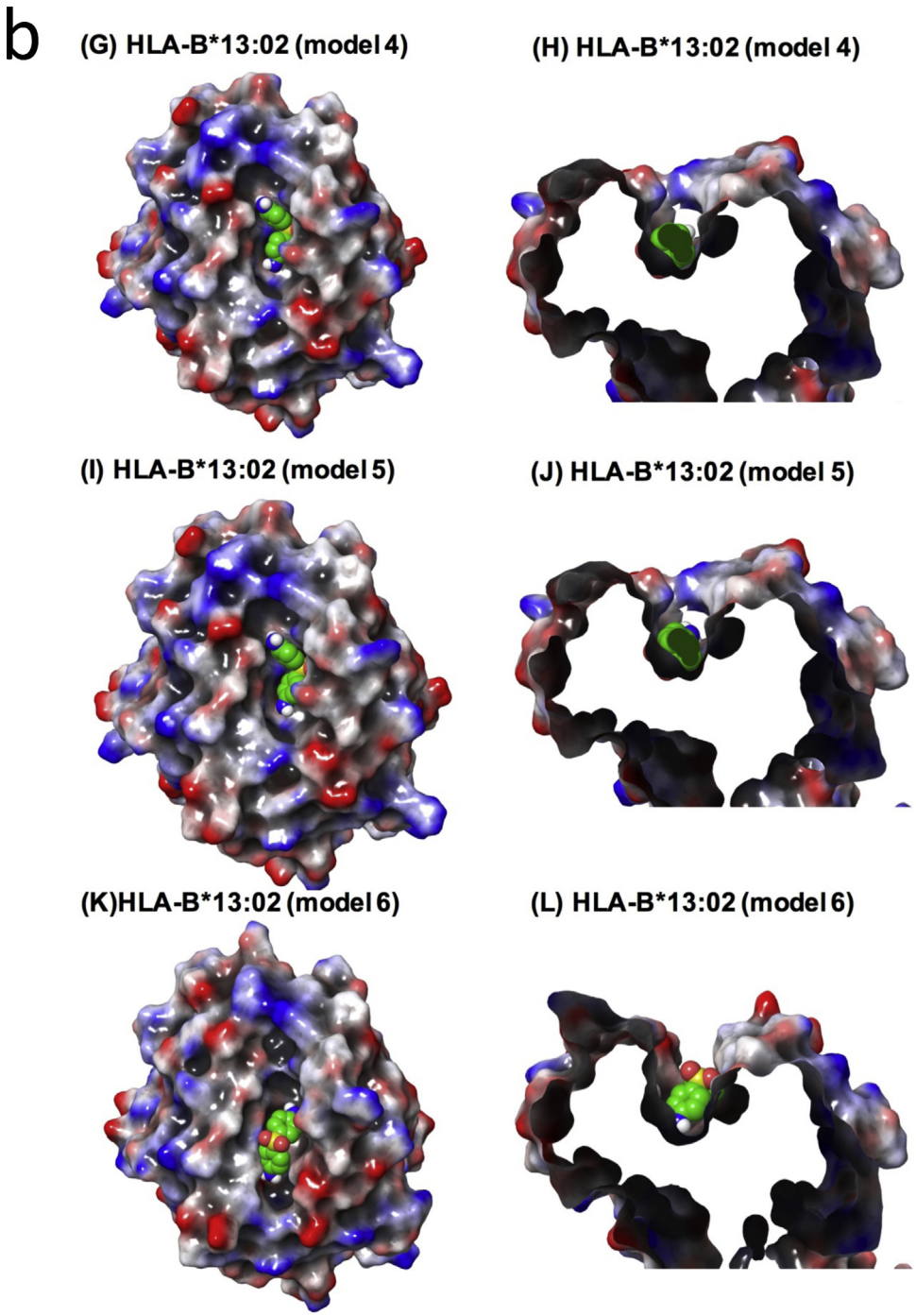

Fig. 4. (Continued)

interactions were investigated for all solution structures of the dapsone–HLA-B*13:01 complex (model 3), which provided the most stable ΔG_{bind} value. In these solution structures, Tyr85 of HLA-B*13:01 was involved in a hydrogen-bonding interaction with an amino group of dapsone, at the very high frequency of 70% (Fig. 5), suggesting that Tyr85 plays an important role in dapsone recognition by HLA-B*13:01 and that hydrogen-bonding is used to anchor dapsone in the unique sub-pocket. Hydrophobic interactions were suggested to exist between one of the aniline groups of dapsone, retained in the extra sub-pocket of HLA-B*13:01, and Ala81, Tyr84, Ile95, Leu116, Ala117, Tyr118, and Tyr123, which constitute the extra sub-pocket of HLA-B*13:01 (Fig. 5). These interactions could contribute to the greater ΔG_{bind} value of dapsone's interaction with HLA-B*13:01.

4. Discussion

Although only three residues were different between the HLA-B*13:01 and HLA-B*13:02 alleles, only HLA-B*13:01 has been linked to DHS. These residues were $I^{94}I^{95}R^{97}$ (HLA-B*13:01) versus $T^{94}W^{95}T^{97}$ (HLA-B*13:02), as reported previously [30]. Our homology modeling study indicated that all three of these amino

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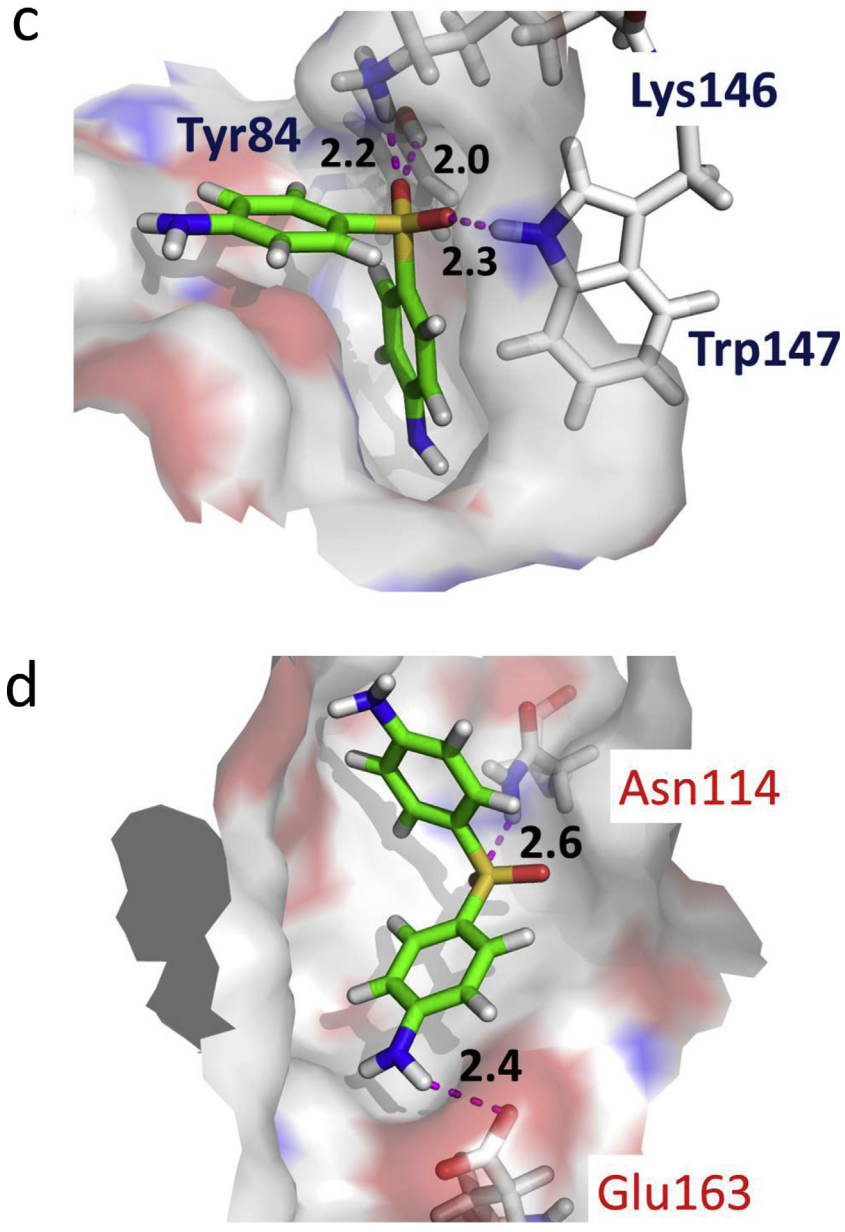

Fig. 4. (Continued)

Table 3
Binding free energies of dapson with HLA-B*13:01 and HLA-B*13:02 calculated using MM-PBSA methods.[a]

Relative dielectric constant for inside of protein: ε = 2						
	dapson-HLA-B*13:01 complex			dapson-HLA-B*13:02 complex		
	model 1	model 2	model 3	model 4	model 5	model 6
ΔG_{bind} (kcal/mol)	−4.52 (2.65)	−4.84 (2.52)	−6.36 (3.05)	−1.28 (2.79)	−1.45 (2.10)	−2.28 (3.39)
$\Delta\Delta G_{bind}$ (kcal/mol)	1.84	1.52	0.00	5.08	4.91	4.08
Relative dielectric constant for inside of protein: ε = 4						
	dapson-HLA-B*13:01 complex			dapson-HLA-B*13:02 complex		
	model 1	model 2	model 3	model 4	model 5	model 6
ΔG_{bind} (kcal/mol)	−7.82 (2.41)	−7.86 (2.32)	−10.08 (3.00)	−6.09 (2.63)	−3.19 (2.25)	−5.52 (3.16)
$\Delta\Delta G_{bind}$ (kcal/mol)	2.26	2.22	0.00	3.99	6.89	4.56

[a] Mean values of 500 frames extracted from 15 to 20 ns. Values in parenthesis were standards deviations.

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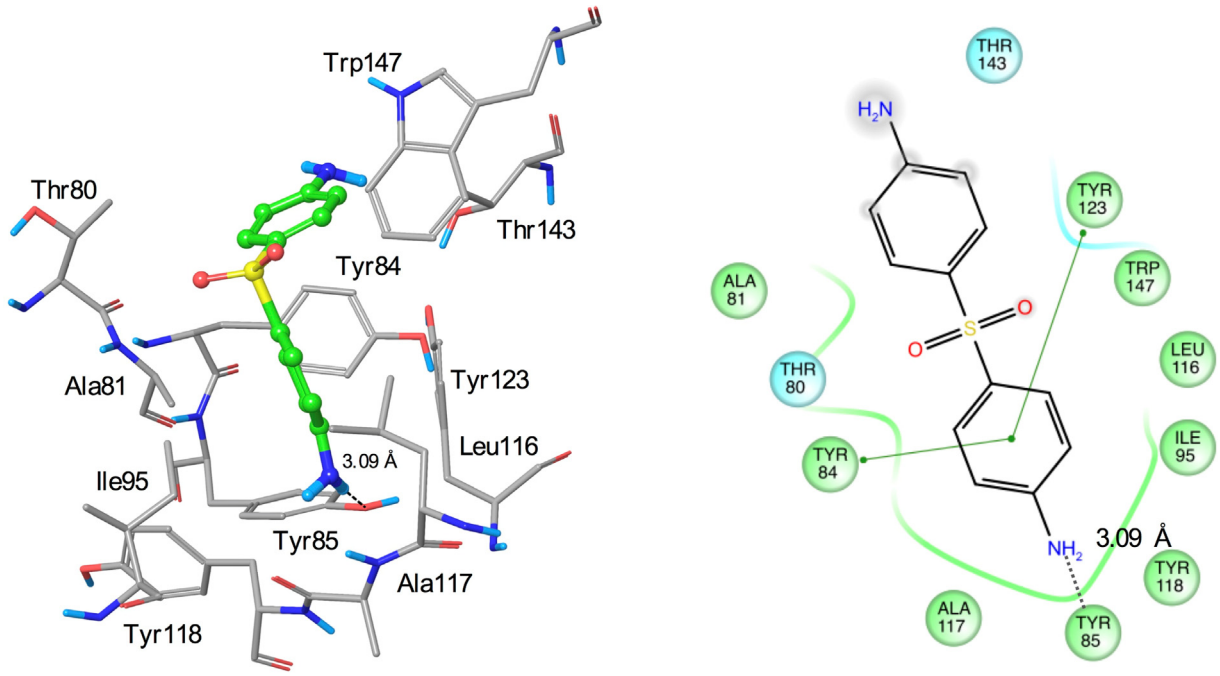

Fig. 5. Residues surrounding the dapsone molecule within 4 Å in the final MD structure of model 3 of the dapsone–HLA-B*13:01 complex (left) and the interaction diagram (right). Polar hydrogens are shown in light blue, and non-polar hydrogens are not shown. Hydrogen bonds are indicated with dashed lines. The average hydrogen bond distance between the oxygen atom of the hydroxyl group of Tyr85 and the nitrogen atom of the amino group of dapsone was 3.09 Å. In the interaction diagram, the hydrophobic contributors are shown as green probes, and π-π interactions are shown as green lines.

acids are located within the antigen-binding site. Li et al. also suggested that residue 95 is a component of the peptide-binding site, called the "pocket F", and it forms a flat structure with Trp^{95} (tryptophan) but not with Ile^{95} (isoleucine) at the bottom of pocket F, based on observations of the stick representation of their HLA 3D homology models [30]. This was consistent with our homology modeling results. Additionally, we used a molecular surface representation to show that HLA-B*13:01 possesses an extra deep sub-pocket around pocket F of the antigen-binding site, which was not observed in HLA-B*13:02. The less bulky Ile^{95} in HLA-B*13:01 could contribute to the formation of the extra sub-pocket.

To date, it has been uncertain how dapsone interacts with HLA-B*13:01. Thus, we performed molecular docking calculations and found that this unique pocket of HLA-B*13:01 could accommodate dapsone very well. In contrast, HLA-B*13:02 seemed to lack a pocket suitable for dapsone binding. The abacavir–HLA-B*57:01 specificity for AHS was also reported to be sensitive to the F-pocket architecture [18,19]. The F-pocket of HLA molecules is an established pocket for binding of the C-terminal amino acid of the antigen peptide, referred to as the anchor residue. Thus, the results above suggest that structural changes in the F-pocket, especially by mutation to less bulky residues, may lead to the formation of a pocket suitable for the binding of a causative drug, with a relatively high probability.

Finally, we performed 20-ns MD simulations and binding free energy calculations to compare the stabilities and binding affinities of these dapsone-HLA complex structures. The ΔG_{bind} value for the dapsone–HLA-B*13:01 complex was much greater than that for the dapsone–HLA-B*13:02 complex by >3.5 kcal/mol. The ΔG_{bind} value is related to the dissociation constant, K_d, according to the following equation:

$$\Delta G_{bind} = RT \ ln \ K_d \quad (1)$$

Here, R is the gas constant and T the absolute temperature. The dissociation constant, K_d, is defined as follows:

$$K_d = \frac{[HLA][drug]}{[HLA-drug]} \quad (2)$$

Here, [HLA] and [drug] are the concentrations of HLA and the drug in their free forms, respectively. [HLA-drug] is the concentration of the HLA-drug complex. According to Eqs. (1) and (2), the value of K_d for the dapsone–HLA-B*13:01 complex was almost 300-fold lower than that for dapsone–HLA-B*13:02 when T = 300 K, indicating that the binding of dapsone to HLA-B*13:01 was approximately 300-fold stronger. From a computational molecular docking investigation, HLA-B*13:01 has a sub-pocket that dapsone binds to, resulting in a change in the structure of the antigen-recognition site of HLA-B*13:01, which may be associated with the incidence of DHS. This specific interaction between HLA-B*13:01 and dapsone may cause structural changes in the antigen recognition site, allowing the protein to recognize peptides that are conformationally altered. This may lead to changes in the self-peptides that can bind to HLA-B*13:01 as like the same mechanism as "altered peptide theory" involved in the binding of abacavir to HLA-B*57:01 [18,19].

The immunogenic complexes involved in T cell-mediated ADRs contain three components: an HLA protein, a peptide, and a drug [19]. To date, three principal models for this interaction have been developed, based on differences in the roles played by cellular metabolism and antigen-processing [18,19,27–29]. These are the hapten/pro-hapten, pharmacological interaction with immune receptors (p.i.), and altered peptide repertoire models. Our model of interaction clearly differs from both the p.i. model and the hapten/pro-hapten model [18,19]. A docking model, whereby dapsone binds to HLA-B*13:01, is suggested to be appropriate by virtue of the fact that a specific interaction triggers structural changes in the antigen-recognition site. Thus, an "altered peptide repertoire" model involving the binding of

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dapsone to HLA-B*13:01 may be appropriate, by analogy to the abacavir allergy model [18,19]. Our results may explain why patients with HLA-B*13:01, but not HLA-B*13:02, are susceptible to DHS.

Funding/Support

None.

Conflicts of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdermsci.2017.08.007.

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LETTER TO THE EDITOR

Case of phenylephrine hydrochloride-induced periorbital contact dermatitis with fulminant keratoconjunctivitis causing pseudomembrane formation

Dear Editor,

Phenylephrine, a selective α1-adrenergic receptor agonist, which is used as an ophthalmic solution for mydriasis inspection and treatment of uveitis, is a well-known contact allergen,[1] however, inflammation is usually limited to the skin. Herein, we report a previously unreported unusual case of phenylephrine hydrochloride (PH)-induced periorbital contact dermatitis with severe conjunctival involvement including ocular pseudomembrane formation. This study alerts readers that acute pseudomembrane formation is not limited to Stevens–Johnson syndrome[2] and ocular mucous membrane pemphigoid.

A 51-year-old Japanese woman with severe blepharitis was referred to our institute. She had been treated for uveitis with various ophthalmic solutions. Twelve days after the treatment with 0.5% PH solution (Mydrin-P®; Santen Pharmaceutical, Osaka, Japan) was initiated, an intense burning sensation in and around the eyes appeared and lasted for more than 18 days. Her medical history was not remarkable, except for vitiligo vulgaris.

On physical examination, well-demarcated erythemas on the periorbital areas and severe swelling with erosions on both eyelids were noted (Fig. 1a). Ophthalmological examination revealed extensive conjunctival injection, pseudomembrane formation and symblepharon (Fig. 1b). Immunochromatography testing for adenovirus conjunctivitis was negative. Laboratory examinations were grossly within normal limits.

Histopathological investigation of the eyelid skin detected spongiosis and perivascular lymphocytic infiltration in the upper dermis, but not epidermal necrosis (Fig. 1c). Direct immunofluorescence was negative.

Immunoblotting analyses using various autoimmune blistering disease antigens, including laminin-332, and enzyme-linked immunoassays for desmogleins 1 and 3, BP180 and 230 were all negative.

Based on these findings, dermatological diagnosis of contact dermatitis was suggested and PH was terminated. However, because ophthalmological findings could not exclude Stevens–Johnson syndrome, i.v. corticosteroid pulse therapy was conducted. The skin lesions and ocular involvements improved, although minimal symblepharon and shortening of the conjunctival fornix were seen in both eyes.

Patch tests of previously used eye drops were all negative except 0.5% PH solution (Mydrin-P®) (data not shown). A

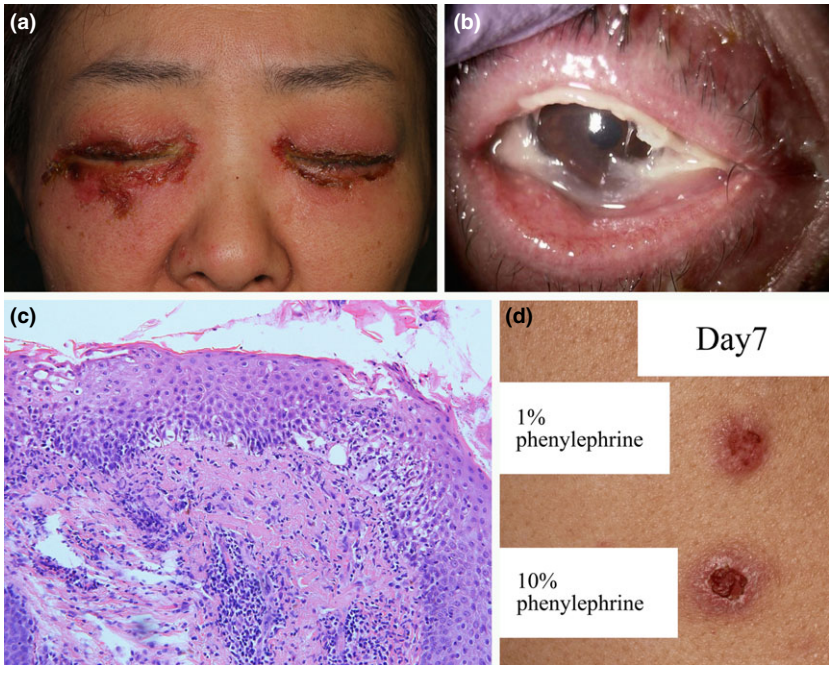

Figure 1. (a) Symmetrical erythemas and erosions on the eyelids and the periorbital areas. (b) Pseudomembrane formation, conjunctival injection and symblepharon on the conjunctivae. (c) Histopathological investigation of the eyelid skin detected spongiosis, exocytosis of lymphocytes and perivascular lymphocytic infiltration in the upper dermis, however, epidermal necrosis was not observed (hematoxylin–eosin, original magnification ×200). (d) Positive patch test (3+) reaction to 1% and 10% phenylephrine hydrochloride on the back at day 7.

Correspondence: Manabu Ohyama, M.D., Ph.D., Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Email: manabuohy@ks.kyorin-u.ac.jp

confirmatory patch test using 1% and 10% PH[3] following the International Contact Dermatitis Research Group criteria yielded a strongly positive reaction, which persisted from day 2 to 7 (Fig. 1d). Additional patch tests of the components of the causative eye drop other than PH were all negative. Finally, the diagnosis of PH-induced contact dermatitis was made.

Villarreal reported that the reagent elicited some allergic reactions in 93.5% of acute conjunctivitis patients.[4] The resultant dermatitis could be very severe, however, ophthalmological symptoms have been reported to be mild, represented by pruritus, lacrimation.[4] Thus, the diagnosis of similar cases with ocular involvement alone would be challenging.

The ocular pseudomembrane formation is a characteristic sign for Stevens–Johnson syndrome, mucous membrane pemphigoid, viral or bacterial infection and chemical burns. However, the ocular pseudomembrane formation can be observed in severe ocular damage producing necrotic cells and fibrin-rich exudates covering the conjunctival surfaces.[5] We speculate that long-term repetitive use of the causative agent potentially contributed to the severe symptom. This report alerts that contact dermatitis can also cause an acute pseudomembrane formation and ophthalmological examination is indispensable in cases with severe blepharitis or contact dermatitis.

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Miyuki KATO,[1] Kiriko NITTA,[1] Yoko KANO,[1] Masakazu YAMADA,[2] Norito ISHII,[3] Takashi HASHIMOTO,[3] Manabu OHYAMA[1]

Departments of [1]Dermatology, and [2]Ophthalmology, Kyorin University School of Medicine, Tokyo, and [3]Department of Dermatology, Kurume University School of Medicine and Kurume University Institute of Cutaneous Cell Biology, Fukuoka, Japan

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杏林大学医学部皮膚科学准教授
水川良子
MIZUKAWA Yoshiko

Q&A FOR SKILL UP

薬疹におけるステロイドの始め方と減らし方を教えてください

A ステロイド投与を必要とする薬疹は，基本的には重症薬疹であり，薬剤性過敏症症候群（DIHS），スティーヴンス・ジョンソン症候群（SJS），中毒性表皮壊死症（TEN）が対象になる．SJS/TENでは例外的な症例を除き，ステロイド投与は迷わずすみやかに十分量から始める．しかし，発症早期に重症薬疹かどうかの判断に迷い，ステロイド開始の決断が難しい症例も存在する．重症薬疹および判断に迷う薬疹を想定し，薬疹におけるステロイド使用の始め方と減らし方を概説する．

1. 重症薬疹（SJS/TEN，DIHS）におけるステロイドの始め方と減量の基本

SJS/TENの診断治療に関しては，2016年に改定された『重症多形滲出性紅斑 スティーヴンス・ジョンソン症候群・中毒性表皮壊死症診療ガイドライン』に詳細が記載されている[1]．SJS/TENでは，発症早期（発症後7日前後まで）でのステロイド開始が，治療効果および副作用抑制の観点から望ましいとされている．開始量はプレドニゾロン換算で0.5～1mg/kg/日で，重症例では1～2mg/kg/日での開始が推奨されており，検査データの推移や臨床症状を参考に3～7日ごとにプレドニゾロン換算で10mg/日程度減量していく．

DIHSでのステロイド治療は，経過中にみられるさまざまなウイルスの再活性化による皮膚症状の再燃および諸臓器症状の出現や，膠原病などの続発症の問題があり難しい．開始する場合には，プレドニゾロン換算で30～70mg/日（0.5～1mg/kg/日）を用い，初期量は原則として7～14日間投与することが推奨されている[2]．中途半端な少量からのステロイド投与開始は，その後の経過を複雑にすることが多く，推奨されていない．

2. ステロイド投与開始を迷うとき

われわれがステロイド投与開始を迷うのは，①重症薬疹との確定診断に至らない，②38度以上の発熱のある多形紅斑（EM）重症型（眼合併症なし），③感染症の合併が疑われるとき，④高齢者，⑤基礎疾患が存在し，その基礎疾患がステロイド使用により悪化する可能性がある，などの諸条件が存在する症例ではないだろうか．感染症の否定や全身状態・基礎疾患の把握は，必ず他科とも連携し，すみやかに行う．発熱があっても重篤感がなく，食事摂取がある程度保たれている，年齢が若く体力に余力があるなどの条件があれば，入院管理下で補液を行いながら数日間経過をみられる場合が多い．数日間の猶予があれば，プロカルシトニンやβ-D-グルカン値の確認，糖尿病や肝・腎・心臓などの諸臓器の評価もある程度はできる．同時に，熱型や皮疹の進行具合を評価し，少しでも重症薬疹であると確定できる所見が得られた時点で，ステロイドを開始する．

3. ステロイド減量時に注意すること —non-HIV IRISという概念について

ステロイド投与は，薬剤によって引き起こされた過剰な免疫応答を抑制する．近年，HIV患者で提唱されてきた免疫再構築症候群（IRIS）が，非HIV感染患者においても認められることが注目されている（non-HIV IRIS）．具体的には，臓器移植，膠原病や悪性腫瘍の治療に用いられるステロイドを含む各種免疫抑制薬，免疫チェックポイント阻害薬などの漸減・中止による免疫機能の回復が，病原体に対する強い免疫反応を引き起こし，さまざまな臓器障害を発症する．薬疹に対するステロイド減量時にも，同様の機序によるnon-HIV IRISと考えられるサイトメガロウイルス（CMV）感染やニューモシスチス肺炎が発症し得ることを念頭に置きステロイド減量を行う．減量中の血小板やグロブリンの減少に留意し，明らかな症状が認められなくとも血中CMV抗原の確認などを行うことで，不用意な減量による日和見感染症の顕在化を防ぎ得る可能性がある．

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固定薬疹の発症機序－なぜ同じ部位に再発するのか－

Mechanisms of fixed drug eruption

杏林大学医学部 皮膚科
Department of Dermatology
Kyorin University School of Medicine

みずかわ よしこ
水川 良子
Yoshiko Mizukawa

水川 良子
1985年 杏林大学医学部附属病院皮膚科入局
2000年 同講座助手
2004年 同学内講師
2010年 同講師
2013年 同准教授
現在に至る。

Key words：固定薬疹，resident memory T 細胞，外傷部位

Abstract

固定薬疹は，同じ部位に皮疹を繰り返す限局性の薬疹である。全身性に皮疹を生じる通常の薬疹と異なり，薬剤に反応するT細胞が末梢血中ではなく皮膚局所に存在し，薬剤抗原の刺激がなくても皮膚局所に長期間常在し続ける。熱傷や外傷が先行病変になることが知られており，外敵から局所を防御する目的で局所に遊走してきた細胞が，薬剤に反応するようになったと考えられている。

1．固定薬疹は同一部位に皮疹を繰り返す限局性の薬疹である

固定薬疹はその名のごとく，被疑薬摂取後，同じ部位に皮疹を繰り返し生じる限局性の薬疹である（図1）。個々の皮疹は米粒大から鶏卵大，小児頭大まで大小様々で，基本的には孤立性だが，ときに融合して躯幹の大部分を占めるほどの局面を形成する場合もある。治癒後，境界比較的明瞭な色素斑として認められ，被疑薬摂取によりこの色素斑に一致および辺縁に拡大しながら紅斑を生じる。全身どこにでも生じるが，最近では口唇や口腔内，陰部などの粘膜に紅斑，水疱，びらんを生じ，Stevens-Johnson 症候群を思わせる症例の報告も多い。固定薬疹が同一部位に皮疹を繰り返すのは，病変部局所にCD8陽性のT細胞が常在し，被疑薬投与によりこの常在T細胞が速やかに活性するためであることを我々は明らかにしてきた（図2）[1]。この固定薬疹病変部に常在するCD8陽性T細胞は，活性化マーカーであるCD69を恒常的に発現する臨戦態勢に近い状態の細胞で，日光や物理的刺激でも容易に活性化しうる。近年，resident memory T細胞（Trm）の概念が提唱され，病変部に常在する細胞の存在がにわかに注目されるようになった[2]。Trmは血液中に存在するCD8陽性T細胞と異なり，皮膚や粘膜などの外界に接する局所に常在し，局所を保護する自然免疫としての役割を果たす細胞と考えられている。固定薬疹病変部にCD8陽性T細胞が常在し皮疹を生じることは，Trmという概念が提唱される前から知られており，固定薬疹はTrmが関与する皮膚疾患の代表とも言える。

2．熱傷などの外傷が先行病変になる

固定薬疹には多くの疑問が存在する。それは，なぜ同じ部位に繰り返すのかであり，次になぜその部位に薬剤に反応する細胞が常在するようになったのかであり，さらに，どのような機

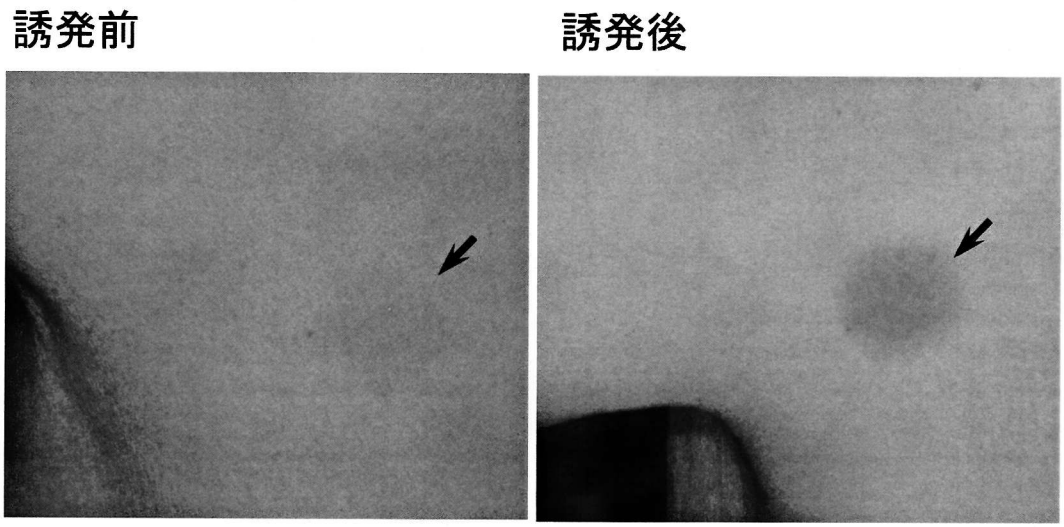

図1　誘発前後の固定薬疹病変部（上腕）
誘発前には淡い褐色斑を認めるのみであるが，被疑薬服用により褐色斑部に一致して紅斑が生じている。

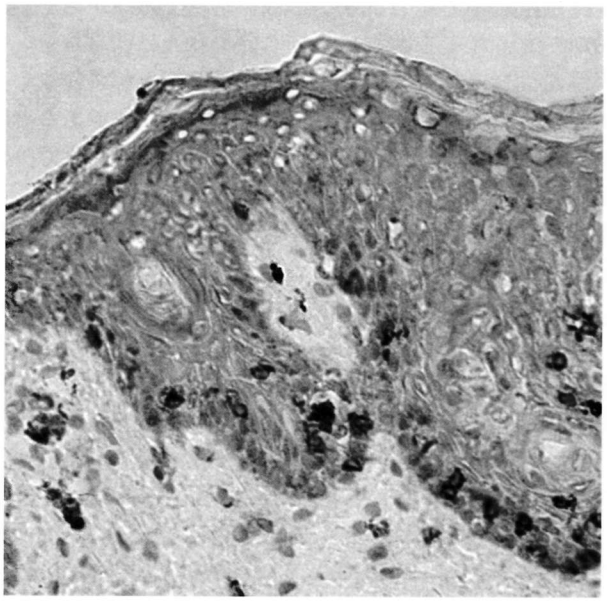

図2　誘発前の固定薬疹病変部（CD8染色）
病変部には基底層部にCD8陽性T細胞が存在している。

序で常在し続けるのかである。我々は，虫刺されや注射部位，熱傷部位が固定薬疹病変部に先行することを経験している[3]。また，単純疱疹後に固定薬疹が生じたと推察される報告もある。これらのことを考え合わせると，固定薬疹病変部に常在する細胞は，局所を外敵（病原体）か

ら保護するために集積した自然免疫担当細胞に近い性質を有する細胞で，局所が治癒した後もそのままその部位に定着した細胞と考えることができる。本来は皮膚を保護するための細胞が，薬剤に反応するようになったのが固定薬疹病変部の細胞ではないだろうか。

3．年単位で病変部にT細胞が常在し続ける

固定薬疹病変部に常在する細胞はどの位の期間存続するのであろうか。固定薬疹の原因薬は，以前からNSAIDsや市販の感冒薬が多いことが報告されている。最近では，カルボシステインの報告や透析患者による造影剤による報告が多くなってきている。原因薬はいずれも屯用薬であり，原因薬が服用されない全く刺激の入らない期間が長期間存在することになる。それにも関わらず，固定薬疹病変部にはCD8陽性T細胞が枯渇することなく常在し，誘発から4年後においてもその数は若干減少しているものの残存していることを我々は確認している[4]。では，なぜ固定薬疹病変部にTrmが存続し続けることが出来るのかは，あまり明らかにされていない。我々は，固定薬疹病変部表皮基底層にはIL-15が発現していることを明らかにし，このIL-15がCD8陽性T細胞常在に関与していると考えている[4]。しかし，単純に基底層におけるサイトカインの発現のみで年単位で何ら刺激のない状態でT細胞が常在し続けることが出来るのか，他の皮膚構成細胞の関与はないのか，なぜIL-15が発現しその発現はどの様な機序で維持されているのかなど疑問は多い。

4．局所に常在するのには理由がある

固定薬疹病変部のT細胞は，薬剤抗原による刺激時にのみ活性化しているのだろうかという疑問がある。このT細胞は前述したように活性化マーカーであるCD69を常時発現している細胞であることから，薬剤以外の刺激によっても活性化している可能性は否定できない。実際に，日光暴露や物理的刺激により病変部局所が原因薬剤の投与なしに発赤する（誘発）ことが報告されており，このような薬剤抗原とは無関係の刺激が常に入り続けることが局所に常在および存続するのに必要なのかもしれない。本来，Trmはヘルペスウィルスなどの表皮細胞に感染するウィルスを抑制するためにその局所に遊走してきた可能性があり，subclinicalなヘルペスウィルスの再活性化が起こるような部位に固定薬疹が生じている可能性も考えられる。実際，臨床的に口唇ヘルペスや陰部ヘルペスと誤診されている固定薬疹は多い。単純な誤診ではなく，当初はヘルペス病変だったものが，その経過中に投与された薬剤に対し反応するようになった結果を，固定薬疹としてみている可能性もあるのではないだろうか。

Köbner現象やrecall現象など，Trmの存在を示唆する皮膚所見は，様々な皮膚疾患で日常的に経験される。固定薬疹の病態を考えることは，薬疹のみでなく広く皮疹発症の機序を考える上での一助になると考えられる。

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