2021 Meeting Abstracts

Abstract #1

Limited Adjunctive Diagnostic Utility of IFN-Gamma Elispot to Identify Offending Drug(s) in Severe Cutaneous Adverse Reactions to First-Line Anti-Tuberculous Drugs in HIV Endemic Setting

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Background:

Severe cutaneous adverse drug reactions (SCAR) such as epidermal necrolysis (EN) and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome are associated with high mortality, long term morbidity and huge healthcare cost. Oral drug provocation testing (DPT) help to limit the unnecessary exclusion of non-causative drugs, but are themselves associated with morbidity and risk. IFN-gamma ELISpot, as an adjunctive in-vitro diagnostic tool, may offer utility if optimised.

Methods:

Patients hospitalised at Groote Schuur Hospital, with treatment-limiting SCAR to FLTD; who required DPT toward reinitiating FLTD; were prospectively consented and enrolled in the IMARI drug allergy registry. IFN-g ELISpot assay was performed using optimised parent stimulating drug concentrations for Rifampicin (25ug/ml), Isoniazid, Pyrazinamide, and Ethambutol (each 500ug/ml). Assays were performed on acute admission, pre- and post in-vivo drug provocation and on follow-up after resolution. A positive ELISpot was >=50 spot forming units/million cells after removal of background (average of no stimulant wells). Diagnostic accuracy was assessed against the gold standard of full dose oral DPT results.

Results:

32 SCAR patients had at least one matched ELISpot and oral DPT to one or more FLTB drug/s - 25 DRESS and 7 EN phenotypes. 81% were HIV positive, 35% of whom were on ART and 41% on sulfamethoxazole/trimethoprim at the time of the SCAR event. 25 patients experienced positive DPT - 17 to a single and 8 to multiple drugs. The sensitivity of ELISpot was 33%(4/12); 13%(1/8); 11%(1/9); and 0%(0/5) for Rifampicin, Isoniazid, Pyrazinamide and Ethambutol respectively. Specificities were 100% for the 11 Rifampicin, 13 Isoniazid, 13 Pyrazinamide and 16 Ethambutol negative DPTs. The sensitivity of Rifampicin ELISpot increased to 3/6(50%) when only samples acquired during the acute stage of admission and rechallenge were included.

Conclusions:

The current low sensitivity of IFN-g ELISpot compared to oral DPT in all FLTD except Rifampicin limit current clinical utility. Alternative approaches, using drug metabolites or different cytokine read-outs should be explored to improve sensitivity.

Abstract #2

SJS/TEN Case Finding in a Large Electronic Health Record Database and Clinical Characteristics of 74 Validated Cases

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Background:
Preventing severe hypersensitivity reactions like SJS/TEN relies on risk stratification strategies that use clinical and genetic risk factors. However, due to challenges in case identification, SJS/TEN prevalence, causative drugs, predictors, and sequelae remain poorly described. We aim to develop reproducible informatics methods to identify and validate SJS/TEN cases using longitudinal EHR data and investigate the demographic, clinical, and genetic risk factors and sequelae of SJS/TEN.

Methods:
We have leveraged 30 years of longitudinal EHR data within our healthcare system to identify SJS/TEN cases using our existing Natural Language Processing (NLP) system, MTERMS. We identified SJS/TEN cases from structured data and free-text data and will validate these cases to create, optimize, and standardize reproducible methods for identifying and validating an SJS/TEN cohort. To identify demographic and clinical risk factors for antibiotic-associated SCAR, we will perform a nested case- control study. We will also conduct patient surveys to study SJS/TEN sequelae. Finally, we will collect saliva samples from our cohort of validated SJS/TEN patients to identify relevant HLA and genetic associations.

Results:
We identified 1,540 possible SJS/TEN cases from structured data, including the allergy list, diagnoses, medical history, pathology reports, and problem list. Of these cases, we identified 1,225 (79.5 %) cases from a single distinct source, 161 (10.5 %) cases from two sources, and 154 (10 %) cases from three or more sources. Our preliminary case validation results showed that the number of sources from which we identified the SJS/TEN is positively correlated with the validity of the case.

Conclusion:
Informatics technology can facilitate rare case identification. In the next steps, we will use NLP to identify SJS/TEN cases that were only mentioned in clinical notes, develop and evaluate machine learning methods to improve case identification, and evaluate the generalizability of our approach using data from another institution.

Abstract #3

Successful Creation of a Prototype Machine Learning Algorithm to Distinguish SJS/TEN from Other Dermatoses

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Background:
Computer vision and machine learning can produce accurate classifications useful in triage and digital alert systems, but typically require thousands to hundreds of thousands of index images for successful training. Steven Johnson Syndrome/Toxic Epidermal Necrolysis represents a relatively rare event and there are simply not a significant number of quality images readily available. However, "one-shot" training methods have been proposed for these situations in other domains. We attempt the creation and testing of one such one-shot training method.

Methods:
EMBASE and MEDLINE databases were searched with keywords "Stevens-Johnson Syndrome, Toxic epidermal necrolysis, and Case*." All studies before 2018 were excluded. This yielded 820 studies to be screened. A total 151 studies with color images were identified representing 172 patients. Images of SJS/TEN were then extracted and prepared for one-shot learning. Of 428 images, 356 were of reasonable quality and 175 representative images were ultimately chosen. Images were pre-divided into training and testing datasets. The training dataset used 100 patient/images of SJS and 449 images of other representative dermatoses. A "twin" one-shot paired network using transfer learning from VGG-16 and a custom embedding layer was constructed and trained to distinguish if two provided images were both SJS/TEN or only one image was SJS/TEN.

Results:
The testing dataset represented all potential pairs of 75 unique images of SJS/TEN and 100 images of other dermatoses. Using default criteria for interpretation the overall accuracy of the network was 93%, with a positive predictive value in identifying SJS/TEN of 79% and a negative predictive value of 98%.

Conclusion:
This initiative demonstrates a theoretic plausibility of using one-shot learning to allow digital systems to identify SJS/TEN. However, we will discuss the many potential pitfalls on the road to sustainable evidence-based implementations.

Abstract #4

Immune-Mediated Over Activation of Coagulation in SJS/TEN

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Background:
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis are life-threatening adverse drug reactions. The role of cytotoxic lymphocytes in initiating the immune reaction in SJS/TEN via a human leukocyte antigen allele restricted pathway is well known. This study highlights the immune-mediated activation of coagulation.

Methods:
Blood samples were obtained from subjects suspected of SJS/TEN and healthy volunteers. Exudates from mucosal swabs were isolated following addition of .25 mL of saline and double centrifugation. Our samples were analyzed via ELISA techniques for thrombin-antithrombin complexes, fibrinopeptide A (F1.2), plasminogen activator inhibitor-1 (PAI-1) and platelet microparticles. Furthermore, antithrombin was measured using a chromogenic method, and protein C was measured using a clotting method. The skin biopsy samples were stained with Granulysin antibodies and studied using immunofluorescence microscopy.

Results:
Although the platelet microparticle levels, PAI-1 levels, Protein C levels, and antithrombin levels did not show a significant difference between the study groups, there was a wider range in all four parameters in the confirmed/unconfirmed SJS/TEN patients. Furthermore, there were statistically significant increases in monocyte chemotactic protein-1 ($p = .0078$), IL-6 ($p= .0078$), and TNF-alpha ($p=.0078$) in the tissue biopsies of confirmed SJS patients when compared to normal human plasma. Analysis of mucosal swab exudates of confirmed SJS patients, using surface enhanced laser desorption-time of flight (SELDI-TOF) technique revealed distinct peaks at 15.1 kDA and 14.2 kDA while a control cohort exhibited a peak at 11.2 kDA. Immunofluorescent staining of the skin biopsy

slides revealed increased expression of granulysin at the epidermal-dermal layer in biopsy confirmed SJS/TEN patients when compared to the controls.

Conclusions:
While the interface between coagulation and SJS/TEN has sparsely been explored, these preliminary results reveal that there may be contribution from widespread hypercoagulability and endothelial dysfunction involved in the disease process.

Abstract #5

Risk Factors and Outcomes Associated with Leukopenia in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Background:
Little is known about leukopenia occurring in patients hospitalized with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN).

Methods:
We conducted a retrospective study using a cohort of 377 patients from the United States to assess the incidence, clinical factors, and outcomes associated with leukopenia in SJS/TEN.

Results:
Of 377 patients, 49 (13.0%) had leukopenia, defined as a white blood cell count of less than 4,000/µL at the time of admission to a tertiary care facility. Age and sex did not differ between leukopenic and non-leukopenic patients. Median body surface area % involvement at admission was higher in leukopenic patients compared to non-leukopenic patients (30% vs. 15%, $p<0.01$). Leukopenic patients had higher rates of malignancy (22.45% vs. 9.45%, $p=0.01$) and connective tissue disease (22.45% vs. 8.54%, $p<0.01$) compared to non-leukopenic patients. Comorbidities like HIV, stem cell transplant, solid organ transplant, immunosuppressant use, and corticosteroid use did not differ between leukopenic and non-leukopenic patients. A total of 179 (47.5%) patients were taking a medication known to cause leukopenia, but use did not differ between leukopenic and non-leukopenic patients. Univariate logistic analysis was subsequently performed to assess relationships between leukopenia and clinical outcomes in SJS/TEN. Leukopenia was associated with in-hospital complications of bacteremia (OR 2.48, 95% CI: 1.19-5.15, $p=0.02$) and pneumonia (OR 2.33, 95% CI: 1.15-4.74, $p=0.02$) but was not associated with other complications, including acute renal failure, major thrombotic events, intubation, sepsis, cellulitis, UTI, or in-hospital mortality, although mortality trended towards statistical significance (OR 1.53, 95% CI: 0.73-3.28, $p=0.28$).

Conclusions:
Our study shows that leukopenia is common in SJS/TEN and is associated with increased disease severity, malignancy, and connective tissue disease. Pneumonia and bacteremia are important complications in such patients. Further work is needed to understand the pathophysiology of leukopenia in SJS/TEN and to establish the role of treatments (e.g., G-CSF) which might improve outcomes.

Abstract #6

A Review of Stevens Johnson Syndrome and Toxic Epidermal Necrosis Cases from Immune Checkpoint Inhibitor Therapy

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Background:
The use of immune checkpoint inhibitors (ICI) has shown promise in the treatment of advanced malignancies, but they have been associated with immune related adverse events (IRAEs) described from mild maculopapular rash to SJS/TEN, a life-threatening complication.1-3

Methods:
A literature review on the PubMed/MEDLINE database was conducted. We identified 23 cases from the literature and two from our home institution for a total of 25 cases. Cases were analyzed for characteristics of reactions and prognosis.

Results:
There were 10 cases of SJS, 14 of TEN, and 1 of SJS/TEN. SJS/TEN reactions to nivolumab had a median onset time of 6 weeks (average of 55 weeks), whereas those secondary to pembrolizumab (eight cases) had a shorter median onset time of 2 weeks (average of 7 weeks). 56 % of cases reported prodromal rashes, ranging from eczematous to morbilliform erythematous eruptions. SCORTEN scores were mentioned in eleven cases and averaged at 3.5. A total of nine cases (36%) were fatal (in-hospital mortality), eight of which were TEN. Of note, TEN was described in all cases secondary to combination ipilimumab and nivolumab therapy (five cases), two of which were fatal. All but one case mentioned management with systemic corticosteroids. Intravenous immune globulin therapy was also used in nine cases.

Conclusions:
This study confirms that SJS/TEN can have delayed onset with ICI use. It also shows that almost 25% of patients may lack oral mucosal involvement. Dermatologists should identify prodromal rashes to SJS/TEN eruptions to ICIs given its high mortality and morbidity.

Abstract #7

Variations in the Medical Management of SJS/TEN: A Survey Study Among North American Dermatology Hospitalists

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Background:
Stevens Johnson Syndrome (SJS)/Toxic epidermal necrolysis (TEN) is a rare, severe cutaneous adverse reaction to medications. Although consensus on conservative management has been developed, no standard currently exists for

the medical management of SJS/TEN. Our study aimed to assess variation of medical management of SJS/TEN among dermatology hospitalists.

Methods:
A web-based survey was distributed to members of the Society of Dermatology Hospitalists. Participants were asked to provide all medical therapeutics used for SJS/TEN in the past 5 years, including administration, dosing, and treatment duration. Clinical vignettes were provided (SJS/TEN with 5% BSA involvement, 5% BSA with ocular involvement, 5% BSA with renal impairment, and 30% BSA involvement with and without bacteremia) and participants were asked to choose their most preferred treatment. Descriptive statistics were used to summarize responses and preferred treatments across clinical vignettes were organized into Sankey plots.

Results:
24 (75% response rate) participants completed the survey. A total of 9 unique medical treatments were used when caring for patients with SJS/TEN, with the most common being IVIg (83%). Physicians often escalated care with greater BSA involvement (i.e., supportive care only to use of cyclosporine or IVIg) and modified the treatment plan with patient comorbidities (i.e., avoiding the use of cyclosporine with renal impairment). Despite these trends, individual medical management plans varied in drug class, administration, dose, and duration of treatment (Number of unique treatment plans: glucocorticoids 22, cyclosporine 23, IVIg 10, TNF-alpha inhibitors 9).

Conclusions:
Although patterns of escalation of care with more severe disease and consideration of patient comorbidities persisted in physician decision-making, our study demonstrates significant heterogeneity in the medical management of SJS/TEN among dermatology hospitalists. This lack of standardization highlights challenges in clinical care and research. Future studies should aim to develop consensus and a standardized treatment regimen on the medical management of SJS/TEN.

Abstract #8

Implementation of Pharmacogenetics into Clinical Practice - A Rapid Pharmacogenetic Test Panel for Cutaneous Adverse Drug Reactions

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Background:
Cutaneous adverse drug reactions (cADRs) are among the most commonly seen adverse events, ranging from mild rash to life-threatening systemic symptoms, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Such severe cADRs can cause permanent physical and psychological harm. Fear of taking any drug in the future is a commonly reported outcome by affected patients. Several HLA variants are robustly associated with a specific severe cADR. Complex laboratory procedures and high sequencing costs are barriers to clinical application.

Objectives:
Develop an HLA allele-specific panel to quickly screen robust HLA markers known to substantially increase the risk of severe cADRs

Methods:
The primer-probe pairs for each target HLA allele were designed for the TaqMan MGB allelic discrimination assay. DNA samples with validated HLA data were used for quality control and to optimize the TaqMan real-time PCR conditions.

Results:
Ten robust associations between particular HLA alleles and specific severe cADRs were included. Chosen HLA alleles place patients at a 3-fold or higher risk of particular severe cADRs and have been in at least 3 independent populations. The drug-allele combinations for testing are: (1) HLA-A*24:02 with lamotrigine; (2) HLA-A*31:01 with carbamazepine; (3) HLA-A*33:03 with allopurinol; (4) HLA-B*13:01 with dapsone or co-trimoxazole; (5) HLA-B*15:02 with carbamazepine, phenytoin or oxcarbazepine; (6) HLA-B*15:11 with carbamazepine; (7) HLA-B*35:05 with nevirapine; (8) HLA-B*51:01 with phenytoin; (9) HLA-B*57:01 with abacavir; (10) HLA-B*58:01 with allopurinol. These 10 assays have been validated by 42 sequenced samples.

Conclusions:
This detective tool has reduced the cost of testing from $900 for traditional HLA sequencing to estimated $25 for TaqMan and reduced laboratory time to approximately 2 hours of PCR running time. This makes the HLA predictive tests more accessible and affordable to all patients and clinicians in order to minimize severe cADR occurrence before administrating specific high-risk medications.

Abstract #9

Investigating the Role of Memory T Cells in Delayed-onset Drug Hypersensitivity Reactions

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Case Report:
Delayed-type drug hypersensitivity reactions (dtDHRs) commonly occur and can have significant morbidity and mortality. Pathogenesis is poorly understood. Using patient samples and a novel mouse model we interrogated the role of memory T cells in disease. Transcriptional profiling of patient samples suggested that severe forms of dtDHRs, DRESS and SJS/TEN, were mediated by central memory T (TCM) cells recruited into skin, while milder dtDHR, morbilliform drug eruption (MDE), may be mediated by skin-resident memory T cells (TRM). Microscopic analysis affirmed T cell infiltrates consisted of skin homing ab type CD45RO+ CD4 and CD8 T cell subsets in dtDHRs. Comparable T cell infiltrates were observed in MDE samples from healthy patients and lymphopenic patients lacking circulating T cells, supporting that skin TRM can mediate MDE. Parallel findings were observed in mice. Dermatitis and increased ear thickness were seen in all treated and contralateral non-treated ears of HLA-B*57:01 mice administered abacavir i.p. and topically. Disease correlated with activation of CD3+CD8+ T cells in cervical lymph nodes, migration through blood, and accumulation in treated and non-treated ears. Disease generated TCM, effector memory T cells, and TRM populations that were present in lymph nodes, blood and treated and non-treated skin 90 days later despite clinical and histologic resolution of inflammation. In vivo challenge with systemic drug exposure alone resulted in clinical dermatitis and increased ear thickness faster and more robustly than primary response, consistent with an allergic memory T cell response. Allergic reaction occurred despite the presence of FTY720, an S1P receptor agonist, indicating that skin TRM were capable of mediating drug hypersensitivity in the absence of circulating T cells. Taken together, these findings suggest that skin TRM can mediate milder, skin limited dtDHR, while severe forms of disease involve activation and recruitment of TCM.

Abstract #10

Regulation of Innate Immune Response by miR-628-3p Upregulated in the Plasma of SJS/TEN with Severe Ocular Complications (SOC)

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Background:
MiRNAs are reported to be involved in many functions of various human diseases.
Objective: To investigate the roles of plasma miRNAs in the pathogenesis of SJS/TEN with SOC.

Methods:
We first performed comprehensive miRNA analysis of their plasma using microarrays. Quantitative real-time polymerase chain reaction (RT-qPCR) assays confirmed the up-regulation of miRNAs of interest. To identify the function of significantly up-regulated miRNA, we transfected their mimics to THP-1 cells, a monocyte cell line, and subjected the transfected cells to comprehensive gene expression analysis. RT-qPCR assays confirmed the down-regulation of genes of interest.

Results:
Our comprehensive analysis showed that hsa-miR-628-3p was significantly up-regulated in the plasma from patients in the chronic stage of SJS/TEN with SOC. Comprehensive gene expression analysis revealed that THP-1 cells transfected with the hsa-miR-628-3p mimic elicited remarkable down-regulation; 50 genes were down-regulated by less than one-third. They included the innate immunity-related genes TLR3, RIG-I, and MDA5, receptors of dsRNA; they induce interferon-related genes. RT-qPCR assay confirmed their significant down-regulation. RT-qPCR assay also showed that STAP1, IFI44L, CXCL11, TNFSF10, AIM2, RSAD2, IFITM1, CXCL10, CCL8, TRIM22, HERC5, IFI27, IFIT2, GBP4, IFIT1, IDO1, HESX1, TNFSF13B, USP41, (TLR3), genes that were shown to be down-regulated by comprehensive gene expression analysis, were significantly down-regulated in the presence of the hsa-miR-628-3p mimic.

Conclusion:
We found that hsa-miR-628-3p was significantly up-regulated in the plasma from patients in the chronic stage of SJS/TEN with SOC, and that miR-628-3p was able to regulate innate immunity by suppressing the PAMPs of TLR3, RIG-I and MDA-5.

Abstract #11

Single-cell Studies of Trimethoprim-sulfamethoxazole-associated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Define an Atlas of Immunopathogenesis and Specific Signatures of Oligoclonal Cd8+ T Cells at the Site of Tissue Damage

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Background:
Trimethoprim-Sulfamethoxazole (TMP-SMX) is one of the most prevalent causes of drug-induced SJS/TEN globally and is thought to be mediated by HLA-class I restricted CD8+ T-cells expressing dominant T-cell receptor(s). The specific HLA-class I restriction and molecular and cellular signatures of TMP-SMX-reactive CD8+ T cells that could have high utility in prevention, earlier diagnosis, and treatment of TMP-SMX SJS/TEN have not been defined.

Methods:
Single cell suspensions were created from thawed cryopreserved blister fluids to define the dominant TCR and unbiased single-cell transcriptome and protein expression at the site of SJS/TEN tissue damage from six patients with TMP-SMX SJS/TEN. Patients included those of African ancestry (n=5) and White/Hispanic/Latino (n=1). Blister fluid samples were analysed by 10X 5' scTCR-RNA-CITE-seq. For the Cite-seq assay suspensions were stained with a panel of up to 137 DNA-sequenced tagged antibodies (Totalseq-CTM, Biolegend). Raw data was normalized using CellRanger 3.1.0, clustered by Seurat v3.1, and data analyses and visualisation by Visual Genomics Analysis Studio (VGAS).

Results:
Unsupervised transcriptome analyses identified the majority (>50%) of the cells in the blister fluid to be CD8+ T-cells with limited CD4+ T-cells (7%) and B-cells (1%); confirmed by CITE-seq. Dominant TCRαβ clonotypes that were unique to each patient were primarily expressed on scCITE-seq-defined activated (ICOS) CD8+ tissue-resident memory (CD103+) T-cells. Five distinct CD8+ T-cell populations were identified, with the dominant TCR for each patient highly expressed in populations 1 and 2, respectively defined by 1) highly cytotoxic (GNLY, GZMB, PRF1, CCL5, IFI27, LAG3, KLRC1, CD27, NKG7) and 2) remodelling/cell cycling (STMN1, TUBA1B, TUBB, H2AFZ, TYMS) transcriptomic signatures.

Conclusion:
The single-cell transcriptome and protein expression profiles of the dominant TCRαβ expressing cytotoxic resident (CD103+ CD8+) T-cells in the blister fluid of diverse patients with TMP-SMX associated SJS/TEN are remarkable for an expanded regulation (CD27, LAG3), T-cell homing (CCL5), antiviral (IFI27), and stress survival (KLRC1) signature. Identification of signatures of antigen-driven oligoclonal T-cells at the site of SJS/TEN tissue damage will help identify biological markers to aid earlier diagnosis and targeted therapy as well as confirm HLA-class I restriction and epitope specificity.

Abstract #12

Drug-specific Exosomes and their miRNA Contents in Patients Diagnosed with Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Exhibited Cytotoxicity Effects on Keratinocytes

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Background:
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are both life-threatening diseases; however, keratinocyte cell deaths are only prominent in SJS/TEN. It is known that exosomes, the small vesicles containing proteins, mRNAs, and microRNAs (miRNAs), could regulate immunological responses. This study aimed to investigate the cytopathic roles of exosomes and their miRNA contents on keratinocytes in SJS/TEN patients.

Method:
Peripheral blood mononuclear cells (PBMCs) from SJS/TEN were stimulated with the culprit drugs or irrelevant drugs. The exosomes were isolated from the supernatant and identified by transmission electron microscope, nanoparticle tracking analysis and Western blot assay. PBMCs from SJS/TEN patients were cultured with the culprit drugs (culprit-SJS) and the irrelevant control drugs (control-SJS), then exosomes in the culture media were extracted. The extracted exosomes were later co-incubated with HaCaT cells to study cytotoxicity effects. Exosomal miRNAs were comparatively isolated and sequenced from SJS/TEN and DRESS subjects.

Results:
The characterization of exosomes revealed a size range of 120 to 165 nm in diameter and expressed common exosome markers, including TSG101, CD63 and CD9. Cytotoxicity effects on HaCaT cells were greater when incubated with exosomes from culprit-SJS compared to those from control-SJS (19.69% vs 7.09%, P-value < 0.05). There were 2,565 miRNAs, approximately 21-22 nucleotides in length, identified from SJS/TEN and DRESS exosomal contents, and the majority were non-coding RNAs. There were significantly different 31 up-regulated and 30 down-regulated miRNAs between SJS/TEN and DRESS. The differentially expressed miRNAs were involved in the MAPK signaling pathway, RAS signaling pathway, cell cycle pathway, and apoptotic pathway.

Conclusion:
Exosomes released from PBMCs of culprit drug-specific SJS/TEN patients could kill keratinocytes and might be due to the different miRNA expression patterns between SJS/TEN and DRESS.

Abstract #13

Modified Technique for Mucous Membrane Grafting for Lid Margin Keratinization: Improving Exposure and Hemostasis

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Introduction:
Labial or buccal mucosal membrane grafting (MMG) has evolved as a technique for treatment of chronic Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) associated lid margin keratinization (LMK). This report demonstrates intraoperative use of a large, oval Desmarres chalazion forceps as an alternative to published methods for exposure, traction, and hemostasis of the everted posterior eyelid margin.

Methods:
This is a retrospective, observational case report of two pediatric patients with SJS/TEN-associated LMK who underwent MMG of all four eyelids utilizing a Desmarres chalazion forceps intraoperatively for surgical site exposure.

Main outcome measures were the extent of intraoperative bleeding or complications, immediate postoperative complications and patient comfort, and mucosal graft survival.

Results:
Intraoperatively, there were no complications and no significant operative site bleeding; no additional prolonged manual pressure, suction cannula, or electrocautery was necessary to achieve hemostasis and maintain visualization of the dissection bed. There were no postoperative complications of graft displacement or necrosis, lid malposition, or recurrent keratinization by postoperative month 3. Both patients remained comfortable throughout the postoperative period with no significant eyelid edema, ecchymosis or subconjunctival hematoma. Vision returned to baseline within 2 weeks postoperatively (after removal of bandage contact lenses).

Conclusions:
Intraoperative use of Desmarres chalazion forceps for surgical site exposure is a safe and effective technique for superior visualization, stabilization, and hemostasis of the posterior lid margin during dissection of keratinized epithelium and fixation of the mucosal graft.

Abstract #14

Severe Cutaneous Adverse Reactions in Medellin, Colombia

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Background:
Epidemiological studies, particularly on SCARs, come predominantly from the U.S., Europe, and Asia, where culprit drugs and genetic risk may differ significantly from Latin American countries. We described the epidemiology of SCARs from two tertiary-care hospitals in Medellin, Colombia.

Methods:
Cross-sectional study of cutaneous adverse drug reaction (CADR) inpatient consults from the dermatology service of CES University in Medellin, Colombia, from 2014-2019. We described the prevalence of the SCARs among the total number of CADRs. We described patients' demographics and potential causative drug(s) based on temporal correlation, eruption morphology, systemic involvement, and improvement on withdrawal and/or recurrence on rechallenge.

Results:
93 patients were diagnosed with a SCAR (19.7% of all CARDs). 13 with AGEP (14%), mean age 51.4 (SD 20.4), females 7 (53.9%). 63 with DiHS/DRESS (67.7%), mean age 42.9 (SD 19.1), females 33 (52.4), mean RegiSCAR 5.2 (SD 1.3). 7 with SJS (7.5%), mean age 53.6 (SD 20.9), females 5 (71.4). 10 with TEN (10.8%), mean age 46.3 (SD 20), females 7 (30%), mean initial SCORTEN 2.8 (SD 1.1), mean 48 hours SCORTEN 2.5 (SD 1). Mortality was 5.4% (1 AGEP, 2 SJS, 2 TEN). A culprit drug was identified in 79 patients (85%). Drug class and allergen (**Table 1)**.

Table 1. Potential causative drug class and allergen for the SCARs

Drug Class and Allergen	SCAR n (%)* AGEP 13 (14.0%)	DiHS/DRESS 63 (67.7%)	SJS 7 (7.5%)	TEN 10 (10.8%)
Antimicrobials — n (%)	**6 (46.2)**	**13 (20.1)**	**4 (57.4)**	**1 (10.0)**
Ampicillin/Sulbactam		2 (3.2)	2 (28.6)	
Azithromycin		2 (3.2)	1 (14.3)	
Cefazolin	1 (7.7)			
Cefepime		1 (1.6)		
Cefotaxime	1 (7.7)			
Ceftaroline		1 (1.6)		
Clindamycin		1 (1.6)		
Doripenem			1 (14.3)	
Nitrofurantoin		1 (1.6)		
Lincomycin	1 (7.7)			
Penicillin	1 (7.7)			
Piperacillin/tazobactam	1 (7.7)			
Sulfamethoxazole/Trimethoprim		2 (3.2)		1 (10.0)
Vancomycin	1 (7.7)	3 (4.8)		
Antiretrovirals — n (%)[†]		**9 (14.3)**	**1 (14.3)**	
Abacavir		2 (3.2)		
Efavirenz		1 (1.6)		
Nevirapine		1 (1.6)		
Antiparasitic		**3 (4.8)**		
Glucantime		1 (1.6)		
Ivermectin		1 (1.6)		
Sulfadoxine/Pyrimethamine		1 (1.6)		
Anticonvulsants — n (%)		**20 (31.7)**	**1(14.3)**	**4 (40.0)**
Carbamazepine		12 (19.0)		2 (20.0)
Lamotrigine		1 (1.6)		
Phenytoin		6 (9.5)	1 (14.3)	2 (20.0)
Valproic Acid		1 (1.6)		
Anti-TB — n (%)	**1 (7.7)**			
Isoniazid				
NSAIDs — n (%)	**1 (7.7)**	**4 (6.3)**		
Diclofenac		2 (3.2)		1 (10.0)
Dipyrone		1 (1.6)		
Ibuprofen		1 (1.6)		1 (10.0)
Meloxicam				
Nimesulide	1 (7.7)			
Others — n (%)				
Allopurinol		1 (1.6)		
Spironolactone	1 (7.7)			
Melatonin		1 (1.6)		
Sorafenib			1 (14.3)	
Sulfasalazine		3 (4.8)		1 (10.0)
Trimebutine				1 (10.0)
Unknown — n (%)	**4 (30.1)**	**9 (14.3)**		**1 (10.0)**

*Denominator used is patients with a SCAR seen by the CES University dermatology service from 2014-2019
[†]Antiretroviral allergen was not identified in 5 patients with DiHS/DRESS and 1 patient with SJS.

Conclusions:

We found a higher prevalence of SCARs (19.7% of all CARDs) compared to other studies where the majority of dermatology inpatient consults (>90%) correspond to mild maculopapular exanthemas. Anticonvulsants (26.9%) and antibiotics (25.8%) were the most common drug classes identified; however, other understudied drug classes such as antiparasitic and non-approved FDA NSAIDs were identified in this population. The majority of patients were females(56%) and the mean age was 45.3 (SD 19.5). Latin American countries, including Colombia, have critical factors that may contribute to significant differences in the epidemiology of SCARs, including unrestrictive access to medications and lack of access to specialized medical care.

Abstract #15

An Exploratory Study of the Efficacy of Blister Fluid as a Diagnostic Sample in Ex-vivo Approaches to Patients with Severe Cutaneous Adverse Reactions

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Background:
Severe cutaneous drug reactions (SCARs) are associated with significant morbidity and mortality. Traditional in-vivo testing such as patch testing and intradermal testing are limited by a lack of standardised approach and poor sensitivity. Modern approaches to testing including ex-vivo IFN-γ release enzyme linked immunospot (ELIspot) uses the patients peripheral blood mononuclear cells (PBMCs) or blister fluid cells (BFC) stimulated with the suspected drug. In an exploratory study we sought to find pathways to improve ex-vivo assay sensitivity in SCAR, examining the differences in ELIspot results using PBMCs compared to BFC.

Methods:
We identified four patients from previous ethically approved studies in Melbourne (VIC), with both PBMC and BFC stored that underwent ex-vivo testing as per previously published methods.

Results:
The implicated drugs were antibiotics (50%) and non-antibiotics (50%). The median latency period was 35.5 days (range 0-162). PBMC and BFC utilised were collected with a median of 15.5 (range 0-48) and 17 days (range 6-49) from date of reaction onset respectively. Two of the patients had positive PBMC and BFC (Case 1 and 4) while the other two had only positive BFC (Case 2 and 3). The cases that were positive on both PBMC and BFC were positive to identical drugs.

Conclusion:
As shown in our cohort, both PBMC and BFC ELIspots results were convergent, however with BFC having a higher sensitivity compared to PBMC for assay positivity. Although there may be difficulty in obtaining samples from blister fluid, future studies should examine the utility of BFC ex-vivo assays such as IFN-γ release ELIspot, due to potential higher sensitivity, whilst retaining correlation with peripheral blood results.

Abstract #16

Teledermatology in the Healthcare System: Utilization and Challenges

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Background:
Both the ease with which telemedicine can be integrated into a multitude of specialties and its flexibility as a means of providing care have led to a dramatic shift in healthcare service delivery in recent years. Over the last two decades, technological advancements have made telemedicine integral to healthcare in many countries. Teledermatology is the interactive practice of remote dermatological assessment, involving both live contact with patients ("live interactive") data access and retrieval ("store-and-forward"), or a combination of the two ("hybrid").

Methods:
A comprehensive literature review, including searching PubMed, Scopus, Embase, Web of Science, and Google Scholar, was performed. The role of teledermatology in medical education and both inpatient and primary care is discussed. Also examined are the status and limitations of teledermatology in Saudi Arabia and some proposed solutions. Institutional Board review (IRB) was not required to conduct this review.

Results:
The current literature reveals that teledermatology effectively serves as a form of triage, particularly for cases of suspected cutaneous malignancy, which requires the shortest referral time. Furthermore, earlier diagnoses, more effective management of chronic skin disease, and inpatient care are all additional benefits offered by teledermatology practice. It also appears that the use of teledermatology is now widespread, with roles extending beyond patient care to medical teaching and training in residency programs. However, patient perception in Saudi Arabia is still lagging and requires improvement, possibly due to information privacy concerns.

Conclusion:
Teledermatology can be used reliably used to advance healthcare services and medical education. Improving patient awareness and perception of this emerging discipline is crucial, and toward that end, patient uploads of photos and video should be stored on an end-to-end encrypted platform to provide optimal service and encourage patients' participation. Physicians should be well acquainted with the medical, ethical, and technical aspects of teledermatology.

Abstract #17

Exposure to Sulfadiazine Following the use of Antimicrobial-impregnated Central Venous Catheter - A Possible Aggravating Factor in Toxic Epidermal Necrolysis Induced by Sulfamethoxazole-Trimethoprim

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Background:
Highly suspected drugs for toxic epidermal necrolysis (TEN) include the anti-bacterial sulfonamides such as sulfamethoxazole-trimethoprim.

Case Report:
We present herein a 73-year-old man with a definite diagnosis of TEN based on clinical and histological parameters. The adverse reaction appeared following intake of sulfamethoxazole-trimethoprim, which was immediately discontinued. A multiple-lumen central venous catheter impregnated with chlorhexidine and silver sulfadiazine (ARROWgard Blue®) was inserted. Further deterioration of the patient's condition was observed, with progression of skin detachment (up to 65% of the body surface area), fever, leucocytosis, gram negative sepsis and impairment of renal function. The potential exposure to silver sulfadiazine released from the catheter to the blood was suspected as a possible aggravating factor. The catheter was replaced by another type, not containing silver sulfadiazine. The SCORTEN predicted a poor prognosis and the patient died 12 days after admission to the hospital.

Conclusion:
This case serves as an important reminder that catheters impregnated with silver sulfadiazine may aggravate the clinical course of patients with known hypersensitivity to silver sulfadiazine and/or sulfa drugs.

Abstract #18

Med Safe Clinic: A Novel Interdisciplinary Approach to Patients with Severe Cutaneous Adverse Reactions

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Background:
MED Safe is an innovative interdisciplinary clinic combining care from Allergy, Dermatology, and Clinical Pharmacology for patients with severe cutaneous adverse reactions (SCAR). Patients are referred to clarify the causative medications or to provide anticipatory guidance regarding safety of future medication exposure. We present two cases of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) to highlight our clinic's approach.

Cases:
Patient A is a 15-year-old healthy male of European descent who was admitted to hospital with SJS. Three weeks prior to symptom onset, he completed 10 days of cephalexin. He developed flu-like symptoms and began taking ibuprofen. He subsequently developed SJS requiring hospitalization. After all medications were stopped, his condition improved. Lymphocyte toxicity assay (LTA) implicated ibuprofen but not cephalexin, suggesting ibuprofen-induced SJS. Patient B is a 32-year-old healthy female of East Asian descent who developed SJS after atovaquone and proguanil was taken for malaria prophylaxis. LTA to both drugs was positive, as well as subsequent testing to doxycycline. She is currently pending LTA testing to other antimalarials to identify a safe alternative. Both patients received pharmacogenomic testing to a panel of 10 HLA genotypes to identify risk with other medication exposure. Both showed positivity to HLA-A and HLA-B alleles associated with developing SCAR to vancomycin and allopurinol and were advised to avoid these medications. In patient A, confirmatory LTA to Vancomycin was positive. LTA to allopurinol is pending.

Conclusions:
Patients who experience SCAR may have significant anxiety related to future medication exposures. Pharmacogenetic screening to a panel of HLA genotypes for patients with SCAR may help stratify future risk with other high-risk medication exposures. LTA can not only help delineate the culprit drug for SJS/TEN, but also confirm genotype-phenotype correlation. Our interdisciplinary care model can potentially optimize care for patients with SJS/TEN and potentially other SCAR.

Abstract #19

Stevens-Johnson Syndrome - Toxic Epidermal Necrolysis Overlap Syndrome Treated with Etanercept

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Background:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are regarded as T-cell mediated disorders. Infiltration of cytotoxic T-lymphocytes is observed in blister fluid and keratinocytes of involved skin lesions. These activated T-cells secrete large amounts of tumor necrosis factor-α (TNFα) and interferon-γ, resulting in Fas-mediated keratinocyte apoptosis. Etanercept, a humanized recombinant TNF receptor dimeric fusion protein, is a biologic that binds to TNF-alpha and TNF-beta to block the TNF activity, thus preventing the downstream apoptotic activity. In several recent reports, etanercept has been introduced as a potential treatment for SJS/TEN and has demonstrated reduction in mortality for SJS/TEN patients. Here we present a case of SJS-TEN overlap syndrome secondary to iohexol contrast successfully treated with etanercept.

Clinical History:

A 30-year-old female with past medical history of sarcoidosis presented three days after computed tomography (CT) scan of chest with iohexol contrast injection (Omnipaque). At presentation, the patient had an estimated 20-25% body surface area involvement and SCORTEN was calculated as 1. Frozen section exhibited a cell-poor subepidermal vesicular dermatitis with scattered necrotic keratinocytes consistent with early SJS-TEN overlap syndrome. Treatment was initiated with cyclosporine 5mg/kg/day divided over three doses per day. However, after three doses of cyclosporine, the patient was complaining of persistent skin pain and pruritus and areas of skin involvement appeared to be expanding. On day 3 of admission, etanercept 50mg was administered subcutaneously with rapid resolution of skin pain and pruritus. Cyclosporine was discontinued and patient did not develop any new skin involvement or cutaneous complications. Re-epithelialization was noted soon after administration of etanercept. Patient was discharged home on day 19 of admission.

Conclusions:

Etanercept is a promising potential therapeutic for the treatment of SJS/TEN and should be considered as adjuvant therapy in patients on cyclosporine with persistent symptoms.

Abstract #20

Stevens Johnson Syndrome Induced by the Combination of Phenobarbital and Sodium Valproate Drugs

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Background:

We report a case of Stevens Johnson syndrome (SJS) which occurred following the concomitant intake of phenobarbital and sodium valproate. The aim of this case is to report the experience of the dermatology department of rabat dealing with the adverse cutaneous effects of antiepileptic drugs and integrate this case into the database of the Moroccan pharmacovigilance center (CPV) in order to raise awareness against the over use of the epileptics drugs.

Case Report:

A 23-year-old patient, with a history of seizures for 1 year on phenobarbital 50 mg per day and sodium valproate 500 mg per day. He started his treatment only 1 month before his admission to the emergency room where he presented a generalized purpuric maculopapular eruption with targoid lesions on the trunk with a detached skin surface area <10% and cheilitis. We hospitalize the patient in a warm environment, and stopped all the medication. The skincare regimen include non-adherent dressings with petroleum jelly ointment on the skin erosions and labial mucosa with vitamin A eye ointment with Hyaluronic acid (HA) ophthalmic solution.

Results:

Blood tests used to investigate liver, thyroid or kidney function were normal. The skin biopsy confirmed the diagnostic of Stevens Johnson syndrome.The French Imputability method of causality assessment revealed the following scores for the 2 drugs: an imputability score of I3 (likely)/ chronological score C2, a semiological score S2 (plausible) and a

extrinsic accountability (Bibliography score) B4. The result of this analysis made it possible to confirm the etiological diagnosis and contraindicating these 2 drugs.

Conclusion:
The prescription of antiepileptics can induce severe lethal skin reactions. It is therefore necessary to re-evaluate the indications for some disease and assess the benefit-risk ratio before any prescription.

Abstract #21

Overlap Between Stevens-Johnson Syndrome (SJS) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) - Evaluation Of Drug Sensitivity by the Profile of in Vitro Drug-Induced Cytokine Release

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Background:
Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (SJS/TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are severe cutaneous adverse drug reactions (SCAR). Anticonvulsants are highly suspected drugs in both SJS/TEN and DRESS. SJS/TEN is characterized by a predominantly Th1 activation pattern or a mixed Th1/Th2 pattern. Major cytokines involved in SJS/TEN are TNFα and IFNγ. The immune responses in DRESS are polarized toward Th2 immune responses, and major cytokines involved are IL-4, IL-5, IL-13 and IFNγ. SJS/DRESS overlap, a rare SCAR, was diagnosed in a 51-year old male following the intake of topiramate (9 days); phenytoin (34 days); and valproic acid (19 months). Vigabatrin was introduced as a potential alternative drug. The study was aimed to identify the offending drug(s) by the profile of in vitro drug-induced cytokine release.

Methods:
Human peripheral blood mononuclear cells (PBMCs) were stimulated with 40 μg/ml PHA, with or without the drugs, or left un-stimulated. After 24-h incubation in 37 °C, 5% CO2, and 95% humidity, the supernatants were collected for cytokine measurement. TNFα and IFNγ were measured using commercial ELISA kits. Measurement of IFNγ, TNFα, IL-2, IL-8, IL-10, IL-13, IL-17A, RANTES, GM-CSF, MIF, and granzyme B was done by Multiplex Immunoassay.

Results:
Based on the latency periods topiramate and phentoin were the highly suspected drugs. Increased release of IFNγ, TNFα (major cytokines in SJS and/or DRESS) and of IL-8 (a minor cytokine in SJS), was observed towards topiramate. Phenytoin, valproic acid and vigabatrin induced increased release of IL-8, RANTES and MIF (minor cytokines in SJS and/or DRESS).

Conclusion:
The profile of cytokines released towards the drugs may imply topiramate as the inducer of SJS/DRESS overlap, and suggests the diagnostic role of drug-induced cytokine release in SCAR.

Abstract #22

Phone Application Utilizing Predictive Modeling to Provide Diagnostic Routes for Stevens Johnson Syndrome and Toxic Epidermal Necrosis. Preliminary Results

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Background:
Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN) lie on a spectrum as a life-threating, mucocutaneous disease that results in vast epidermal cell death, often as a result of medication exposure; it falls in the broader category of severe cutaneous adverse reaction (SCAR) which includes other entities such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and acute generalized exanthematous pustulosis (AGEP). Rapid diagnosis and discontinuation of the offending agent is critical to minimize morbidity and mortality for afflicted patients; however, diagnosis requires careful review of the rash timeline, including detailed medication intake history.

Methods:
A predictive model was developed via logistic regression by Weinkle et al. to act as an aide for clinicians as they separate SJS/TEN from mimicking diseases, and further validated by Kolitz et al.2,3 Based on this quantitative model, an initial build of a risk calculator application was developed for clinicians to use at the bedside to incorporate into their assessment. Three SJS/TEN rule-out cases were used by a dermatology resident to preliminary test the application.

Results:
One patient with SJS presented with fever, positive Nikolsky sign, atypical targets, and mucosal involvement within different regions and the predicted probability of SJS/TEN was calculated at 99%. Two patients, who had DRESS and AGEP, showed signs of fever and had a predicted probability at ~ 1%.

Conclusion:
Using this calculator, rapidity of diagnosis may be improved among residents, non-dermatology physicians, and dermatologists. The risk calculator is not intended to supplant physician judgement or act as a sole arbiter for diagnosis; it serves as a continuous measure that provides a quantitative summary of clinical features. Increased awareness of this tool will allow for prospective validation and ideally, increased utility to the medical community faced with triaging patients with SJS/TEN and mimicking entities.

Abstract #23

T-Cell Receptor (TCR) Sequencing of Drug-specific T-Cells Reveals Shared, Polymorphic, but not Restricted TCRβ Usage

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Background:
A formation of HLA/TCR/peptide/drug complex is a puzzling molecular interaction that is crucial for the initiation of drug hypersensitivity reactions. Only certain HLA class I and II molecules have the specificity to bind to drug antigen and present it to the TCR molecule. Meanwhile, the extent of TCR heterogeneity that could recognize the drug antigen is much less understood. Herein, we characterized and compared the TCRs of CD4+ and CD8+ drug-specific T-cell clones (TCCs) to determine a possible relationship between TCR property and drug responsiveness.

Methods:
T-cell cloning methods were used for generation of monoclonal drug-specific T-cells from 2 drug-naïve healthy donors and 5 hypersensitive patients (3 for carbamazepine and 2 for sulfamethoxazole). Drug responsiveness and cross-reactive properties were determined by analysis of proliferative responses. The obtained TCCs were characterized for their CD4/CD8 phenotype by flow cytometry. HLA restriction property was determined by anti-HLA blocking analyses and antigen-presenting cell mismatched analysis. TCR α/β sequencing libraries were generated from RNA of the TCCs (Takara Bio) and subsequently used for long-read sequencing analysis (Pacific Biosciences). Bioinformatic analysis was performed using MiXCR.

Results:
A total of 25 CD4+ and 1 CD8+ carbamazepine-specific TCCs and 7 CD4+ sulfamethoxazole- and nitroso-sulfamethoxazole-specific TCCs were generated, characterized, and used for the TCR sequencing. All TCCs showed at least 1 pair of productive TCR α/β chains. Preferential TCRβ usage was observed across TCCs and individuals via skewed CDR3 length distribution and preferential TRBJ usage. No characteristic was found to be linked with drug responsiveness, cross-reactive property, or HLA restriction property.

Conclusions:
Drug-specific TCRs are greatly polymorphic. TCRβ could be a possible marker of drug-mediated T-cell responsiveness.

Abstract #24

The Ocular Manifestations of SJS/TEN are Common and Universal Across a Diverse Demographic Spectrum

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Background:
Early identification of ophthalmologic presentations of SJS/TEN can minimize long term sequelae.[1] SJS/TEN is associated with known racial and sex disparities. In a recent retrospective analysis in a high-volume academic institution, we found demographic trends associated with elevated risk of mortality from SJS/TEN.[2] Here, we present an analysis of the incidence and evolution of the ocular manifestations of SJS/TEN within our demographically diverse cohort.

Methods:
A retrospective chart review was completed on 121 inpatients with dermatologist-confirmed SJS/TEN between January 2009 - October 2020.

Results:
In our sample, 68 patients were female, 14 were HIV positive, 26 White, 67 Black, 12 Asian, 7 Hispanic, 9 Other. 87% had ocular involvement upon initial examination. Common acute manifestations included conjunctival hyperemia (79%) and lid margin staining (35%). 48% of cases were acutely classified as mild and 30% as severe or very severe. The incidence and severity of ocular manifestations were stable across the demographic spectrum upon univariate analysis ($p>0.05$). Chronic sequelae were seen in 50% of patients with symblepharon being most common (41%). Serial evaluation revealed decreased vision in 30% and development of delayed ocular involvement in 33%. Ocular disease resolution was seen in 28%. The findings of delayed ocular involvement and ocular disease resolution were also stable across the demographic spectrum upon univariate analysis ($p>0.05$).

Conclusions:
We found a high incidence of ocular manifestations of SJS/TEN, which were ubiquitous across demographic groups in our large urban cohort. Delayed onset and chronic complications were also common. Therefore, serial eye examinations are warranted for all SJS/TEN patients in both the acute and recovery phase.

Abstract #25

Cases of SJS and TEN with Nivolumab and Nivolumab/Ipilimumab Combination Therapy in Metastatic Melanoma

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Background:
Nivolumab (anti PD-1 antibody) and ipilimumab (anti CTLA-4 antibody) are immune checkpoint inhibitors (ICI) that are approved for the treatment of metastatic melanoma. However, ICIs are associated with higher risk for cutaneous immune-related adverse events (irAEs).

Methods:
We report a fatal case of SJS associated with nivolumab and a non-fatal case of TEN with nivolumab/ipilimumab combination therapy in patients with metastatic melanoma.

Results:
The first case describes a 62-year-old man with stage 4 metastatic melanoma with brain metastasis who was directly transferred from an outside hospital for management of acute widespread rash 17 days after the last cycle of ipilimumab and nivolumab. The diagnosis of toxic epidermal necrolysis was supported by a biopsy of the right hand demonstrating full thickness necrosis and lichenoid interface dermatitis with frequent necrotic keratinocytes. The patient improved with antibiotics, intravenous immunoglobulin, and corticosteroids, and was discharged on hospital day 18. The second case reports an 81 year old man with metastatic melanoma on maintenance nivolumab therapy who presented with obstructive jaundice secondary to pancreatic adenocarcinoma. On day 4 of hospitalization, he developed scaly plaques on lower extremities that progressed to a superficial desquamation of the extremities hemorrhagic crusting of the lips. A biopsy showed cytotoxic and lichenoid drug eruption with eosinophils, consistent with Stevens Johnson Syndrome. Nivolumab was established as the causative agent since the recent dose was two weeks prior. The patient received methylprednisone and intravenous immunoglobulin which improved the rash, but his condition ultimately deteriorated due to renal failure and hypoxemic respiratory failure.

Conclusion:
It is not unusual to develop SJS or TEN after weeks or months on ICIs. Given the high rate for mortality, dermatologists and other clinicians should closely follow any rash from these immunotherapies due to the risk for future development of SJS or TEN.

Abstract #26

Characteristics of SJS/TEN in Patients Exposed to PD-1/PD-L1 Inhibitors: A Case Series and Review of the Literature

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Background:
Immune checkpoint inhibitors, including programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, have become mainstays of therapy for an increasing number of advanced malignancies. These drugs activate the adaptive immune system to target cancer cells, but immunomodulation also leads to a high rate of adverse effects, including frequent cutaneous toxicities. Most cutaneous eruptions associated with PD-1/PD-L1 inhibition are relatively mild, but a number of case reports have noted associations between PD-1/PD-L1 inhibition and life-threatening manifestations of Stevens-Johnson syndrome / toxic epidermal necrolysis (SJS/TEN). The rarity of severe reactions has thus far limited our ability to discern differences between the clinical course, optimal treatment, and underlying mechanism for SJS/TEN associated with PD-1/PD-L1 inhibition compared to more well-established causative agents.

Methods:
Here, we describe five cases of SJS/TEN associated with initiation of PD-1 inhibitor therapy at our institution. These cases are compared to similar presentations reported in the literature, and characteristics that may be suggestive of SJS/TEN induced by PD-1/PD-L1 inhibitors are explored.

Results:
Notably, in cases associated with PD-1/PD-L1 inhibitors, the time between initiation of the suspected causative drug

and development of SJS/TEN was significantly longer and more variable. In addition, the period between development of skin eruption and significant desquamation was also more variable in cases associated with PD-1/PD-L1 inhibitors.

Conclusions:

Severe cutaneous toxicities have been reported to occur in the setting of PD-1/PD-L1 inhibitor therapy. Our experience treating five patients with SJS/TEN in the setting of immune checkpoint inhibitor exposure, as well as a review of the limited number of cases of PD-1/PD-L1 inhibitor-induced SJS/TEN in the literature, suggest that these cases may be more slowly progressive that classic presentations of SJS/TEN. These findings raise questions about the role that immune checkpoint regulation plays in the pathogenesis of SJS/TEN.

Abstract #27

Human Leukocyte Antigens Associated with Ocular Sequelae Following Nsaid-induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

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Background:

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) induced by non-steroidal anti-inflammatory drugs (NSAIDs), may result in severe ocular complications (SOCs). The purpose of this study was to investigate the human leucocyte antigen (HLA) polymorphism pattern in NSAID-induced patients with SJS/TEN developing SOCs.

Methods:

Patients with SJS/TEN (n=33) and control patients (n=98) were enrolled at Chang Gung Memorial Hospital in Taiwan. SOCs were diagnosed (n=26) via a chart review or eye examination. Patient saliva was collected with commercialised kits and genotyped with PCR assays followed by hybridisation with sequence-specific oligonucleotide (SSO) probes (PCR-SSO) using commercial bead-based typing kits.

Results:

In all patients with SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was significantly higher than that in controls (OR=3.24, 95% CI=1.09 to 9.60, p=0.049), as was the genotype frequency (OR=3.89, 95% CI=1.49 to 10.16, p=0.007). In patients with NSAID-SJS/TEN with SOCs, the HLA-A*02:07 carrier frequency was higher than that in controls (OR=5.56, 95% CI=1.52 to 20.00, p=0.016), as was the allele frequency (OR=6.67, 95% CI=2.33 to 20.00, p=0.001). In patients with NSAID-SJS/TEN with SOCs, the HLA-B*46:01 allele frequency was significantly higher than that in controls (OR=3.85, 95% CI=1.52 to 10.00, p=0.008).

Conclusions:

The HLA-A*02:07 and HLA-B*46:01 alleles were significantly associated with SOCs among Han Chinese patients with NSAID-SJS/TEN.

Abstract #28

Photographic Documentation of the North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) Study

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Background:
Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) is a rare, potentially life-threatening disease. The percent of epidermal detachment expressed as the percentage of body surface area (BSA) involved has been a key metric driving SJS/TEN morbidity and mortality and has been used to monitor patient progress and response to treatment. Medical photography is useful to document initial %BSA and to track changes over time but is associated with significant variability affected by common factors such as room lighting and camera orientation.

Methods:
We developed a full-body photography protocol using 21 different body regions to improve consistency and reduce variability across different study personnel in preparation for a randomized double-blind treatment trial for SJS/TEN.

Results:
We present the results of our photography protocol that involved taking photos of 21 different regions of the body twice: with and without a camera flash and using a color standard to correct color variation due to room lighting. An iPad app was developed in partnership with SkinIO a skin imaging company, to facilitate consistent camera orientation and imaging accomplished by showing the outline of a previously imaged skin area.

Conclusion:
Our protocol presents an example of a validated approach to overcome inconsistencies in photographic documentation that will be tested in the North American Therapeutics in Epidermal Necrolysis Syndrome (NATIENS) Study: a randomized double-blind controlled trial to determine the mechanisms and optimal management of SJS/TEN. These approaches will also be applicable to other dermatological studies in the future.

Abstract #29

Associations of HLA-B Alleles in the HLA-B75 Serotype with Carbamazepine Induced-Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Background:
Carbamazepine (CBZ) is a common cause of severe cutaneous adverse drug reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in several countries, particularly in Asian countries.

Although genetic polymorphism of the human leukocyte antigen (HLA), HLA-B*15:02 allele, is well recognized key element for the susceptibility to CBZ-induced SJS/TEN, some patients who did not carry this allele were still at risk of CBZ-induced SJS/TEN. This study aimed to determine the associations between the several HLA-B alleles in the HLA-B75 serotype and CBZ-induced SJS/TEN in a well-defined Thai SJS/TEN patients.

Methods:
Eighty-eight CBZ-induced SJS/TEN Thai patients and 144 CBZ-tolerant patients were enrolled in the study. The HLA-B alleles were genotyped by using the polymerase chain reaction-sequence-specific oligonucleotide probes (PCR-SSO) method.

Results:
Three HLA-B alleles in HLA-B75 serotype including HLA-B*15:02, HLA-B*15:11 and HLA-B*15:21 were identified in the study population. The HLA-B*15:02 was the most common allele and its association with SJS/TEN caused by CBZ was the strongest association (OR = 44.33, 95% CI = 20.24 - 97.09, Pc = 6.80 x 10-29). By combining all three alleles in the HLA-B75 serotype, the risk of CBZ-induced SJS/TEN was increase to 81.00 (95% CI =32.39 - 202.56, Pc = 3.84 x 10-34). The results from ROC curves for single and multiplex HLA-B genetic testing in CBZ-induced SJS/TEN showed that the total AUC for the proposed three-allele test (HLA-B75 serotype) was significantly higher than for the single HLA-B*15:02 allele testing.

Conclusions:
Not only the HLA-B*15:02 allele, other alleles in the HLA-B75 serotype are also significantly related with CBZ-induced SJS/TEN. Thus, multiplex genetic testing of HLA-B alleles in the HLA-B75 serotype will help to increase the sensitivity for predicting patients who may at risk of CBZ-induced SJS/TEN.

Abstract #30

Perspectives on Long-Term Health Needs Relating to Severe Cutaneous Adverse Drug Reactions (SCARs) in Nigeria

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Background:
Adverse drug reactions (ADRs) are deleterious responses resulting from the use of medicinal products. Severe cutaneous adverse drug reactions (SCARs), such as Steven Johnson's Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) which are one of the various manifestations of ADRs are idiosyncratic immune complex mediated hypersensitivity reactions causing sloughing of the skin and mucous membrane; they account for about 10-70% mortality and morbidity rates globally. SCARs are associated with significant physical and psychological sequelae hence long-term care is required. The study explores the perspectives of different stakeholders (including survivors, caregivers, healthcare providers, and staff of the national pharmacovigilance center) on the long term health needs relating to SCARs in Nigeria. There is scarcity of qualitative data on this subject both at global and national levels therefore qualitative data will provide insight into, and highlight the needs relating to SCARs.

Methods:
Using a combination of purposive, opportunistic and snowball sampling methods, the study employs a qualitative approach (interpretive approach), involving individual semi-structured interview to explore the perspectives of key stakeholders in Nigeria. Interview data was coded and thematic analysis was carried out using atlas.ti software.

Results:

Medical care, psychosocial, physical, and financial support were identified as long-term needs. Finance, lack of healthcare specialists, lack of awareness, lack of medical infrastructure, and absence of a community on SCARs in Nigeria, were seen as barriers to accessing long-term needs. Healthcare providers such as doctors and pharmacists, personal research online, international online SCARs support communities, and personal networks, were found to be the major sources of information. SCARs data were found to be collected primarily from healthcare providers.

Conclusion:
Continued support is important to improve the quality of life of SCARs. Adequate information, data management and follow up helps to provide awareness on SCARs and prevent their reoccurrence.

Abstract #31

Understanding Postmarket Pharmacovigilance of Severe Cutaneous Adverse Reactions

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Background:
FDA-approved Prescribing Information (USPI) provides healthcare providers up-to-date, evidenced-based information allowing safe and effective use of the drug for its intended use. Rare adverse reactions (AR), such as Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), are typically not identified prior to product approval and become known once the drug is more broadly used. FDA routinely surveilles cases reported to the FDA Adverse Event Reporting System (FAERS) and medical literature to identify new safety concerns. This study evaluates the latency between the first report for SJS/TEN in FAERS and the medical literature to the inclusion of SJS/TEN in the USPI.

Methods:
We used FDALabel to identify drugs and therapeutic biologic products with USPIs with SJS/TEN that were approved on or after January 1, 2016 to September 30, 2020. For each USPI that did not include SJS/TEN at approval, FAERS and the medical literature was searched to identify the earliest published date and earliest FAERS date for a case describing SJS/TEN attributed to the product. For each product, latency was calculated as time in months (days/30) between "date of inclusion" and "first published date," and time between "date of inclusion" and "first FAERS case date".

Results:
Six USPIs were identified. Mean latency from FAERS case to date SJS/TEN USPI inclusion was 19 months (range: 4 to 26 months prior to labeling). Mean latency from literature case to date SJS/TEN USPI inclusion was 8 months (range: 25 months prior to and 3 months after labeling).

Conclusions:
Latency from first FAERS/literature case to SJS/TEN USPI inclusion is variable. This evaluation is limited by small sample size and absence of comparator data. Further characterization of the underlying cases, therapeutic area, and other possible contributing factors are planned to better understand the latency and prominence of SJS/TEN in the USPI.

Abstract #32

Carbamazepine-induced Toxic Epidermal Necrolysis: The Importance of HLA-B*1502 Testing in at-risk Populations Prior to Therapy Initiation

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Case:

A 31-year-old Han Chinese woman with a 3-month history of seizures was started on oral lacosamide and carbamazepine. The patient was not tested for HLA-B*1502 despite her ethnic background. The patient re-presented several days later with fever and progressive new-onset rash and was transferred to our Burn ICU for possible toxic epidermal necrolysis (TEN). Upon presentation, the patient had dusky macules coalescing into patches with overlying bullae covering >70% body surface area, a positive Nikolsky's sign, and substantial mucosal involvement. A skin biopsy obtained from her chest was consistent with SJS/TEN.

Despite treatment with high-dose IVIG, the rash progressed, and the patient developed high-grade fevers, lactic acidosis, and abdominal distention. Imaging demonstrated intraabdominal air and laparotomy revealed diffuse, non-viable small and large bowel. Comfort care was initiated, and the patient expired shortly thereafter. During hospitalization, the patient's HLA-B*1502 status Returned positive.

Discussion:

SJS/TEN is a known complication of carbamazepine therapy, particularly in those of East Asian descent possessing the HLA-B*1502 allele.1 In many Asian countries, government health organizations have instituted recommendations for HLA testing before initiating carbamazepine therapy which has reduced the annual incidence of carbamazepine-induced SJS/TEN by about ninety percent. 4,5 Given the severity of carbamazepine-induced SJS/TEN, clinicians should consider alternative antiepileptic therapies or await relevant HLA test results prior to carbamazepine initiation in patients who may be genetically susceptible. Let our case serve as a potent reminder that, prior to carbamazepine initiation, HLA testing is necessary in patients from at-risk populations to reduce the incidence and morbidity/mortality of SJS/TEN.

Abstract #33

Reassuringly Rare: Stevens-Johnson Syndrome After Covid-19 Vaccine Administration

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Introduction:

A range of cutaneous reactions have been documented after administration of mRNA-based COVID-19 vaccines. From December 24, 2020 to July 15, 2021, the American Academy of Dermatology and International League of Dermatological Societies (AAD/ILDS) COVID-19 Dermatology registry has recorded 849 cases of skin reactions after COVID-19 vaccination.

Cases of SJS following any vaccine administration are rarely reported. Studies of SJS after varicella zoster, MMR, and influenza vaccination have been noted, but a positive causal relationship between vaccinations and SJS has not been established.

Methods:
This case of SJS reported after COVID-19 vaccination was entered into the AAD and ILDS COVID-19 Dermatology Registry and was diagnosed clinically due to the patient's refusal of a skin biopsy. All other differentials were excluded by a trained SJS/TEN center (Ludwig Maximilian University Hospital Munich).

Results:
The patient is a 32-year-old white male with diabetes, cardiovascular disease, and fragile-X syndrome. He received the Pfizer/BioNTech vaccine and developed the cutaneous reaction seven days after his first dose. The patient was not taking any medications at the time and the only potential trigger was the vaccine. He presented with diffuse erythema, blisters, detached epidermis (<10% BSA) and systemic symptoms including fever, chills, and headache clinically diagnostic of SJS. The second dose was held due to the patient's reaction.

Conclusion:
The COVID-19 Dermatology registry recorded one case of SJS after COVID-19 vaccination to date. Since the registry lacks a denominator, we are unable to calculate incidence of SJS/TEN from the registry. However, it is reassuring that only a single case has been reported, which suggests that if any association does exist, it is rare. Healthcare workers should continue to encourage vaccination and counsel patients on the benefits of COVID-19 vaccination. Further population-level studies would be required to determine if an association between COVID-19 vaccination and SJS exists.

Abstract #34

Evaluating Etanercept in the Management of SJS and SJS-TEN Patients

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Background:
Steven-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN) is a severe condition involving skin necrosis and mucosal erosions for which there is no standardized evidence-based therapy. Supportive care is the mainstay of management followed by other treatments including systemic corticosteroids, immunoglobulins (IVIG), and cyclosporine. The overall mortality rate ranges from 10% for SJS to over 30% for TEN. The goal of our study was to retrospectively evaluate SJS and SJS-TEN overlap patients treated with etanercept monotherapy vs. alternative therapies at our institution.

Methods:
A retrospective case series of 24 patients with SJS and SJS-TEN admitted to a single institution was performed. Patients were grouped depending on etanercept monotherapy (n=8) and alternative therapies (n=16). The clinical severity of the disease for each patient was determined using SCORTEN. Standardized mortality ratios (SMR) were calculated, and Kaplan-Meier survival curves for length of hospital stay for each treatment group were calculated and compared using Wilcoxon and log-rank non-parametric tests.

Results:
For all patients, the SMR for etanercept was 0.00 (CI 95% = 0.0,0.0) vs. 0.56 (CI 95% = 0.07, 2.03) for alternative therapies. Among SJS patients, the SMR for etanercept was 0.00 (CI 95% = 0.0,0.0) vs. 0.63 (CI 95% = 0.08, 2.28) for alternative therapies. Duration of hospital stay in SJS and SJS-TEN overlap patients differed significantly between the two groups (P=0.0427 by Log-rank and P=0.0365 by Wilcoxon). The duration of hospital stay in SJS-only patients did not reach statistical significance (P = 0.0614 by Log-rank test and P=0.641 by Wilcoxon test).

Conclusions:

These preliminary results suggest the possibility that etanercept may be used in SJS patients to reduce mortality and duration of hospitalization. Limitations of our study include a small sample size, retrospective study design, lack of randomization and single center experience.

Abstract #35

Bullous Pemphigoid Secondary to Saxagliptin Mimicking Toxic Epidermal Necrolysis

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Case Report:

Gliptin-associated bullous pemphigoid (BP) is increasingly well-described in the literature. We report a case of BP secondary to saxagliptin mimicking toxic epidermal necrolysis (TEN). A 72-year-old man presented with a rapid onset of erythrodermic macular erythema involving 90% of his body surface area (BSA) and desquamation of 70% of BSA. He was on saxagliptin for over three years for type 2 diabetes mellitus. Nikolsky sign was positive. Initial histopathology showed full thickness epidermal necrosis and direct immunofluorescence (DIF) was negative. However, 10 days after his initial presentation, his blood for skin anti-basement membrane antibody returned 1:640 and ELISA was positive for anti-BP180. Repeat DIF showed weak linear staining of IgG and C3 at the basement membrane. Given the clinical features, pathology results and history of gliptin use, the patient was diagnosed with TEN-like BP. Prednisolone 0.5mg/kg/day and mycophenolate mofetil 500mg twice daily were commenced, and the erosions improved within two weeks. No new blisters emerged, and erythema improved within two months. TEN-like presentations of autoimmune bullous disease and lupus erythematous are well-described. This case highlights the importance of considering BP, especially in patients on gliptins, as a differential for TEN-like desquamation, and combining clinical examination and pathological tests, including ANA and anti-skin antibodies, to optimise diagnostic accuracy.

Abstract #36

Frozen and Fixed Section Analysis in Diagnosis of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

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Background:

Emergent frozen sections are sometimes used to evaluate patients for Stevens Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) because they can provide a more timely tissue assessment than their fixed section counterparts. However, few studies assess the utility of frozen sections for this particular indication.

Methods:

We conducted a retrospective review of our inpatient database to identify patients (n = 39) who received frozen sections (n= 41) specifically for the evaluation of SJS/TEN. All patients also received fixed section tissue analysis. We coded frozen section pathology reads and fixed section pathology reads as not suggestive of SJS/TEN, equivocal, or suggestive of SJS/TEN.

Results:
When using the final diagnosis rendered by the last inpatient dermatology note to determine whether SJS/TEN was present or absent in each patient, frozen sections had a sensitivity of 52% (95% confidence interval (CI) 33-71%), specificity of 89% (95% CI 52-100%), negative predictive value of 36% (95% CI 27-47%), and positive predictive value of 94% (95% CI 70-99%) and fixed sections had a sensitivity of 77% (95% CI 61-88%), specificity of 75% (95% CI 48-93%), negative predictive value of 55% (95% CI 39-69%), and positive predictive value of 89% (95% CI 78-95%).

Conclusions:
Our data suggests that while frozen sections are likely poor screening tests for SJS/TEN, a positive result (suggestive of SJS/TEN) implies a high likelihood of SJS/TEN. Our data also highlights the limitations of both frozen and fixed sections in diagnosing SJS/TEN and underscores that diagnosis of SJS/TEN must consider both clinical and histopathological impressions.

Abstract #37

The Role of Non-Esterified Fatty Acids (NEFA) in the Pathogenesis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

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Background:
Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) are classified as Severe Cutaneous Adverse Reactions (SCARs). These are life- threatening immune-mediated hypersensitivity drug reactions affecting the skin and mucous membranes resulting in significant ocular inflammation that may lead to ocular blindness requiring amniotic membrane transplantation and corneal transplantations. There could be wide-spread cutaneous necrosis resulting in sloughing of the skin. The causes of death may include infections, sepsis and multiorgan failure. Non-esterified fatty acids (NEFAs) have been shown in animal models to induce overactivation of inflammatory cytokine production through the nuclear factor kappa beta (NF-κB) pathway. Furthermore, human studies have shown free fatty acids and lactate uptake in the human heart during severe sepsis. This study highlights the role of non-esterified fatty acids in the pathogenesis of SJS/TEN.

Methods:
Under an Institutional Review Board approved protocol, de-identified and discarded blood samples from patients with biopsy confirmed SJS/TEN patients were collected from the core labs at Loyola University Medical Center. The blood collected in Ethylene diamino tetra acetic acid (EDTA) were centrifuged at 3000 rpm for 20 minutes to obtain platelet poor plasma. The plasma samples were aliquoted, labeled and frozen at -70ºC until the analysis. The plasma samples were then thawed and used for the colorimetric measurement of NEFAs using the NEFA-HR (2) kit purchased from Fujifilm Wako Diagnostics. After following the manufacturer's recommended Standard Operating Procedure, NEFA concentrations were interpolated by plugging absorbances into the linear standard curve obtained. This yielded the final NEFA concentration present in each plasma sample. The results were tabulated and statistically analyzed. NEFA analysis was also performed on a set of normal human plasma (NHP) samples as controls. The NHP samples were commercially obtained from George King Biomedical Inc.

Results:
The NEFA concentrations on plasma samples from SJS/TEN patients (n=15) and NHP as controls (n=26) were statistically analyzed to test if there was a statistically significant difference between the means of the two populations, using the Mann-Whitney Test. The patient samples had a higher NEFA concentration (mean=1.01 mEq/L, SEM=0.128) when compared to the NHP samples (mean=0.626 mEq/L, SEM=0.0665). The patient samples showed a significant increase of 61.5% higher NEFA concentrations compared to the NHP controls. There was a statistically significant difference between the SJS patient samples when compared to NHP controls (p= 0.0095).

Conclusions:
A statistically significant increased levels of NEFA concentrations in plasma samples from patients when compared to the NHP controls shows that NEFA plays a role in the pathogenesis of SJS/TEN. Further studies are warranted to investigate the significance of NEFA in severity of disease progression and development of multiorgan failure and sepsis in patients with SJS/TEN.

Abstract #38

Single-cell Studies of Lamotrigine-associated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Identify Dominant TCR Clonotype-expressing CD8+ T-cells with Unique Gene and Protein Expression Profiles

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Background:
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe cutaneous reaction that is typically drug-induced and associated with epidermal necrosis and high morbidity and mortality. HLA-class I restricted CD8+ T-cells expressing dominant T-cell receptor(s) reactive to a specific drug/metabolite are thought to be the drivers of tissue damage, however their molecular and cellular signatures that could have high utility in prevention, earlier diagnosis, and treatment have not been defined.

Methods:
To define the dominant TCR and unbiased single-cell transcriptome and protein expression at the site of SJS/TEN tissue damage, single-cell suspensions were created from thawed cryopreserved blister fluid cells and affected and unaffected skin digested through a standardized collagenase-P method from a lamotrigine SJS/TEN patient. These paired samples were analyzed by 10X 5'-sc-RNA-TCR-CITE-seq. For the Cite-seq assay, suspensions were stained with a panel of 137 DNA-sequence tagged antibodies (Totalseq-CTM, Biolegend). Raw data was normalized using CellRanger, clustered using Seurat, and analyzed using Visual genomics analysis studio (VGAS).

Results:
Expression of three dominant TCR clonotypes were identified from cytotoxic CD8+ T-cells across affected skin and blister fluid. Six CD8+ T cell populations were identified with the dominant TCR located on two surface-activated (ICOS, CD27) clusters. These CD8+ T cells were absent from unaffected skin and distinguished by proliferation/cell-

cycling (TUBA1B, STMN1, TUBB, MKI67, MCM7) and cytotoxic/chemotactic (GNLY, CCL5, CST7, CD27, GZMA) signatures. Differential skin-blister fluid analysis of dominant TCR-expressing CD8+ T-cells identified that blister fluid expressed significantly higher PRF1, KLRD1, CCL3-4, CCL4L2, IFI6 and LAG3.

Conclusions:
Dominant TCR clonotypes are expressed by CD8+ T cells in the blister fluid and affected skin of lamotrigine-SJS/TEN that are defined by cytotoxic and chemotactic signatures that are particularly enriched in the blister fluid. Identifying single-cell molecular and cellular signals helps define SJS/TEN immunopathogenesis paving a pathway for identification of diagnostic markers and targeted therapies.

Abstract #39

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in the FDA Adverse Event Reporting System (FAERS)

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Background:
Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are one disease across a spectrum of severity that is associated with significant morbidity and mortality. Knowledge of the distribution of commonly associated drugs and changes over time has been lacking.

Methods:
The publicly available FDA adverse event reporting system (FAERS) database was reviewed from Jan 1st, 1995 to Dec 31st, 2020. Reports that contained the term "SJS", TEN, or "SJS-TEN Overlap" were sorted by generic drug names, number and sex of cases, median age of cases, and reported deaths.

Results:
Overall, 30202 (0.15%) of 20,406,852 adverse drug events reported in FAERS were reported as "SJS", "SJS/TEN", or "TEN". The median reported age was 51 years with a distribution of 57% female and 43% male of 27,500 (91.1%) reports with sex information. Over time the top 5 drugs associated with SJS/TEN included lamotrigine, phenytoin, sulfamethoxazole-trimethoprim, allopurinol, and acetaminophen that accounted for 10,124 (33.5%) of reported cases and 34.5% of reported deaths. Acetaminophen although a potential cause of SJS/TEN has been more commonly protopathically implicated. More females than males were affected by lamotrigine SJS/TEN (67%). Reports of death were highest with allopurinol SJS/TEN (690/2158 (32.0%)). Increasing reports of SJS/TEN for all drugs except phenytoin were observed over time. New drugs showing an increasing trend over the last 5 years included the immune checkpoint inhibitors nivolumab and pembrolizumab which accounted for 1.1% and 2.4% of reports of SJS/TEN and death respectively.

Conclusions:
Over a period of 15 years of FAERS reports, the same drugs account for a high proportion of SJS/TEN cases and deaths. Allopurinol is associated with the highest mortality, and all but phenytoin continued to increase over time. Newly described causes of SJS/TEN such as cancer immunotherapy have been more prevalently reported over the last 5 years.

Abstract #40

Trends in Incidence and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in The United States: A 10 Year National Analysis

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Background:

We used the National Inpatient Sample to analyze incidence and mortality of Stevens-Johnson Syndrome, (SJS), Toxic Epidermal Necrolysis Overlap (TEN) and SJS/TEN Overlap (SJS/TEN) in the United States from 2009-2018.

Methods:

ICD-9 and ICD-10 codes were used to select patients aged > 18 years with a diagnosis of SJS, SJS/TEN, or TEN from 2009-2018. Poisson and logistic regressions were used to determine changes in incidence and mortality rates, respectively. Subgroup analysis was performed for age, sex, and race.

Results:

The incidence of SJS was 12.5 cases per million adults annually and decreased by 0.6% annually (95% CI -1.0, -0.2). The incidence of SJS/TEN was 2.6 cases per million adults annually and increased non-significantly by 0.3% annually (95% CI -0.6, 1.1). The incidence of TEN was 2.5 cases per million adults annually and decreased by 3.2% annually (95% CI -4.0, -2.3). In black patients, the combined incidence of SJS, SJS/TEN, and TEN increased by 0.8% per year (95% CI 0.1, 1.5). Patients 65 years or older, male, or white had a significant decrease in the incidence of SJS, SJS/TEN, and TEN ($p < 0.001$). The mortality rate of SJS or TEN did not significantly change ($p > 0.05$), but the mortality rate of SJS/TEN decreased (OR = 0.94, 95% CI 0.89, 0.99). In patients with SJS, mortality increased in black patients (OR = 1.107, 1.013, 1.21) and decreased in patients age 18-24 years (OR = 0.473, 95% CI 0.414, 0.541).

Conclusion:

The combined incidence of SJS, SJS/TEN, and TEN decreased without a significant change in mortality. Black patients saw an increase in combined disease incidence and an increased mortality in SJS.

Abstract #41

Management of Acute-phase SJS

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Purpose:
To evaluate the prognosis of systemic and topical steroid treatment of acute-phase Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

Methods:
We retrospectively analyzed the details of the acute-phase management and prognosis of 20 eyes of 10 SJS/TEN cases with ocular involvement [3 males/7 females; mean age 38.2±24.0 (6-78) years] that were started on steroid pulse therapy and topical steroid treatment within 4 days post disease onset.

Results:
Steroid pulse therapy was started at 2.1±1.2 days post onset, and in 3 cases, immunoglobulin therapy was combined. Systemic steroid administration was tapered off after the steroid pulse therapy, and the total dose was 648±288mg of prednisone equivalent. In all cases, topical betamethasone was started at 2.4±1.5 days post onset; mean frequency of use (times/day): 9.4±4.1 (eye drops)/1.8±1.8 (ointments) at start, and increased to 11.4±3.6 (eye drops)/2.0±1.7 (ointments) at the acute phase. There were 7 cases of superficial punctate keratopathy, 2 cases of trichiasis, 1 case of corneal opacity, and 1 case of eyelid/ball adhesion, yet no serious ocular sequelae (limbal stem cell deficiency/keratinization) occurred. No steroid-related systemic adverse events (e.g., sepsis) occurred, yet ocular-surface commensal bacteria was detected in 4 patients (6 eyes) and an intraocular pressure of over 21mmHg was detected in 3 patients (4 eyes) that did not lead to infection/glaucoma.

Conclusions:
Intensive use of topical and systemic steroid at the acute phase of SJS/TEN is key to avoiding chronic ocular sequelae.

Abstract #42

Vision-related Quality of Life in Patients with Stevens-Johnson Syndrome with Ocular Complications who Received Protocol-Based Management in the Acute Phase

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Background:
To report the vision-related quality of life (VF-QOL) using the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).and the ocular surface disease index (OSDI) in the chronic phase of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) who presented with ocular involvement and received protocol-based management in the acute phase.

Methods:
NEI-VFQ-25 questionnaire was administered to 15 patients who received protocol-based care in the form of topical medications with or without amniotic membrane transplantation (AMT) for acute SJS/TEN. The scores obtained were compared with scores from a healthy population. The associations between the NEI-VFQ-25 and dry eye symptoms measured by OSDI questionnaire were also studied.

Results:
Patients were surveyed at a mean follow-up period of 4.47 ± 2.22 years after acute SJS/TEN. Eleven patients received AMT in the acute phase. The median best corrected visual acuity at the time of administration of the questionnaire was 20/20. The mean composite NEI-VFQ-25 score was 86.48 ± 12. Patients who received protocol-based treatment in the acute phase of SJS/TEN had comparable NEI-VFQ-25 scores with healthy subjects on all subscales except

ocular pain (p=0.027) and mental health (p=0.014) which were significantly reduced. The NEI-VFQ-25 composite scores significantly correlated with OSDI (R = −0.75, p=0.001).

Conclusions:

A protocol-based management comprising early ophthalmic evaluation, grading based on severity, the use of topical steroids and AMT in the acute phase of SJS/TEN in patients with ocular complications helped preserve the VF-QOL. This study highlights the impact of appropriate management of the ocular complications in the acute phase of SJS/TEN.

Abstract #43

Serious cutaneous adverse reaction related labeling changes: An evaluation of supporting evidence and labeling features

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Background:

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are serious, rare, and life-threatening dermatologic adverse reactions that are rarely detected in pre-market drug development programs. The lack of diagnostic testing, terminology changes over time, and infrequent occurrence can create challenges for consistent management of SJS/TEN postmarket safety signals. Understanding the evidence and other factors associated with safety-related labeling changes (SrLCs) may provide information to enhance current postmarketing pharmacovigilance practices. Therefore, our goal is to characterize the evidence supporting SJS/TEN SrLCs and language used to convey the risk in the Prescribing Information (PI).

Methods:

FDALabel and FDA's SrLC database were utilized to identify all approved drug and therapeutic biological products in which SJS/TEN terms were added to the labeling between January 1, 2016 and December 31, 2020. Attributes of each SrLC were collected for analysis including the labeling section modified and terminology utilized. Two reviewers retrospectively reviewed FDA's internal document repositories to identify the initiator of the SrLC (i.e., applicant or FDA) and evidence source supporting each SrLC.

Results:

In the study period, 63 products (57 drugs, 6 biologics) had an SJS/TEN related SrLC. New additions to the Adverse Reaction (AR) section alone (n=19, 30%), elevations from AR to Warnings and Precautions (WP) (n=16, 25%), and new additions to both the AR and WP (n=14, 22%) were the most common labeling changes. Most PI included both SJS and TEN terminology (n=50,79%). Of the 46 labels that included SJS/TEN in the WP, 25 different section titles were used. More SrLCs were applicant initiated than FDA initiated (63% vs 27%). The applicant's safety database (n=21, 33%), medical literature (n=11, 17%), foreign regulatory agencies (n=10, 16%), and spontaneous reports (n=9, 14%) were the most frequent sources triggering the SrLC.

Conclusion:

Case reports serve as the primary data source for postmarket SJS/TEN SrLCs. While variation in SrLCs for a particular risk is not unexpected given the context of each change may be unique (e.g., magnitude of risk, evidence quality, therapeutic area), the variability observed in SJS/TEN SrLCs provides an opportunity to further evaluate factors influencing safety labeling decisions.