Pharmacosurveillance for SJS/TEN in the US

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Outline

• List Tools currently in use at FDA
• Describe each tool in terms of
  – Characteristics & Uses
  – Strengths
  – Limitations
• Summarize & identify gaps in PS
• Suggestions for possible improvement
Pharmacosurveillance (PS)
Tools Used by FDA

- Pharmacovigilance (PV)
  - FDA Adverse Event Reporting system (FAERS)
  - (Data mining)
  - Medical Literature (PubMed Alerts)
  - VigiBase
PS Tools – Pharmacoepidemiology (PE)

• National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance (NEISS-CADES)

• PE (Database) studies

• Sentinel / Mini-sentinel
FAERS
PV - FAERS

- Computerized database
- Spontaneous adverse event reports
- Associated with human and therapeutic biologic drug products
- > 10 million reports since 1969
- ~ 1 million new reports in 2013 & 2014
Sources of FAERS Reports

- Patients, consumer, and healthcare professionals
  - Voluntary
  - Direct < 5% of all reports
- Manufacturer
  - Voluntary 95% of all reports
  - Regulatory Requirements
  - FDA 95% of all reports

Adapted from OSE archived slide presentations
FAERS Strengths

- Simple, relatively inexpensive
- Very good for detecting rare AEs with short latency period (e.g. SJS/TEN) that are difficult to detect in clinical trials
- Inclusive
  - All ages & populations
  - All marketed drugs & biologics in US
Limitations

• Underreporting (cannot be used for incidence; no denominator)
• Information not always complete
• Reporting varies over time and with other activities
  – e.g. publicity, litigation
Proportion of SJS TEN Reports in FAERS 2010 - 2014

- Jan 2010 – December 2014
- Total FAERS reports – 4,734,000
- Total SJS/TEN reports – 5,700
- 0.12%
Signal Detection for SJS/TEN

- Regular review of FAERS – daily / weekly alerts
- (Data mining- Empirica software)
- Medical literature alerts
- Information from other Regulatory authorities
- VigiBase
Sample1, FAERS SJS/TEN report

- Reporter: Nurse practitioner via sales rep.
- Female patient, unknown age, developed SJS on unknown date while on Drug A
- Concomitant meds, comorbidities unknown
- Outcome unknown
- Follow-up not successful
Sample 2, SJS/TEN FAERS report

- M, 52 yo on drug X for diabetes
- Not well controlled after 9 months
- Drug Y added
- 13 days later – generalized erythematous rash, bilateral conjunctival hyperemia
- Visited dermatologist, diagnosis SJS, hospitalized, all drugs discontinued, treated with systemic steroids, ophthalmology consultation
- Discharged after 1 month – all symptoms resolved
SJS/TEN diagnostic Criteria for FAERS cases

• Diagnosis likely:
  – Diagnosis made by dermatologist
  – Good clinical description, with record of % BSA affected
  – ICU or Burn unit admission
  – Biopsy confirmation
• Less likely, still possible
  – Diagnosed by non dermatologist, no supporting information
Causality Criteria – modified WHO-UMC

• Probable:
  – Reasonable temporal association
  – Absence of confounding factors
  – Positive dechallenge +/- positive rechallenge

• Possible:
  – Reasonable temporal association
  – Confounded – alternative causes possible
Comparison with ALDEN causality scoring system

- Similar elements considered e.g. reasonable temporal association, dechallenge, rechallenge, alternative causes etc.

- Different in that ALDEN more detailed
  - ascribes a particular score
  - one element requires prior knowledge of the drug - often assessing new drugs at FDA
NEISS-CADES

- Collaboration of CPSC, CDC, and FDA
  - Active surveillance for adverse drug events (ADEs) treated in Emergency Departments (EDs)

- National Probability sample of ~ 60 US hospitals
  - With a minimum of 6 beds and a 24-hour ED
  - Excludes psychiatric and penal institutions

- ADE: an ED visit for a condition that the treating clinician explicitly attributes to therapeutic use of a drug or drug product
Additional coding and data validation (including assignment of MedDRA codes)

Data transferred to CPSC

SJS/TEN Case Definition

MedDRA terms

SOC (*System Organ Class*):
Skin and subcutaneous tissue disorders

HLGT (*High Level Group Term*):
Epidermal and dermal conditions

HLT (*High level term*):
Bullous conditions

PT (*Preferred Term*):
Erythema multiforme, Stevens Johnson syndrome, or Toxic Epidermal Necrolysis
NEISS-CADES - Strengths

- Nationally representative, so can be used to calculate incidence rates
- Can also be used as an additional source of cases in PV to supplement FAERS
- Diagnosis made by ED clinician, so better than ICD codes
NEISS-CADES - Limitations

• Diagnosis not confirmed by dermatologist / biopsy (use hospitalized cases to ↓ misdiagnosis)
• Lag time of ~15 months for database to be updated
• Does not capture:
  – SJS/TEN not caused by drugs
  – cases in hospitalized patients
  – cases dying on way to ED
Pharmacoepidemiology (PE) Studies
PE studies in PS for SJS/TEN

- Prospective data collection; e.g. registries
  - Challenging in the U.S. because of fragmented healthcare system
  - Large number of enrolled patients is needed
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PE studies cont.

- Retrospective studies; e.g. administrative databases
  - **Strengths:** real world settings, potentially large number of patients with longitudinal follow-up
  - **Main limitation:** SJS/TEN cases poorly captured by administrative codes (medical record validation needed)
Sentinel
 Sentinel

- Launched in 2008 by FDA; pilot program Mini-Sentinel

- Active surveillance system for monitoring safety of marketed FDA regulated products
  - complements other safety surveillance systems

- PE - based on electronic health records –
  electronic medical records, administrative claims data, registries

- Pre-specified modular programs developed, ready for implementation so can be completed quickly
Sentinel

- Transition to Sentinel now in progress
- Awarded to Harvard Pilgrim Healthcare Institute
- 50+ healthcare and academic organizations
- Current total – 180 million covered lives
  - ~ 50 million /year in last 5 years
- Limitations: SJS/TEN ICD codes do not have high PPV
Summary

- FAERS – Main PV tool for SJS/TEN
- NEISS-CADES useful, but more could be done as more data accumulate
- PE studies limited by poor validation of ICD codes
- Sentinel – not yet useful
- MASE – still under development
Suggestions for improvement in PV in US

• Targeted active surveillance
  – ICU & burn units
• Follow-up of cases identified in NEISS-CADES
  – Confirmation of diagnosis
  – Treatment
  – Length of stay
  – Mortality & associated risk factors
• Network of dermatologists – based on DILIN model – DISIN? DISCARN?
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Back Up Slides
Molecular Analysis of Side Effects (MASE)

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FDA contact: Keith Burkhart
MASE


• Mechanistically evaluate an adverse event by highlighting molecular targets, enzymes and transporters that may be disproportionately associated with an AE.
MASE - Limitations

- Research Hypothesis Generation Tool
- Uses PRR as a disproportionality analysis tool
- 5-Year RCA (Research Collaboration Agreement) with Molecular Health