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Invited Review Article

SJS/TEN 2019: From science to translation

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Abbreviations: ADR, Adverse drug reaction; AIDS, Acquired immunodeficiency syndrome; ALDEN, Algorithm of drug causality for epidermal necrolysis; ALK, Anaplastic lymphoma kinase; AUS-SCAR, Australian registry of severe cutaneous adverse reactions; CBZ, Carbamazepine; CFH, Complement factor H; CLET, Cultivated limbal epithelial sell transplantation; COMET, Cultivated oral mucosal epithelial transplantation; CPNDS, Canadian Pharmacogenomics Network for Drug Safety; DILI, Drug-induced liver injury; DRESS, Drug reaction with eosinophilia and systemic symptoms; EHR, Electronic health records; EMA, European Medicines Agency; EpiPGx, Epilepsy Pharmacogenomics; eRMR, Electronic Reaction Monitoring Report; FDA, Food and Drug Administration; GWAS, Genome-wide association study; HIV, Human immunodeficiency virus; HLA, Human leukocyte antigen; IVIg, Intravenous immune globulin; iSCAR, International Congress on Cutaneous Adverse Drug Reaction; ITCH, International Consortium on Drug Hypersensitivity; LSCD, Limbal stem cell deficiency; MPE, Maculopapular eruption; NATIENS, North American Therapeutics in Epidermal Necrolysis Syndrome Network; PGx, Pharmacogenomics; PMDA, Pharmaceuticals and Medical Devices Agency (in Japan); PRAC, Pharmacovigilance Risk Assessment Committee; QOL, Quality of life; RegiSCAR, Multinational registry of Severe Cutaneous Adverse Reactions to drugs and collection of biological samples; SCAR, Severe cutaneous adverse reaction; SDH, Society of Dermatology Hospitalists; SEAPharm, Southeast Asian Pharmacogenomic Network; SOMET, Simple oral mucosal epithelial transplantation; SJS, Stevens-Johnson syndrome; TB, Tuberculosis; TCR, T cell receptor; TEN, Toxic epidermal necrolysis; TFDA, Taiwan Food and Drug Administration; T-SCAR, Taiwan Severe Cutaneous Adverse Reaction Consortium.

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ABSTRACT

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are potentially life-threatening, immune-mediated adverse reactions characterized by widespread erythema, epidermal necrosis, and detachment of skin and mucosa. Efforts to grow and develop functional international collaborations and a multidisciplinary interactive network focusing on SJS/TEN as an uncommon but high burden disease will be necessary to improve efforts in prevention, early diagnosis and improved acute and long-term management. ***SJS/TEN 2019: From Science to Translation*** was a 1.5-day scientific program held April 26–27, 2019, in Vancouver, Canada. The meeting successfully engaged clinicians, researchers, and patients and conducted many productive discussions on research and patient care needs.

1. Introduction

Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe, life-threatening, and mainly drug-induced cutaneous adverse reactions, causing blistering, mucosal sloughing and epidermal necrosis. The global clinical and financial burden of SJS/TEN is considerable, resulting in prolonged hospital stays, mortality of up to 50 % in the elderly and considerable long-term multi-system physical and mental health morbidity that is still poorly understood qualitatively and quantitatively [1]. The last 15 years have seen significant advancements in our understanding of the immunopathogenesis and genetic risk factors for SJS/TEN that have fueled preventive efforts leading to successful pre-prescription screening programs in some countries [2–5]. Research progress requires a collective effort to advance and translate science into prediction, prevention, earlier diagnosis and more targeted and effective treatments that will lead to improved short- and long-term patient outcomes.

The SJS/TEN 2019 meeting built upon the outcomes and success of a 2015 workshop [6] and the inaugural SJS/TEN 2017 meeting [1] by further expanding the multidisciplinary engagement and communication between Networks and participants. Cutting-edge research and treatment presentations, interactive discussions, and breakout sessions were featured to present the recent advances and provide a global context of SJS/TEN. This article is a summary of the proceedings of the conference that brought together healthcare providers, researchers, regulators, government agencies and funders, as well as patients and families in a 1.5-day networking meeting to define strategies for multidisciplinary collaboration to address critical research gaps and improve SJS/TEN outcomes.

1.1. Pharmacogenomic network and panel discussion

An opening plenary from Neil Shear provided a thoughtful perspective on the past, present, and future of the SJS/TEN research. Dr. Shear emphasized the “just do” aspect of implementation science necessary to move research and translation forward and the critical nature of teamwork in building global research networks. A pharmacogenomics panel was made up of diverse stakeholders from six different countries. The panel covered a wide range of topics but highlighted that regulations aimed at facilitating the routine clinical use of pharmacogenomics should follow evidence-based science and that diverse groups should be involved in these decisions. It was also mentioned that health economic and social science studies are increasingly important, as well as improving pharmacogenomic decision support systems and turnaround times. Finally, these systems should be dynamic, to allow for the inclusion of new biomarkers as they are discovered and replicated, and that the community should explore the repurposing of disease-related genomic data for pharmacogenomic applications.

Unmet need: To build a global research network and develop consensus on the implementation of pharmacogenomic testing in order to improve the prevention and treatment of SJS/TEN.

1.2. Regional networks and registries

Nine representatives from regional or international networks and registries focused on studies associated with severe immune-mediated adverse reactions and shared recent progress in the field of SJS/TEN (Fig. 1). These leading groups have committed time and energy to establishing strong networks to facilitate prospective studies of genetic and mechanistic basis and provide an evidence base for treatment approaches. This has included the implementation of post-marketing safety surveillance systems and patient health information paired with the development of biological banks to store DNA, RNA, PBMCs and tissue samples. The risk of SJS/TEN has significant racial/ethnic disparities across drugs used and risk. Currently, Asians have been reported as a significantly affected population where much progress has been made on the discovery of etiologic genetic markers; however, the burden of TB-HIV co-infection in the African continent is high and the incidence of SJS/TEN and associated genetic risk factors have not been adequately studied.

Unmet need: Coordination of research networks to coordinate mechanistic, genetic and treatment studies across ethnically diverse populations.

1.3. Clinical approaches and management

The clinical approach to the management of SJS/TEN is multidisciplinary, including dermatologists, burn surgeons, ophthalmologists, gynecologists, pharmacologists, immunologists, psychiatrists, pharmacists, and other healthcare providers, involved in rehabilitation as indicated by the clinical case.

Diagnosis of SJS/TEN is critical to optimal management and subsequent outcomes analysis. Recent work has highlighted that up to 1/3 cases may be misdiagnosed, which emphasizes the importance of gaining histological confirmation from a skin biopsy at the outset of the rash [7]. The management of SJS/TEN should be undertaken in specialized centers with capabilities for complex skin care and appropriate intensive care for more severe cases, such as dermatology departments or burn units, which has been shown to improve outcomes [8]. Although stopping the culprit drug is associated with a better prognosis, every day of delay also worsens the outcomes [9]. However, identification of the causal drug can be challenging particularly acutely and currently relies mainly on expert judgment and clinical causality assessment. Further research is critical to develop better ways of “immunophenotyping” patients such as with novel validated biomarkers, immunoassays and genetic studies for acute identification of the causal drug.

Acute active management is controversial, and there is little consensus on medical interventions because of the lack of high-level evidence that any treatment (such as steroids and IVIg) is superior to supportive care alone. Newer treatments such as etanercept (TNF-α receptor antagonist) and cyclosporine (calcineurin inhibitor, immunosuppressant) have shown promise in a recent non-blinded randomized controlled study (etanercept) and several observational studies (cyclosporine and etanercept) [10,11]. Information on the management of children versus adults is also lacking given that a much higher proportion of cases in children are mediated by infectious and non-drug triggers. However, recent guidelines are useful for clinicians if such cases arise [12].

In management of the skin, there is consensus about the important need for non-adherent dressings and generous and frequent application of paraffin emollient. While some centers undertake debridement of blistered areas, others do not recommend this approach, and the issue remains a source of disagreement [13]. This would be a high priority area to address with future research, so that the field can develop a unified approach to skin care. Urogynecologic manifestations of SJS/TEN warrant further attention as evidenced by the fact that scarring and stenosis arise in 18–28 % of cases [14,15]. All female patients of SJS/TEN should be seen by a gynecologist early where interventions including topical corticosteroid therapy, catheterization, and vaginal dilation may be considered. These patients also need to schedule follow-up appointments following discharge to ensure any vaginal adhesions

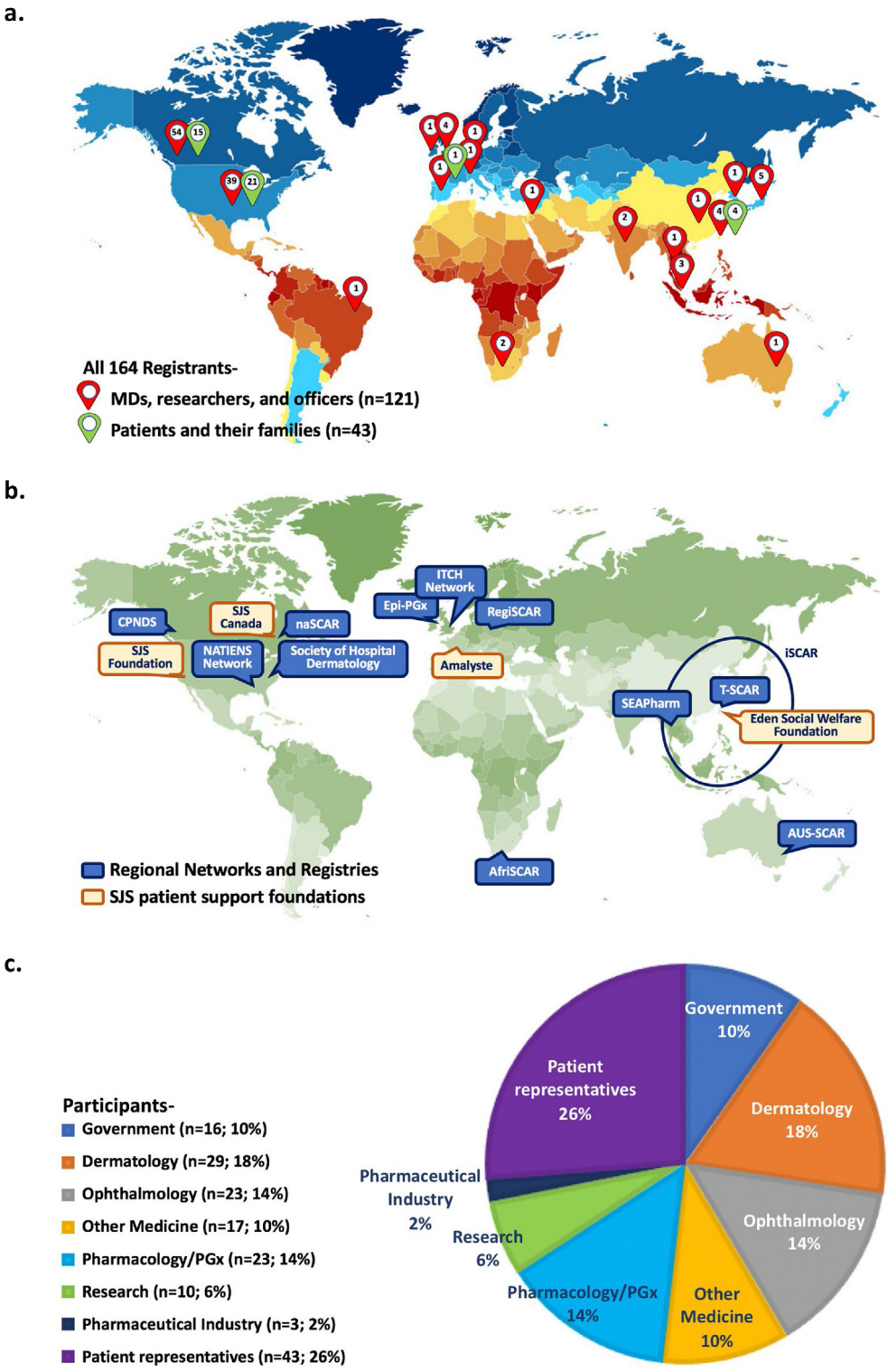

Fig. 1. SJS/TEN 2019: From Science to Translation conference participants.
The ***SJS/TEN 2019: From Science to Translation*** conference was organized by the three co-chairs of the congress: Drs. Elizabeth J. Phillips (Vanderbilt University Medical Center), Bruce C. Carleton (University of British Columbia), and Wen-Hung Chung (Chang Gung University). **a. Global distribution of participants.** A total of 164 participants, representing 19 countries across six continents, engaged in this meeting, which took place at the British Columbia Children's Hospital Research Institute in Vancouver, Canada. **b. Regional networks and registries and SJS patient support foundations.** This was of special significance because it was the largest SJS/TEN event that gathered together 16 government representatives, as well as 12 regional SCAR networks and registries from countries in North America, Europe, Asia, Africa, and Australia. Forty-three local and international SJS/TEN survivors, their families, and local community advocacy groups also attended. Six representatives from government drug regulatory and research funding agencies in the United States and Canada provided updates on regulatory science and funding opportunities related to SCAR and drug safety. **c. Each sector shows the percentage of each group of participants.** Participants comprised 43 (27 %) patient participants, 29 (18 %) dermatologists, 23 (14 %) ophthalmologists, 23 (14 %) experts in pharmacogenomics or clinical pharmacology, 17 (10 %) other medical disciplines, 16 (10 %) government officers, 10 (6 %) basic science researchers, and 3 (2 %) from the pharmaceutical industry.

and other complications that could lead to long-term reproductive morbidity are adequately managed.

Unmet need: To improve evidence-based approaches to the acute and chronic management of SJS/TEN (Table 1).

1.4. Ocular science

SJS/TEN is commonly accompanied by acute ocular disease, leading to chronic complications. Ophthalmology should be involved as early as possible and at the least there should be a bedside eye exam within 24–48 hours of disease onset and/or diagnosis. Long-term eye morbidity is prevalent even in the absence of defined acute disease and continued regular follow-up after discharge is recommended.

Acute ocular involvement presents with eyelid margin inflammation and hyperkeratosis, conjunctivitis with membranes/pseudomembranes, as well as corneal/conjunctival epithelial defects (which can progress to corneal melt, perforation, or infectious keratitis). Mild disease can be managed with topical corticosteroids, antibiotics, frequent administration of lubricants, and careful periodic removal of membrane/pseudomembranes. For more severe cases, urgent placement of amniotic membrane over the ocular surface within the first week can potentially avoid severe debilitating chronic complications [16].

Chronic manifestations include dry eye, eyelid margin keratinization, symblepharon and eyelid malposition, chronic conjunctivitis, limbal stem cell deficiency (LSCD), corneal thinning/melt, and infectious keratitis, resulting in discomfort, pain and potential vision loss. Treatment options include topical corticosteroids, lubricants, and antibiotics, specialized contact lenses for ocular surface protection and visual rehabilitation, eyelid malposition corrective surgery, and surgical procedures for LSCD. These include cultivated

Table 1
Summarized key points from breakout sessions.

Patients' perspective-

Diagnosis-

- Improving awareness of physicians and other healthcare providers about SJS/TEN will facilitate patient communication, so that patients will have a better understanding of this condition. Many feel that healthcare providers are uninformed about SJS/TEN and believe it is so rare that they will never see a case.
- A checklist that would promote early identification and diagnosis of the disease should be developed. This would assist physicians and other critical multidisciplinary team players, especially those who were never exposed to SJS/TEN patients in their pre-clinical and clinical training, to have a heightened suspicion for this disease.
- An electronic medical record (EMR) that highlights some common causative medications and provides decision support to physicians for early identification of the potential culprit drug would be helpful.
- A standard protocol for clinicians including questions about new drug exposure is critical to ensure early causality assessment. Ask patients about medications that started within the previous 4–6 weeks. This may help confirm or rule out high-risk culprit drugs.

Acute Care Management-

- A streamlined protocol to facilitate earlier transfer of possible SJS/TEN patients to a specialized facility with dermatology ward or burn unit and other subspecialty assessment for earlier diagnosis and management.
- In regions where SJS/TEN presents as an unfamiliar disease and lack of available expertise, a detailed and accessible checklist outlining care guidelines that includes supportive care and education for medical teams, patients, families, and caregivers.
- The creation of a multidisciplinary team that includes dermatology, ophthalmology, gynecology, urology, and pulmonology, gastroenterology, psychiatry, pharmacy, and rehabilitation medicine that is established within 24 hours of admission.
- Protocol to assess and acutely manage the eyes and mucosal tissues to help prevent further damage and loss of function.

Discharge-

- The needs around the discharge process were paramount. Most survivors felt isolated in the process, while some felt as if they were sent home to die with little or no guidance or confidence in their follow-up care with physicians and other healthcare workers who were knowledgeable and competent to care for patients with SJS/TEN for follow-up care for their future.
- Recovery from SJS/TEN in physical, mental, and emotional aspects is a gradual, ongoing process which requires professional assistance from specialists at different stages. Post-traumatic stress disorder-like symptoms are common for survivors who are worried about any medication exposure in the future.
- A holistic post-discharge educational checklist that includes the effect of SJS/TEN not only on skin, wounds, eyes and urogenital tract but the potential short- and long-term implications for health-related quality of life, mental health and recovery. This would include a checklist and instructions on recovery care.
- An "SJS/TEN discharge passport" that includes information on drugs both to avoid and safe to take in the future and follow-up appointments with specialists and other supportive healthcare resources made prior to discharge.
- Patients, families, and SJS/TEN advocacy/support groups are eager to participate actively in scientific meetings like SJS/TEN 2019, and like being asked questions from clinicians and scientists about their experiences to raise attention to this rare but life-threatening disorder.
- A list of community and psychosocial support groups including links to other SJS/TEN survivors.

Clinicians' perspective-

- Education programs and basic training with standardized diagnosis and treatment protocols, white papers and clinical practice guidelines are essential and important for all healthcare providers and particularly those involved in the diagnosis and care of SJS/TEN to gain a better understanding of the early diagnosis and acute and chronic clinical care of patients with SJS/TEN.
- Providing general educational materials, e.g. booklets, handouts, and videos, with plain language is a good way to help inform patients; developing support groups and creating websites or social media (e.g. Facebook clubs) are also helpful for patients to get support from peers.
- One of the biggest challenges is that some specialists (e.g. dermatologists, allergists, ophthalmologists, and gynecologists) might be not available acutely, which increases the risk of complications that are permanently disabling.
- More high-quality and evidence-based research and clinical trials are needed to be conducted to help determine best practices for diagnosis and management.

Pharmacogenomics experts' and basic scientists' perspective-

- A global effort to establish a "Network of Networks" to leverage available resources and engage multidisciplinary experts, as well as SJS/TEN patients, will help overcome limitations (e.g. rarity of condition, small sample sizes, inclusion of all ancestry groups) and boost academic development and innovation.
- The key to SJS/TEN clinical research is precise phenotype adjudication, suggesting that standardized, independent case validation is critical.
- Further investigation is warranted to fulfill the knowledge gap of immunopathogenic mechanisms in SJS/TEN patients without prior drug exposure.
- The lack of stable and sufficient funding useable across international boundaries remains one of the major barriers to conducting further studies of global impact and maintaining a long-term, productive collaboration.

limbal epithelial cell transplantation (CLET), cultivated oral mucosal epithelial transplantation (COMET), and simple oral mucosal epithelial transplantation (SOMET). Boston type 1 and 2 keratoprosthesis may be helpful in more severe cases [17]. Though sometimes necessary, outcomes following ocular surface surgeries are generally poor in SJS/TEN. As such, recent work has emphasized the importance of early intervention with amniotic membrane grafting [18]. This approach may be accomplished in a sutureless manner, thus avoiding the necessity to transfer patients to an ophthalmic theatre [19].

Finally, genetic risk factors may be associated with SJS/TEN with "severe ocular complications (SOC)" and this warrants further study, in particular, to prioritize patients for prognostication and follow-up. SOC has been linked to "cold-medicines" in some populations with *HLA-B*44:03* (Japanese, Thai, Brazilian, and Indian) and *HLA-A*02:06* (Japanese and Korean) [20]. However, it has been suggested that these HLA-alleles may rather reflect an infectious trigger than a heterogenic group of drugs that were initiated to treat the prodromal symptoms of SJS/TEN [21]. A network of susceptibility genes for SJS/TEN (*TLR3*, *EP3*, and *IKZF1*) may trigger the inflammation associated with SJS/TEN with SOC (Supplemental Figure S1) [22].

Unmet need: To further evidence-based approaches to understanding short- and long-term mechanisms of morbidity and the prevention and treatment of ocular disease associated with SJS/TEN (Table 1).

1.5. Updates in global regulatory science, pharmacovigilance, and data mining

Cases of SJS/TEN and SCAR can be identified from many sources, including post-marketing adverse event reporting systems, disease registries, electronic health records (EHRs), literature, observational studies, and clinical trials. Cross-sectional studies used EHR allergy lists to identify SCAR cases. Causative drugs, including some rarely implicated in SJS/TEN in the literature, and differences in patient demographics, were reported [23,24]. An English-language PubMed literature search from 1980 to 2017 yielded 851 cases categorized as "probable" or "definite" SJS/TEN cases, 80.6 % of which were drug-induced (unpublished data).

In FDA regulatory actions involving labeling for SJS/TEN from 2016 to 2018, products with SJS/TEN labeled in Warnings/Precautions at initial approval or added post-market included 17 hematology/oncology products, 8 antimicrobials, 6 radiocontrast agents, deflazacort, and febuxostat. Post-market reports were the primary source of information for the labeling actions.

The EMA Pharmacovigilance Risk Assessment Committee (PRAC) monitors the Eudravigilance database (>50 million records) and uses disproportionality tools (electronic Reaction Monitoring Report, eRMR) to identify emerging signals. Since July 2012, PRAC has evaluated 21 drugs for SCAR risk [25]. From the Eudravigilance data, the fatality of SJS, SJS/TEN overlap and TEN is 7.4 %, 12.1 %, and 22.4 %, respectively.

Performance and quality of pharmacogenetic tests assessing SJS/TEN drug-associated risks are also regulated by some health authorities; risks to patients with life-threatening diseases of treatment decisions based on erroneous testing are also considered. Health Canada's evaluations are becoming more context-aware, placing more emphasis on patients' needs, real-world evidence issues and collaborative health system models, which will inform evolutions in regulatory science and decisions about pharmacogenetic testing and patient safety.

An example of beneficial impact of regulatory action on reducing SJS/TEN is a "Dear Health Care Professional Letter" issued by the Singapore Health Sciences Authority and Ministry of Health in 2013, advising that genotyping for *HLA-B*15:02* would be standard of care in Singapore before initiating carbamazepine (CBZ) in new patients of Southeast Asian ancestry. SCAR guides highlighted the importance of prompt withdrawal of drugs in suspected SCAR cases. Post-market reports of CBZ-induced SCAR cases subsequently decreased by >95 % [26]. Usage of CBZ decreased modestly overall, though new CBZ users declined by 40 %. Meanwhile, new users of levetiracetam increased 2.7-fold highlighting other factors that have contributed to the reduction in SJS/TEN in Singapore overall.

Unmet need: Studies are needed to leverage large-scale EHR data and advanced informatics technology to improve local and international SCAR case-finding methods to advance the science of SCAR research (Table 1).

1.6. Prediction, prevention, earlier diagnosis, and treatment

A foundation of research to identify predictors of SJS/TEN is careful ascertainment and specialist clinical phenotyping, to facilitate accurate diagnosis. In this context, RegiSCAR has developed an algorithm for assessment of drug causality for epidermal necrolysis (ALDEN), which is being used by a number of collaborative networks studying SJS/TEN across genetically diverse populations [27]. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) has also developed data collection materials to ensure proper SJS/TEN case ascertainment is occurring at each of its centers across Canada. In addition, an algorithm for causality assessment has been developed, from which, CPNDS recommendations have been made regarding the use of *HLA-B*15:02* and *HLA-A*31:01* genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions [28]. Genetic studies continue to refine the existing scientific knowledge and identify novel predictors of drug-induced hypersensitivity reactions (Table 2) [2–5,29–31]. A recent meta-analysis of two genome-wide association studies (GWAS) identified *HLA-A*31:01* as a strong predictor of both CBZ-induced SCAR and drug-induced liver injury (DILI) [32]. The same study reported a new association between variation in the anaplastic lymphoma kinase (*ALK*) gene and CBZ-induced SCAR [32].

Another novel report is the association between variation in the complement factor H (*CFH*) gene and phenytoin-induced maculopapular exanthema in individuals of European-ancestry [33]. With all the hypersensitivity-related genetic data that is being generated globally, an opportunity exists for a large meta-analysis to identify additional predictors and inform accurate prevention models. Strong associations have been reported between IL-15 and granulysin levels and severity and mortality of SJS/TEN suggesting that these could be utilized in earlier identification and prognostication [34,35]. Current suggested interventions and therapeutic strategies are highlighted in Supplemental Figure S2. Further prospective, randomized controlled studies are needed to provide more definitive conclusions and determine optimal treatment strategies in patients with SJS/TEN.

Unmet need: To fuel discovery and implementation of additional genetic predictors and biomarkers for earlier diagnosis and treatment across diverse populations (Table 1).

1.7. Special populations

The etiology, pharmacogenomic risks, epidemiology, clinical features and outcomes of SJS/TEN vary considerably in special patient populations. SJS/TEN in children is more frequently non-drug related; with SJS/TEN very uncommon in the very young (< 2 years old) [36]. SJS/TEN is considerably more common (up to 150-fold) in certain immunocompromized patient populations, such as patients

with cancer and HIV/AIDS [37]. Newer immunomodulatory treatments such as the immune checkpoint inhibitors used for treatment of previously untreated cancers such as melanoma have been transformative but have been associated with severe and unpredictable adverse events. In these populations, there is still much to be learned about the clinical presentation and treatment, pre-disposing factors including host genetics, the tumor type, and the type and combination of immunomodulatory therapy used. Since SJS/TEN has been reported several months after the administration of these agents, a high index of suspicion needs to be maintained. SJS/TEN mortality is higher in the elderly with malignant co-morbidity (>50 %) and pre-existing hepatic disease [37–39].

Although the smaller number of patients in certain subgroups and unclear pathogenesis increase difficulties in SJS/TEN research in special populations, pharmacogenomics and associated mechanistic studies show promise for predicting SJS/TEN to population

Table 2
Evidence-based pharmacogenomics and clinical implementation.

Associated drug	Genetic variant	Hypersensitivity	Ethnicity and Carriage rate (%)	Level of evidence	Stage of implementation
Abacavir	*HLA-B*57:01*	Hypersensitivity syndrome (**NOT** SJS/TEN) [2]	• European (5–8 %) • African American (2–3 %) • Southeast Asian (<1 %) • Sub-Sahara African (<1 %)	• CPIC Level[1]- High • PharmGKB Level[2]- 1A	• U.S FDA[3,4]- PGx testing required • Health Canada- PGx testing required • EMA- PGx testing required • PMDA- PGx testing required • Singapore- PGx testing should be considered
Allopurinol	*HLA-B*58:01*	SJS/TEN and DRESS [5]	• Southeast Asian (10–15 %) • Sub-Sahara African (10 %)* • European (1–6 %)* • African American (4 %)	• CPIC Level- High • PharmGKB Level- 1A	• American College of Rheumatology guideline- PGx testing recommended • EMA- PGx testing recommended • PMDA- Actionable PGx# • TFDA- PGx testing recommended • Singapore- PGx testing is not required as a standard of care
Carbamazepine	*HLA-B*15:02*	SJS/TEN [3,27,31]	• Asian, particularly Han Chinese (10–15 %) • African (<1 %) • European (<0.1 %)	• CPIC Level- High • PharmGKB Level- 1A	• U.S FDA- PGx testing recommended • Health Canada- PGx testing recommended • EMA- PGx testing recommended • PMDA- Actionable PGx • TFDA- PGx testing required • Singapore- PGx testing required
	*HLA-A*31:01*	SJS/TEN and DRESS and MPE [27,31]	• European (≤6 %) • Korean (10 %) • Japanese (18 %) • Sub-Sahara African (<1 %)	• CPIC Level- High • PharmGKB Level- 1A	• U.S FDA- Actionable PGx • Health Canada- PGx testing recommended • EMA- PGx testing recommended • PMDA- Actionable PGx
Dapsone	*HLA-B*13:01*	DRESS and SJS/TEN [4]	• Southeast Asian (Chinese and Thai populations) (2–52 %) • European (Up to 4 %)	• CPIC Level- Low • PharmGKB Level- 2A	Not available
Oxcarbazepine	*HLA-B*15:02*	SJS/TEN [29]	• Asian, particularly Han Chinese (10–15 %) • African (<1 %) • European (<0.1 %)	• CPIC Level- High • PharmGKB Level- 1A	• U.S FDA- PGx testing recommended • EMA- PGx testing recommended • PMDA- Actionable PGx • TFDA- PGx testing recommended
Phenytoin	*CYP2C9*3*	SJS/TEN and DRESS and MPE [28]	• European (≤8 %) • Southeast Asian (≤5 %) • African (<1 %)	• CPIC Level- High • PharmGKB Level- 1A	• TFDA- Actionable PGx
	*HLA-B*15:02*	SJS/TEN and DRESS [28]	• Asian, particularly Han Chinese (10–15 %) • African (<1 %) • European (<0.1 %)	• CPIC Level- High • PharmGKB Level- 1A	• U.S FDA- Actionable PGx • Health Canada- PGx testing recommended • TFDA- Actionable PGx
Vancomycin	*HLA-A*32:01*	DRESS [30]	• European (6–7 %) • African American (3 %)	• Preliminary	• Single allele testing methodology available

CPIC, Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org); CYP, Cytochromes P450; DRESS, drug reaction with eosinophilia and systemic symptoms; EMA, European Medicines Agency; FDA, Food and Drug Administration; HLA, human leukocyte antigen; MPE, maculopapular eruption; PharmGKB, a pharmacogenomics knowledge resource (https://www.pharmgkb.org); PMDA, Pharmaceuticals and Medical Devices Agency in Japan; PGx, pharmacogenomics; SJS/TEN, Stevens-Johnson syndrome and toxic epidermal necrolysis; TFDA, Taiwan Food and Drug Administration.
[1]The levels of evidence graded by the Clinical Pharmacogenetics Implementation Consortium as defined at https://cpicpgx.org/levels-of-evidence.
[2]PharmGKB Clinical Annotation Levels of Evidence as defined at https://www.pharmgkb.org/page/clinAnnLevels.
[3]PharmGKB Drug Label Annotations- https://www.pharmgkb.org/labelAnnotations.
[4]U.S FDA Table of Pharmacogenomic Biomarkers in Drug Labeling- https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling; https://www.fda.gov/media/124784/download.
*NPV of *HLA-B*58:01* for SJS/TEN and DRESS and Africans and Europeans is lower than Southeast Asians (explains approximately 60 % of disease).
#Actionable PGx- Product labeling includes specific actions to be taken based on the biomarker information.

relevant drugs as was illustrated in the now routine pre-prescription screening of *HLA-B*57:01* to prevent abacavir hypersensitivity (Table 2) [2]. Large scale therapeutic intervention and long-term outcome studies should also endeavor to include populations equally balanced across age, sex, pregnancy, ethnicity and co-morbidities.

Unmet need: To better understand and personalize approaches to SJS/TEN across the heterogeneous populations affected (Table 1).

1.8. Beyond acute care and long-term considerations

Awareness of SJS/TEN-associated long-term sequelae is increasing. The RegiSCAR study was the first to systematically quantify higher mortality, morbidity and lower quality of life (QOL) beyond the acute stage by following up a cohort of SJS/TEN survivors at 8 ± 2 weeks, one year and five years. At eight-weeks, 88 % and 70 % of survivors reported skin and eye symptoms, respectively. These persisted in 77 % and 61 % at one year, and 73 % and 67 % respectively at five years. Ocular symptoms, reported by patients as the most bothersome, developed despite optimal acute care and sometimes only months later. Oral and genital sequelae manifested features reflective of localized scarring and functional dryness, such as dental caries and genital pain, bleeding, dyspareunia, and hypogeusia. Surprisingly, severity of mucosal sequelae did not correlate with disease severity in the acute stage (unpublished data) [38].

A pattern of psychological sequelae amongst survivors is also emerging. Clinical criteria for anxiety, posttraumatic stress disorder and depression were fulfilled in approximately half, one-third and one-third respectively in several studies [40,41]. Five years post-discharge, >50 % of survivors still avoid medication. These long-term sequelae do not only reduce patient's QOL, but also their ability to work. Five years after the acute stage of SJS/TEN, <50 % had returned to their normal premorbid activities. Approximately 10 % of survivors were not back to gainful employment after five years, compared to 25 % at one-year follow-up (unpublished data) [38].

Cutaneous scarring and dyspigmentation are common features of SJS/TEN and occur in 46 % and 77 % of cases, respectively [42]. The amount of scarring present may be extensive and associated with hypertrophic and keloid variants resulting in chronic pain and pruritus [13,43–45]. The etiology of the scarring is unknown; however, it is possibly impacted by the following: delayed re-epithelialization, non-standardized/optimized wound care, differences in systemic treatments and comorbid conditions, and genetic predisposition to develop hypertrophic scars.

Conventional treatment options have been adapted from lessons learned by caring for burn patients. Common modalities include scar massage, silicone sheeting and the use of pressure garments. While there is evidence that these modalities have been and continue to be helpful, there have been many recent advancements in the non-operative management of scarring with an emphasis on the use of medical laser devices [46,47].

More specifically, medical laser devices have been shown to improve scar tissue pliability and flexibility leading to improvements in range of motion and symptomatic improvements that can result in decreased pain, burning and pruritus. Additionally, restoration of pilosebaceous unit functionality with return of sweating and hair growth has been observed. These benefits have been achieved predominantly through the use of devices that target hemoglobin and water, including the 595 nm pulsed dye laser and fractional ablative carbon dioxide lasers. SJS/TEN patients with symptomatic and/or disfiguring scarring should be considered for such treatments [46,47].

With increasing awareness, multidisciplinary and system-specific strategies and protocols are needed to prevent, diagnose and treat these sequelae. Routine ophthalmic and psychiatric follow-up assessments of survivors are recommended [40].

Unmet need: To understand the nature of, prevalence of and risk factors for long-term complications and to develop holistic and novel approaches to their management (Table 1).

1.9. Models and mechanism

The immunopathogenesis of SJS/TEN remains to be fully elucidated, thus hampering prevention and treatment efforts. A major breakthrough arose from the discovery that specific *HLA* alleles predispose and, in most cases, appear necessary but not sufficient for the development of SJS/TEN and other SCAR upon exposure to particular drugs, which directly implicated T cells as key mediators of disease. Drugs, considered as foreign antigens, likely interact with particular HLA/peptide/T-cell receptor (TCR) complexes on keratinocytes to trigger the adaptive immune response and adverse reactions. CD8+ cytotoxic T lymphocytes (CTLs), that recognize HLA-drug epitopes, along with natural killer (NK) and NK T cells infiltrate skin lesions and secrete cytolytic proteins/chemokine mediators (e.g. granulysin), causing disseminated keratinocyte death in SJS/TEN [1]. Multiple predictive genomic markers (Table 2) are subsequently determined to prevent drug-specific SJS/TEN and serum biomarkers such as IL-15 and granulysin [34,35] may have roles in predicting the prognosis of acute stage SJS/TEN. Single-cell (sc) T-cell receptor (TCR) sequencing and repertoire analysis are novel approaches to investigate drug-specific T cell populations and can be paired with sc-RNAseq and Cite-seq to examine expression of the related transcriptome and proteome of total cell populations on interest [48,49]. Dominant TCRαβ clonotypes have been identified in single cells sorted from blister samples of patients with *HLA-B*58:01* restricted allopurinol-SJS/TEN and *HLA-B*15:02* restricted carbamazepine-SJS/TEN which in the case of the latter represent a public TCRαβ clonotype that is shared amongst unrelated *HLA-B*15:02* positive patients with carbamazepine SJS/TEN [48,49]. These new technologies, combined with traditional analysis of prospectively collected blister fluid, skin, and blood, allow the identification of new biomarkers of disease and an avenue to define novel and more targeted treatment approaches. The insights generated from these combined efforts have led to the development of much-needed mouse models of SJS/TEN and other SCAR. A mouse model of abacavir hypersensitivity provides a potential mechanism to explain tolerance in the presence of the *HLA-B*57:01* risk allele [50]. For SJS/TEN, mouse models have allowed for further delineation of disease pathogenesis and provide a system to test potential therapeutic interventions [1,50]. Collectively, though much research remains to be done in SJS/TEN, a solid framework is now in place upon which further progress can be built.

Unmet need: To utilize new technologies and scalable approaches to defining the specific immunopathogenesis of SJS/TEN that will lead to biomarkers for prevention, earlier diagnosis and treatment (Table 1).

1.10. The patient and family perspective

Most notably, this conference offered an opportunity to identify critical unmet needs within the SJS/TEN patient community. Patients described SJS/TEN as a disease that burned their body from the inside out, that ravaged and charred their bodies, altered their appearance, and wrecked their lives.

From the symptomatic phase through hospitalization and discharge, survivors identified multiple gaps in the continuum of care that they felt contributed to the sequelae of SJS/TEN. The three

most notable areas were diagnosis, acute care management, and discharge care plans, discussed in Table 1.

Overall, due to the atypical and rare features of SJS/TEN, many patients and their families felt an overwhelming disconnect with the medical community and could only hope that the healthcare providers and scientists working together as represented at SJS/TEN 2019 to move science and clinical care forward would be the ones to bridge the gap.

Unmet need: To develop universal patient-centered approaches to diagnosis, acute management and follow-up with significant involvement of patients and survivor groups and families in this process (Table 1).

2. Conclusions

As the global landscape of treatment for high burden diseases, such as tuberculosis, HIV and cancer, evolve, and as an even larger number of new drugs are administered globally, increasing concerns arise about the severe adverse drug reactions such as SJS/TEN that threaten public health and drug safety. The ***SJS/TEN 2019: From Science to Translation*** conference highlighted how clinical implementation of predictive screening for *HLA* risk alleles before initiating some well-known culprit drugs has made important progress in lowering the incidence of SJS/TEN and improving the safety of medication use. *In vitro* tests, animal models, and novel experimental approaches for SJS/TEN research have facilitated a better understanding of the causative drugs, the drug-gene interactions, the immune response, and the pathogenic mechanisms. Further research is still needed to address the clinical burden, epidemiology, drug- and population-specific genetic basis and immunopathogenesis of SJS/TEN globally. Leveraging existing resources and integrating research networks, registries and clinical experts will help facilitate this cause. The ultimate goal is the development of evidence-based and personalized approaches to patients with SJS/TEN that will fuel prediction, prevention, and improved short- and long-term clinical outcomes at the population and individual levels.

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Declaration of Competing Interest

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Author contributions

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Web resources and support services for patients with SJS/TEN: General SJS Foundation (http://www.sjsupport.org); Stevens-Johnson Syndrome Canada (http://www.sjscanada.org); Amalyste (France; http://www.amalyste.fr); Taiwan Eden Social Welfare Foundation (Mandarin/English; https://eden.international).

For more information, please visit the SJS/TEN2019 official website at https://medsites.mc.vanderbilt.edu/sjsmeeting/welcome or you may view the presentations from the meeting at https://nexusweb-cast.mediasite.com/Mediasite/Catalog/catalogs/sjs-ten-2019-event.

Appendix A. Supplementary data

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