Hepatotoxicity of Antimycobacterials

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Antimycobacterials

• Epidemiology of anti-TB DILI
  – Clinical presentation & outcomes
  – Detection and management
  – INH hepatotoxicity: Susceptibility & outcome

• DILIN efforts
  – Prospective & retrospective Studies
  – Genetic studies

• Potential collaboration
Drug Induced Liver Injury

• Most common reason for regulatory actions concerning drugs
  – Denial                 Withdrawal           Restriction
  – Ximelagatran          Lumiracoxib         Telithromycin

• Significant morbidity & mortality
  – Leading cause of ALF in the US (13%)
  – Hepatocellular jaundice ‡ 10% mortality

• No reliable means to predict/ prevent

(Ostapowicz Ann Int Med 2002; 137)
Challenges in studying DILI

• DILI is a rare disease
  – 10 – 15 per 100,000 pt-years \(^1\)
    • < 1% of acute liver injury \(^2\)
  – 1 in 10\(^4\) to 10\(^6\) prescriptions

• Clinical diagnosis
  – Exclude competing causes
    • Dechallenge requires time
  – Variable latency, lab profile
    • Polypharmacy common
  – No objective/ confirmatory test

\(^1\) Sgro Hepatology 2002; 36: 451
\(^2\) Galan J Clin Gastro 2005; 39: 64
Spectrum of DILI

ALF
(Death, Txp)
0.0001 - 0.01%

Symptomatic
disease
0.01 - 1.0%

Mild liver injury
(ALT < 3X ULN)
0.1 - 10%
Phenotypic forms of DILI

- Immunoallergic hepatitis
- Autoimmune hepatitis-like
- Acute hepatic necrosis
- Acute liver failure
- Cholestatic hepatitis
- Bland cholestasis
- Acute fatty liver with lactic acidosis
- Sinusoidal obstruction syndrome
- Nodular regeneration
- Vanishing bile duct syndrome
- Cirrhosis
- Benign neoplasms

(Hepatology 2010; 52: 730)
Isoniazid Hepatotoxicity

• 200 - 400,000 Americans treated/ year
  – Prevent 4 to 11,000 TB cases/yr
• Mild ↑ AST/ ALT in 20-30%
  – Self limited (Adaptation)
    • Rechallenge equivocal
    • Hypersensitivity & autoimmunity uncommon
• INH hepatitis + jaundice in 0.1-0.5%
  – ↑ Risk: Age > 40 ? Alcohol ? Liver dz
• ATS/ CDC monitoring guidelines
  – Baseline LFT’s & clinical assessment

(AJRS Med 2006; 174)
(MMWR 2000; 49 (RR-06))
Safety of INH in latent TB
CDC Passive SAE Surveillance ‘04-’08

- 17 cases of severe liver injury
  - 15 adults 2 children
  - 100% correct dose & indications
    • 10/10 monthly clinical monitoring
    • 70% SAE diagnosed by other clinician
- Med age 39 (19-63)
  - 65% female 47% Hispanic
  - 2nd to 9th mon of therapy
  - 16 HAV, HBV, HCV negative
    • 1 HCV-HIV co-infected
- Outcomes: Median ALT = 2200
  - 5 liver transplants & 5 deaths

(MMWR 2010; 59: 224-229)
Isoniazid Hepatotoxicity in the US

- ALFSG registry ‘98 –’11
  - 133 DILI cases
  - 15 INH alone    9 Anti-TB drugs

- UNOS ALF Liver txp recipients ‘90-’02
  - 137 ALF DILI cases
  - 24 INH (17%)
    - Med age =39 yrs
    - 67% Female   33% Black

(Reuben Hepatology 2010; 52: 2065)
(Russo Liver Txp 2004; 10: 1018)
DILI pathogenesis

**Drug**
- Class
- Dose
- Duration

**Environment**
- Diet, toxins and exposures (tobacco, alcohol, coffee, chemicals, pollutants, oxidants, probiotics)

**Host**
- Age, gender, weight, genetic factors, immune factors, other diseases
INH Hepatotoxicity

Isoniazid (INH) can be hydrolyzed by amidase to form Hydrazine (Hz). Hydrazine can then be oxidized by CYP2E1 to form a toxic reactive metabolite. Acetyl hydrazine (AcHz) can also be formed by acetylation of hydrazine by NAT2. Acetyl hydrazine can be hydrolyzed by amidase to form Diacetyl hydrazine. The toxic reactive metabolite can be detoxified by GST.
Inclusion criteria

• Age > 2
• Within 6 months of DILI onset *
• On 2 consecutive blood draws *
  – AST or ALT > 5 X ULN (baseline)
  – Alk phos > 2 X ULN (baseline)
  – T bilirubin > 2.5 mg/dl
• Chronic HBV, HCV, HIV allowed

* Exemption committee

(Fontana Drug Safety 2009; 32: 55)
Genetic studies of DILI

• DILI susceptibility may be shared
  – Metabolism, transporters, cell response, and innate/adaptive immunity involved in disposition of multiple drugs
  - Some DILI patients afflicted by multiple drugs

- Candidate gene vs genomics
  - Candidate: plausible hypothesis (CYP2E1, NAT)
  - **GWAS**: Unbiased assessment of >1 million SNP’s per case with MAF of 1 to 5%
    - Automated commercial platforms
DILIN & iSAEC Collaboration

• After ancestry pruning of Caucasians,
  – N=783 DILI cases       N=307 replication cases
    • 401 DILIN     382 iSAEC
    • > 200 total drugs
  – N=3,000 population controls
    • WTCCC & POPRES

• Genotyped on Illumina 1M or 1M duo array
  – 800,769 SNPs overlapping after QC

• Amox/clav and flucloxacillin (n=296)

(Urban et al, Submitted 2012)
## DILIN & iSAEC GWAS

<table>
<thead>
<tr>
<th></th>
<th>Discovery cohort N=783</th>
<th>Replication cohort N=307</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 (2-98)</td>
<td>53 (5-83)</td>
</tr>
<tr>
<td>% Female</td>
<td>58%</td>
<td>56%</td>
</tr>
<tr>
<td>Latency (d)</td>
<td>24 (0-7045)</td>
<td>39 (0-11463)</td>
</tr>
<tr>
<td>% Hepatocellular</td>
<td>33%</td>
<td>45%</td>
</tr>
<tr>
<td>% Cholestatic/ mixed</td>
<td>44%</td>
<td>50%</td>
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<tr>
<td><strong>Causality score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Definite, very likely, prob</td>
<td>79%</td>
<td>56%</td>
</tr>
<tr>
<td>% Possible/ Unlikely</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>% Amox/ clavulanate</td>
<td>26.6%</td>
<td>13.7%</td>
</tr>
<tr>
<td>% Diclofenac</td>
<td>3.8%</td>
<td>1.3%</td>
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<tr>
<td>% Nitrofurantoin</td>
<td>3.1%</td>
<td>4.9%</td>
</tr>
<tr>
<td>% Isoniazid</td>
<td>2.2%</td>
<td>2.3%</td>
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(Urban et al, Submitted 2012)
All Non-Augmentin/Flucloxacinillin DILI Cases (n = 487)

- No deviation from expected p-value distribution
DILIN and iSAEC GWAS

• No association by liver injury pattern, age, immunoallergic features, latency, severity, causality score, or drug class
  • 193 autoimmune SNP’s in 285 hepatocellular cases with trend at rs7574865 $p=4.5 \times 10^{-4}$ (STAT4)
    • Replicated in 168 DILI cases

• Conclusions: Lack of GWAS findings suggest that genetic susceptibility may be due to rarer variants or drug specific

(Urban et al, Submitted 2012)
Isoniazid Hepatotoxicity

58 of 800 (7.2%) from ‘04- ’11

- 38 cases adjudicated
  - 22 definite 14 high likely 2 probable
  - 79% latent TB
- Med age = 49 (4 to 70)
  - 66% female
  - 53% Cau 23% Black 18% Hispanic
- 47% hospitalized
  - Latency = 58 d (2-271)
  - 3% fatal 13% Transplanted
<table>
<thead>
<tr>
<th>Whole genome</th>
<th>Whole exome</th>
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<tbody>
<tr>
<td>• More comprehensive</td>
<td></td>
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<tr>
<td>– Novel genes/ exons</td>
<td></td>
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<tr>
<td>– Can detect regulatory (non-coding) variants</td>
<td></td>
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<tr>
<td>• Discovery of fine scale structural variants</td>
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<tr>
<td>• Higher cost ($5k)</td>
<td></td>
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<tr>
<td>• Generally lower coverage (30 X)</td>
<td></td>
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<tr>
<td>• Biased</td>
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<tr>
<td>– Known genes &amp; exons</td>
<td></td>
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<tr>
<td>– Allelic bias</td>
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<tr>
<td>– Misses functional non-coding variants and structural variation</td>
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<tr>
<td>• Less expensive (&lt;$2k)</td>
<td></td>
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<tr>
<td>– High throughput</td>
<td></td>
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<tr>
<td>• Generally higher coverage (60 X)</td>
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Whole Exome Sequencing of INH cases

- 47 whole exomes sequenced
  - 23 validation cohort

- In 12 Black pts
  - T-Cell maturation and IgE SNP’s implicated

- In 21 Caucasian pts
  - Hepatocyte chromatin assembly & pro-inflammatory caspases implicated
Retrospective study
Idiosyncratic Liver Injury Associated with Drugs

• Single drugs associated with serious liver injury and characteristic phenotype
  – Isoniazid  phenytoin valproate amox/clav

• **Inclusion criteria**
  – Onset after January 1, 1994
  – Total bilirubin >2.5 mg/dl
  – Enrollment
    • Medical records
    • Blood-draw (DNA)
  – Recruitment is ongoing !!
A comprehensive and up-to-date e-book of DILI culled from the world’s literature

- Enhance knowledge and awareness of DILI
- > 600 agents with hepatotoxicity pattern, mechanism, management; case examples, annotated references, links to product insert
  - Prospective cases with pathology from DILIN
- Interactive site to report cases

http://Livertox.nih.gov/
Isoniazid Hepatotoxicity 2012

- **Anti-TB DILI** remains a leading cause of ALF and severe liver injury in the US

- DILI may have a genetic basis
  - **GWAS**: Susceptibility not due to common SNP
  - Whole genome and exome studies may identify causal variants with smaller sample size
  - Recruitment and enrollment of well-phenotyped cases is rate limiting step

- Collaboration of interested parties is critical
• UNC          P Watkins/ P Hayashi, H Bonkovsky
• Indiana University   N Chalasani/ R Vuppalanchi
• CPMC                   T Davern/ M Bonacini
• University of Michigan R Fontana/ H Conjeevaram
• UTSW - Dallas          W Lee/ D Rockey
• USC/ UCLA              A Stolz/ F Durazo
• Thomas Jefferson/ U Penn V Navarro/ R Reddy
• Mayo Clinic            J Talwakar
• DCRI                    H Barnhart/ H Tillman
• CHGV                   T Urban/ D Goldstein
• NIDDK               J Hoofnagle/ J Serrano

• 2U01-DK065176-06 (Duke), 2U01-DK065201-06 (UNC), 2U01-DK065184-06 (Michigan), 2U01-DK065211-06 (Indiana), 5U01-DK065193-04 (UConn), 5U01-DK065238-08 (UCSF/CPMC), 1U01-DK083023-01 (UTSW), 1U01-DK083027-01 (TJH/UPenn), 1U01-DK082992-01 (Mayo), 1U01-DK083020-01 (USC).
Hepatocellular liver Injury

Ultrasound/CT

- Viral (A, B, C, CMV, EBV, HEV, HSV)
- Autoimmune (SPEP, ANA, SmAb)
- Ischemia (History, 2D-Echo)
- Metabolic (Iron, TIBC, ferritin, ceruloplasmin, SPEP)

Mass (AFP, MRI)

NAFLD

Observe/biopsy

Biliary (ERCP)

DILI < 1%

(Gordon J Clin Gastro 2005; 39: 64)
Recruiting pts with rare ADE

- **Retrospective approaches** \(^1,^2\)
  - Medical records
    - History Competing causes

- **Population based studies**

- **Prospective multicenter registries** \(^3,^4\)
  - Interview, careful phenotyping
  - Expensive, labor intensive

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1 Moore Arch Int Med 2007; 167  
2 Daly Nat Gen 2009; 41: 816  
3 Andrade Gastroenterology 2005; 129: 512  
4 Chalasani Gastroenterology 2008; 135