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Research Directions in Genetically-Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)
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Executive Summary

Recognizing recent breakthroughs in identifying genetic causes of SJS/TEN and the relative dearth of U.S. funded research in this area, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) sponsored a workshop on research directions in genetically-mediated SJS/TEN. The primary meeting objectives were to: 1) review the current state of knowledge of surveillance, pathogenesis, and treatment of SJS/TEN; 2) examine the role of genomics and pharmacogenomics in etiology, treatment, and eradication of preventable causes of drug-induced SJS/TEN; and 3) identify gaps, unmet needs, and priorities for future research to eliminate genetically mediated SJS/TEN globally.

State of the Science Highlights

- Our understanding of science of SJS/TEN has evolved greatly over the last 10 years
  - Improved diagnostic criteria
  - New mechanistic theories of how HLA and T-cell receptors (TCR) impact drug hypersensitivity
  - Identification of specific genetic risk factors for specific drugs, including human leukocyte antigen (HLA) risk alleles for carbamazepine (HLA-B*1502) and allopurinol (HLA-B*5801)
- Some SJS/TEN risk alleles are population specific, others more generalizable across populations
- Detection of an HLA risk allele can support diagnosis and prevention and suggest the offending drug
- Studies of risk allele carriers who do not have an adverse drug reaction (ADR) will be informative
- Granulysin and TCR profiles are potential areas for research on diagnostic biomarkers
- Key challenges and unmet needs include: defining the phenotype, improving pharmacosurveillance, acquiring appropriate tissue-specific samples, understanding immunopathogenesis, improving management, and building a translational roadmap for prediction and prevention
- HLA types are associated with multiple outcomes, so including them in electronic medical records (EMRs) could facilitate research and clinical implementation for SJS/TEN and other diseases
- We need effective approaches to improve health care provider education and awareness of SJS/TEN

International Experiences Highlights

- The RegiSCAR project, the International Serious Adverse Event Consortium (iSAEC) and the Canadian Pharmacogenomics Network for Drug Safety are examples of scientific networks that have provided insight into etiology and mechanisms of SJS/TEN
- Pharmacogenomic screening has been implemented in Taiwan, Thailand and Singapore; in all three countries rates of SJS/TEN then decreased, although causal inference is limited by small case numbers and other temporal trends, including changes in drug prescription patterns
- HLA risk alleles are at appreciable frequencies in Indonesia, additional research is merited
- ADR surveillance programs at U.S. institutions could provide infrastructure for research

Challenges in Case Findings and Surveillance Highlights

- More targeted active (or even mandated) reporting and case follow-up could improve surveillance
- SJS/TEN is rare, making prospective data collection challenging; SJS/TEN is also poorly captured by administrative codes, which is a challenge for retrospective studies
- Electronic Medical Record (EMR) phenotyping may facilitate case identification and implementation
- Key data, including biopsies and images, are often in PDFs and difficult to access with e-algorithms
- Patients often take multiple drugs concurrently, making it difficult to identify the causal drug

Special Topics Highlights

- The FDA has proactively incorporated genomic risk factors for SAE in labeling; however challenges exist in interpreting evidence, communicating risks, and formulating testing recommendations
- Functional data are invaluable for attributing causation to a genetic association in the HLA region
- The Drug-Induced Liver Injury Network (DILIN) provides a model for coordinated research on ADRs
- Evidence from Asian countries indicates that HLA testing to prevent SJS/TEN is a good economic value; additional research is needed in specific patient populations in the US and other regions

Working Group 1: Basic Research Opportunities

- Identify biomarkers in acute phase of disease to improve diagnosis, prognosis and treatment
- Identify new predictive markers in addition to HLAs, both genetic and metabolomics
- Improve chemiinformatics of drug culprits and develop small molecule assays

Working Group 2: Clinical Implementation Opportunities

- Develop low-cost pharmacogenomics assay for implementation in state/national health programs
- Expand beyond one gene-one drug models in research to multi-gene panels or genomic sequencing
- Consider universal HLA typing and linking to EMR for association with multiple health outcomes

Working Group 3: Pharmacosurveillance Opportunities

- Improve case ascertainment, including development of a standardized case definition
- Improve understanding of factors associated with disease progression and long-term outcomes
- Address challenges with current screening recommendations such as low positive predictive value
- Collect race/ethnicity information and study key U.S. population subgroups
- Partner with burn units for case identification and follow-up

High Priority Research Areas

- Develop *in vitro* models to inform studies of causative drugs and preclinical testing of new drugs
- Improve electronic phenotyping and develop robust algorithms for case identification
- Develop a large international network to collect and pool large numbers of diverse cases, including:
  - Standardized case definitions for both prospective and retrospective studies
  - Biospecimens from early in course development for diagnostic and prognostic biomarkers
  - Long-term outcomes, including morbidity and mortality and downstream sequelae
- Identify factors that discriminate risk allele carriers who have a reaction from those who do not
- Conduct additional epidemiologic studies
  - Foundational data needed for cost-effectiveness and other health economic research
  - Burden and risk studies of racial-ethnic groups within the U.S. and other global regions
- Conduct additional cost-effectiveness research to encourage implementation by hospitals/systems
- Develop pilot projects using qualitative and mixed-model research, including patient preferences

Opportunities and Next Steps

- Aggregate and harmonize existing case-report forms to inform standardized phenotype definitions
- Work with patient advocates to encourage adoption of ADR reporting more broadly
- Engage burn units in SJS/TEN collaborative efforts
- Improve collection of detailed ethnicity information in surveillance data
- Facilitate providing electronic case reports directly to FDA, and FDA collaborations with HMOs
- Identify potential joint efforts among U.S. federal partners (AHRQ, CDC, FDA, NIH, ONC, PCORI)
- Stimulate interest amongst international participants' home agencies in joint collaborative efforts