Streamlined Drug Induced Liver Injury Detection
with Hy’s Law and Temporal Visualization

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Drug-Induced Liver Injury (DILI)

- Leading cause of safety-related drug withdrawal
- Severe DILI cases rare (1/10,000)
- Safety signals to detect POTENTIAL DILI in clinical trials

Important Considerations
- Incidence between treatment arms
- Time course of injury
- Alternative causes for liver damage
- History of liver disease
Clinical Evaluation of DILI Signals

- Hepatocellular injury
  - Elevated aminotransferase (AT) serum levels
    - Alanine Aminotransferase (ALT)
    - Aspartate Aminotransferase (AST)
  - Necessary, not sufficient DILI signal

- Impaired Liver Function
  - Jaundice, increased Total Bilirubin serum (TBL or BILI)
  - Accompanying or following hepatocellular injury

- No evidence of Cholestasis
  - Gall bladder or bile-duct disease
  - Elevated levels of alkaline phosphatase (ALP)
Hy’s Law Signal Detection

- Hepatocellular injury that impairs bilirubin excretion led to 10-50% mortality (Zimmerman 1978, 1999)
- Hy’s Law (Temple 2001; Reuben 2004)
  1. ALT or AST elevation ≥ 3*ULN, higher incidence in treatment
  2. BILI ≥ 2*ULN following ALT/AST elevation, without ALP elevation (cholestasis evidence)
  3. No reason for combined elevation (hepatitis, pre-existing liver disease, concomitant medications)
Hy’s Law In Practice

- Scatterplot view of peak liver test measurements
  - FDA eDISH (Evaluation of Drug Induced Serious Hepatoxicity)
- Flag AT elevation accompanied/followed by Bilirubin elevation
- AT elevation incidence across treatment arms
- Time Course
  - Drill down to temporal views
  - Cumulative days in Hy’s Law
- Cross-Domain Analysis
  - Patient clustering, patient profiles
- Patient Narratives
JMP Clinical Software System

- Provides easy-to-use, interactive displays for safety analysis

- Tools that can be used by:
  - Medical Monitors, Reviewers, Writers
  - Clinicians
  - Biostatisticians

- Relies on Standards
  - CDISC data Standard (SDTM and ADaM)
  - Standard Reporting (FDA Reviewer Guidance, ICHE3)
  - Standard Industry Visualizations
  - Standard Tools: JMP, SAS
Hy’s Law Screening Dashboard Analysis

- Interactive dashboard of Hy’s Law liver test elevations
- Drill down to Patient Profiles, Narratives, Clustering, Time Trends
Hy’s Law Screening: Scatterplot View

Hys Law Cases are flagged if ALT or AST >= 3*ULN and BILI >= 2*ULN within 3 Days of ALT/AST peak

Scatterplot Matrix

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<th>Hys Law Case</th>
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Cholestasis  Hy’s Law  Temple's
Hy’s Law and AT Elevation by Treatment

Contingency Analysis of Days in Hys Law By Planned Treatment for Period 01

Mosaic Plot

Contingency Analysis of Elevated AT Tests By Planned Treatment for Period 01

Mosaic Plot

Contingency Table

### Days in Hys Law

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Contingency Table

### Elevated AT Tests

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Graph Time Trends Drill Down

Liver Test Time Trends Trellis Plot

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<td>Log2(Peak AST/ULN)</td>
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<td>Log2(Peak BILI/ULN)</td>
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</table>

Study Day of Specimen Collection

Liver Test

3xULN

–2 0 2 4 6 8 10 12
**Patient Clustering Drill Down**

- Find patterns across all safety domain data
- Look for co-occurring adverse events, con meds, and medical history
- Find trends that may explain liver test elevation
Exported Patient Profile
Automated Patient Narratives

Subject: 282031
Randomized Arm: NIC .15
Investigator: 282A
Drug and Dose at Event Onset: 54 mg/h of NIC .15

Serious Adverse Event (coded term [reported term]): HEPATIC FUNCTION ABNORMAL [HEPATIC FUNCTION ABNORMAL]

Subject 282031 was a 53-year-old black or african american female. Her medical history included headache associated with sah (1988), hypertension with this sah (1988), cerebrovascular disease (1986), hepatic disease (1986), allergies (start date unknown), hypertension prior to sah (start date unknown), other medical condition (start date unknown) and stroke (start date unknown). She began dosing with 54 mg/h of nic .15 on 29JUL1988 (Day 1). The subject discontinued the trial on 05AUG1988 (Day 8) due to death.

On 01AUG1988 (Day 4) the subject experienced a hepatic function abnormal (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. At the time of the event, the subject was taking 54 mg/h of nic .15 and had been at this dose for 4 days. The SAE occurred 3 days after the first dose of any study medication. Trial medication had an action of dose modified as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a ±3-day window of the onset of the SAE included anaemia (moderate), atelectasis (mild), coagulopathy (severe), coma (severe), enanethma (mild), gastrointestinal haemorrhage (moderate), gastrointestinal haemorrhage (severe), hepatitis (severe), hyperglycaemia (severe), hypotension (moderate), isosthenuria (severe), oedema peripheral (moderate), platelet destruction increased (severe), pneumothorax (moderate), urinary tract infection (moderate) and vomiting (mild). Concomitant medications taken at the onset of the SAE included dexamethasone, phenobarbital and insulins.

On the closest lab test day on or prior to the start of the event, the subject had the following abnormal on-study lab tests: high bun [8.925 mmol/L, range = (2.499 - 7.497)], high creat [0.1326 mmol/L, range = (0.05746 - 0.10608)] and low plat [34 U/L, range = (100 - 500)]. On the closest lab test day subsequent to the start of the event, the subject had the following abnormal on-study lab tests: high aptt [39.599998 sec, range = (20 - 30)], high bili [35.5 sec, range = (20 - 30)], high bun [11.067 mmol/L, range = (2.499 - 7.497)], high bili [11.424 mmol/L, range = (2.499 - 7.497)], high creat [0.15028 mmol/L, range = (0.05746 - 0.10608)], high creat [0.21216000884 mmol/L, range = (0.05746 - 0.10608)], high gluc [23.643 mmol/L, range = (3.33 - 16.65)], low hgb [8.6000004 g/dL, range = (9.5 - 17.5)], high idh [5724 U/L, range = (105 - 333)], low plat [45 U/L, range = (100 - 500)], low plat [36 U/L, range = (100 - 500)], low prot [3.8 U/L, range = (100 - 500)], low prot [4.6999998 g/dL, range = (6 - 8.2)], high pt [23.700001 sec, range = (11 - 12.5)], high pt [43.5 sec, range = (11 - 12.5)] and high uate [0.548700118 mmol/L, range = (0.1239 - 0.5015)].

The investigator considered the AE to be possibly related to study medication. The final outcome of the event was reported as fatal on 02AUG1988 (Day 5).
Conclusion

- Signal detection for DILI is a complex but necessary safety measure
- Requires looking at all the clinical data not just labs
- Ideal Workflow
  - Evaluate elevations of liver lab tests across treatment arms
  - Flag temporally relevant elevations
  - Drill down to time trend lab views, patient profiles, cross-domain clustering, narratives to investigate reasons for liver injury signal
Thank You!

Questions?