Hepatotoxicity of Anti-Tuberculosis Therapy

- Recent Research Advances in Drug-Induced Liver Injury 2009
  April 9, 2009

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Pulmonary Center
Boston University School of Medicine
Overview

- TB epidemiology
- Advances in TB-DILI
  - Mechanisms
  - Isoniazid (H), rifampin (R), pyrazinamide (Z)
- Viral co-factors
- TB clinical trials
- Opportunities for collaboration
World TB Day, March 24, 2009

- Robert Koch’s 1882 discovery of *M. tuberculosis*.
- 1/3 of world’s population infected
- Approximately 10% develop active disease
- Globally small decline in incidence
  - 2007 9.27 million new cases of TB
  - 2006 9.24 million new cases
  - driven by HIV/AIDS in Africa.
- 1.7 million deaths in 2004 from TB
  - a leading cause of infectious death

World Health Organization
Slightly declining rates of TB incidence, prevalence, and mortality.
U.S. & Massachusetts: TB Case Rates, 1982 - 2004

- 2005 rate lowest in U.S. since 1953
- Average 7.1%/yr decline to 3.8%/yr
- In MA same trend for a decade
- 2005 rate lowest in U.S. since 1953

MDPH/DIVISION OF TB

2004: US: 14,517; MA: 284
Number of TB Cases in U.S.-born vs. Foreign-born Persons
United States, 1993–2007

TB rate in foreign-born 8.7 X > U.S.-born

All case counts and rates for 1993–2003 have been revised based on updates received by CDC as of April 1, 2005.
Changing Medical Landscape of Tuberculosis

- In US, TB is orphan disease
- Emphasis on case-finding
- Treatment of high-risk latent TB infected individuals
  - Contacts, converters, HIV, medical conditions, etc
- Changing TB demographics
  - Foreign-born individuals
  - Hepatitis B, C, HIV, diabetes
  - May be treating older patients
Concerns about TB-DILI

• Demographic changes
• Co-morbidities
• Polypharmacy, few studies of drug co-factors.
  – >900 hepatotoxic drugs in pharmacopoeia
  – Alternative medicines & supplements
• Challenge applicability of previous data
• Concerns may deprive patients of TLTBI.
  – undermine efforts to eliminate TB.
Perceptions of TB medications for LTBI

- Formed by clinics, other patients, media
- Risk of progression to TB vs DILI
- Predictors of 6INH non-completion, 217 pts.
  - Multivariate analysis
  - Low risk perception of progression to TB
    - RR 0.42 (0.21-0.83, 95%CI), p= 0.012
  - Reluctance to have venipuncture
    - RR 0.57 (0.36-0.90, 95%CI), p= 0.017
Frederic Chopin
Advances in TB-DILI

- Mechanisms
- Evaluation of regimens
TB-DILI and gene polymorphisms

- N-acetyl transferase 2
- Cytochrome p450 2E1
- Glutathione S-transferase
Slow acetylation genotype assoc with “hepatotoxicity”

- Possuello et al

- Bozok Cetintaş et al
  - Tuberk Toraks. 2008;56(1):81

- Cho et al
  - Tuberculosis (Edinb). 2007 Nov;87(6):551

- Huang et al
Free radicals: glutathione S-transferase mutations and TB-DILI

- Polymorphisms at loci and alleles in TB-DILI patients (n=33) vs controls (n=33)
  - GSTM-1       GSTT-1           NAT-2
    %null               %null
  - Cases 52 *                   15                    44
  - Controls 24                       3                     31

p<0.05                Roy et al J Gastro Hep 16: 1033
Free radicals: N-acetylcysteine protective in INH/Rif oxidative hepatic injury

• Injury accompanied by
  – decreased GSH and thiols,
  – increased lipid peroxidation,
  – hepatocellular injury

• NAC prevented morphological injury in animal model

Attri et al Hum Exp Tox 19: 517, 2000
Clinical trials of NAC and TB-DILI

- NACHO-TUB
- National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran, Islamic Republic of Iran
TB: illness as metaphor
Grade 3/4 TB-DILI Risks: Isoniazid

- Symptomatic, ALT/AST 5 X ULN
- Overall, 0.1%
- Age > 35
  - Up to 35: 0.3-0.8 cases/1000
  - 35-64: 1-->2 cases/1000
  - >65: 3 cases/1000

(Nolan JAMA)
Tennessee retro: 3,337 patients on INH

- AST >5xULN
- 5.6 per 1,000 patients.
  - 1/19 had pro-dromal symptoms.
- Age-related data
  - 4.40/1000 25 to 34 years
  - 8.54/1000 35 to 49 years
  - 20.83 > or = 50 years old.
- Age > 49 years (p < 0.02) and baseline AST >ULN (p < 0.0003) risks
TLTBI: AE’s & Completion with open label 4RIF vs 9INH (McGill)

- 847 patients requiring TLTBI without contras
- Adverse events overall, Grade 3-4
  - Isoniazid 17/422 (4.1%)
  - Rifampin 7/418 (1.7%)
  - risk difference [R-H], -2.3% [95% CI, -5% to -0.1%]; P = 0.040
- Hepatitis, Grade 3 or 4
  - Isoniazid 16/422 (3.8%)
  - Rifampin 3/418 (0.7%)
  - risk difference, -3.1% [CI, -5% to -1%]; P = 0.003)
- Completion
  - Isoniazid 60%
  - Rifampin 78%
  - Risk difference, 18% [CI, 12% to 24%]; P < 0.001)

TLTBI: AE’s & Completion retro chart review 4RIF vs. 9INH (Hopkins)

- Treatment completion
  - Isoniazid: 770 52.6%
  - Rifampin: 1,379 71.6% (p<.001)
- Adverse events overall
  - Isoniazid 4.6%
  - Rifampin 1.9%
- Clinical hepatitis (ATS)
  - Isoniazid 1.8%
  - Rifampin group 0.08%, P<.001
  - Page et al Arch Intern Med. 2006 Sep 25;166(17):1863-70
TLTBI: Completion 4RIF vs. 9INH retro chart review 2 historical periods

- **Treatment completion**
  - Isoniazid 261 53.1%
  - Rifampin 213 80.5%
    - \( p < 0.0001 \)
  - \( p = <0.0001 \)

- **Lost to follow-up**
  - Isoniazid 34.7%
  - Rifampin 12.6%
    - \( p = <0.0001 \)

- **AE’s overall**
  - Isoniazid 5.8%
  - Rifampin 3.1%

Anton Chekhov
TB-DILI mechanisms: PZA

- Dose related
- Alters nicotinamide acetyl dehydrogenase levels in rat liver $\rightarrow$ ROS
- Shared mechanisms with H and Z as there is similarity in structure.
- H DILI $\rightarrow$ some more severe with Z
- Idiosyncratic hypersensitivity reaction?
- $t_{1/2}$ 10 hours
  - longer than INH (1-3h) or Rif (3.4h)
In vitro INH-PZA hepatotoxicity

- HepG2 hepatoma cells & WST cytotoxicity assay
- INH and HYD pre-treatment decreased PZA IC$_{50}$ by 30% and 38%.
- HYD and RIF toxicity not affected by pre-treatments.
Hepatotoxicity of pyrazinamide in treatment of TB infection—recent studies

- Latent TB Infection (LTBI)
  - 2RZ
  - ZE, ZL, ZO for MDR-TB
- TB disease
**SCRIPT: Hepatotoxicity Rates in 411 Patients**

<table>
<thead>
<tr>
<th>Hepatotoxicity Grade</th>
<th>RIF/PZA (N=207)</th>
<th>INH (N=204)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (AST 51-125)</td>
<td>29 (14%)</td>
<td>27 (10%)</td>
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<td>2 (AST 126- 250)</td>
<td>9 (4%)</td>
<td>3 (2%)</td>
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<tr>
<td>3 (AST 251-499)</td>
<td>7 (3.4%)</td>
<td>0 (0%)</td>
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<tr>
<td>4 (AST&gt;500 or 250 + sx)</td>
<td>9 (4%)</td>
<td>2 (1%)</td>
<td>0.001</td>
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<tr>
<td>Total</td>
<td>54 (26%)</td>
<td>32 (16%)</td>
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</tbody>
</table>

**Discontinuation of medication due to hepatotoxicity**

- RIF/PZA (N=207): 12 (6%)
- INH (N=204): 2 (1%)

p value: 0.033
### Hepatotoxicity

<table>
<thead>
<tr>
<th>Patients with transaminases at 1 month</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>2RZ (n = 207)</td>
<td>8.46</td>
<td>1.9-76.5</td>
<td>7.75</td>
<td>1.74-71.3</td>
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<tr>
<td>INH (n = 204)</td>
<td>ref</td>
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<tr>
<td>p=</td>
<td>0.001</td>
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<td>0.003</td>
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</tbody>
</table>
2RZ Trials & Hepatotoxicity

- **Bock et al:** 168 inmates Z (15-20 mg/kg)
  - 2 (1.2%) with Grade 3 or 4 hep
- **McNeill et al:** 110 adults and Z (15 mg/kg)
  - 7.3% with grade 3 or 4 hep vs. 0% on H
- **Lobato et al:** 848 inmates + 362 homeless
  - 5.8% with grade 3 or 4 hep
- **Cook et al:** Grades 3 and 4 DILI
  - 2RZ 6.1%
  - Isoniazid 2.0%
- **Stout et al:** (5XULN) rate 5.3%
- **Gordin et al:** HIV study population
Z in MDR contacts

- ALT/AST > 4 x ULN
- ZE: 7/12 (58%)
- ZL: 3/17 (18%)
  - Papastavros et al. *CMAJ* 2002;167: 131
- ZO: 9/22 (41%)… > 5 XULN
  - Ridzon et al. *Clin Infect Dis* 1997;24:1264
Hepatotoxicity of Z in Active TB
Kwok et al, HK

- Hepatotoxicity: 5.0% at any time.
- >12 weeks after starting treatment, estimated risk of hepatotoxicity was 2.6% for HRZE vs. 0.8% for HR.
- Adjusted OR (95% CI) of hepatotoxicity for HRZE vs HR: 2.8 (1.4–5.9).
Tokyo study results

- Transaminase elev in CH group
  - HRZ: 22.4%* vs 6.9% controls
    - Hep C 27.8% vs 5.6% in controls
    - Hep B 15.4%
    - Alcohol 11.1%
    - 3 continued treatment without change
    - 9 changed to HR, 1 changed to HEL
  - HR: 2/49 (4.1%) vs 2/49 (4.1%) controls
  - Max AST/ALT not sig different CH vs controls

*(p<0.05)*
TB-DILI & HIV during active TB treatment

- Often high rates of IVDU, viral hepatitis, EtOH use
- No controlled trials, overall 4-18% HATT
- Eur TB Group Abs AIDS MTG 1992
  - 463 patients, 67% IVDU, mostly low CD4
  - Treatment limiting hepatitis in 10%
  - HATT 3xULN in 15%, HATT 5%
  - 55% r/t INH
- Adult Spectrum of Disease 2000
  - 11-18% grade 3/4 during Rx
  - Concomitant liver disease in 24% of these
Malaysia retrospective case-control study 473 patients 1/03-6/05

- Population
  - mean age 44 years
  - abnml baseline transaminase was exclusion
- 46 (9.7%) with AST /ALT $\geq$ 3xULN; bili > 1.5
  - irrespective of sx—non-standard definition
- MV analysis: HIV infection and extrapulmonary TB were significant.
- Most patients safely restarted on previous regimen of the primary drugs.

  - Marzuki et al. Singapore Med J. 2008 Sep;49(9):688-93
Thailand: prospective cohort observation of 769 HIV+ TB patients

- Population:
  - HepC 31% assoc c IVDU
  - Hep BsAg+ 9%
  - NR 63%

- Occurrence during TB treatment of “clinical hepatitis” dx by MD with hepatitis, jaundice, or cirrhosis or death (5%)
  - similar in patients regardless of viral serologic status
HIV and Hep C co-infection increase HATT risk during active TB treatment

<table>
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<tr>
<th>Serology</th>
<th>Patients (n)</th>
<th>DIH (%)</th>
<th>p</th>
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<tbody>
<tr>
<td>HIV-HCV-</td>
<td>55</td>
<td>5</td>
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<tr>
<td>HIV-HCV+</td>
<td>29</td>
<td>24</td>
<td>0.028</td>
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<tr>
<td>HIV+HCV-</td>
<td>33</td>
<td>21</td>
<td>0.036</td>
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<tr>
<td>HIV+HCV+</td>
<td>11</td>
<td>45</td>
<td>0.002</td>
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</tbody>
</table>

Ungo et al AJRCCM 157: 1871, 1998
Taiwan: 261 patients treated for TB, 7/1/00-7/31/01

- Population
  - median age 58 years (range, 17-90 years),
  - 17.7% abnml baseline transaminases
  - 18.4% concurrent hepatotoxic drug use.
  - 5.7% hep B virus infection
  - 6.5% hep C virus infection,
  - 5.4% liver cirrhosis
  - 5.7% HIV
- TB DILI* occurred in 42 (16.1%),
- > 5 XULN(asxic) or > 3 X ULN (sx) or bili > 3 mg/dL.
- 60% of events in the first 2 months of treatment.
- multivariate analysis for indep risks for TB-DILI,
  - abnormal abnml baseline transaminases
  - liver cirrhosis

Symptomatic TB-DILI & Hep B: active TB treatment

- **Taiwan, Wu Gastroenterology 1990**
  - 42 (2.4%) / 1,783 rxed with HRE had symptomatic hepatitis.
  - 15 HepBsAg+
    - 7/15 died of hepatic failure.
  - 1/27 HepBsAg- died of hepatic failure

- **Hong Kong** Wong et al Hep 31: 201, 2000.
  - Excl. alcoholic and non-viral liver diseases
  - HepBsAg+ 16% more severe; 4.7% disc
  - HepBsAg- 4.7% 2.5% disc
**Hep B and hepatoxicity in TB disease 2**

  - No increased risk in Hep B carriers vs non-carriers in over 1700 patients.
  - Age >35 was only risk
  - HepBsAg+ 8%
  - HepBsAg- 2% p>0/05
  - Successful re-intro of HR
- Overall: 2 studies say increased risk/severity
Hepatitis B and Risk of TB-DILI in TLTBI

- McGlynn: chronic hepatitis B carriers and noncarriers indistinguishable. (77).
- Patel: Vietnamese immigrants;
  - HBeAg+: 3/21 (14%)
  - HBeAg-: 0/121 (0%)
  - experienced symptomatic AST/ALT >5 x ULN
- active, but not quiescent, hepatitis may be a risk factor
Hep C and TLTBI

- Sadaphal et al CID 33: 1687, 2001
  - 138 patients, TST+, Hep C+, 22% 3XULN
  - Risk assoc with EtOH
  - Not higher than TB-DILI in low Hep C pop
Franz Kafka
Conventional Sequential Drug Development

ABCD → BCDE → CDEF → DEFG → EFGH

ABCD → 6 years → BCDE → 6 years → CDEF → 6 years → DEFG → 6 years → EFGH

ABCD → 24 years → EFGH
# Global TB Drug Portfolio

## September 2005

<table>
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<tr>
<th><strong>Discovery</strong></th>
<th><strong>Preclinical</strong></th>
<th><strong>Clinical Testing</strong></th>
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<td>Carboxylates</td>
<td>Diamine SQ-109</td>
<td>Diaryquinoline TMC207</td>
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<td>TB Alliance, Wellesley College</td>
<td>Sequella Inc.</td>
<td>Johnson &amp; Johnson</td>
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<td>Cell Wall Inhibitors</td>
<td>Dipiperidines (SQ-699)</td>
<td>Gatifloxacin</td>
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<td>Colorado State University, NIAID</td>
<td>Sequella Inc.</td>
<td>OFLOTUB Consortium, Lupin, NIAID,</td>
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<td>TaGen</td>
<td>Bayer Pharmaceuticals, CDC TBTC,</td>
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<td>Screening and Target Identification</td>
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<td>NIAID, NIH</td>
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GATB
Clinical Testing

- Diarylquinoline TMC207, Johnson & Johnson
- OPC-67683, Otsuka
- Nitroimidazole PA-824, GATB
- Linezolid, TBTC
- Gatifloxacin OFLOTUB Consortium/WHO
- Moxifloxacin, TBTC, JHU, NIAID TBRU
- Pyrrole LL-3858, Lupin Limited
- Rifapentline (TBTC)
- Rifamycin, high dose (PIH,TBTC)
Other consortia/studies

- OFLOTUB (Africa): 2000 patients
  - 2 HRZG / 2 HRG vs. 2 HRZE / 4 RH
- ReMox (Africa): 1500 patients
  - 2HRZE → 4HR
  - 2MRZM → 2MRE
  - 2HRZM → 2HRM
- Hopkins
  - HRZE vs HRZM in active TB
  - HRZE vs MRZE in active TB
  - MPlacebo vs OZ x 6m for MDR contacts
Other consortia/studies

• Rifaquin (Africa)
  – 2HRZE → 4HR
  – 2HRZ → 4HP_{1200}/wk
  – 2MRZE → 2MP_{1200}/wk
22 Study 27 sites worldwide

CDC Administrative, Statistical, and Data Management Center

2 TBTC sites did not participate in Study 27

Kampala

Durban
Recent TBTC Studies

- Study 22: Rifap/ INH qwk vs rifam/INH 2x/wk
- Study 23: Rifabutin/ARV
- Study 24: Treatment of INH-resistant TB
- Study 25: RPT dose escalation
- Study 26: LTBI treatment INH vs INH/RPT
- Study 26a: Hepatitis substudy
- Study 26 Hypersensitivity Sub-Study
- Study 26 Rifapentine PK study
- Study 27 HRZE vs HRZM
- Study 28: HRZE vs MRZE
- Study 29 Rifamycin dose escalation
- Study 30 Linezolid vs placebo with OBT for MDR/XDR TB
TBTC Study 22

- Standard HRZE for 2 months induction
- Continuation phase: Rifapentine/INH weekly versus rifampicin/INH 2x/week
- 1004 patients
TBTC Study 22: ALT >5 xULN

Standard HRZE for 2 months

INH/RPT

INH/Rifampin

(n=502) (n=502)

Events 15 24

Patients 13 (2.6%) 18 (3.6%)
TBTC Study 25

- Phase I-II: (150 patients)

- 3 patients with elevated transaminases,
  - treatment limiting in one (0.67%) *AJRCCM*, 2001
TBTC Study 26: INH vs INH/RPT for TLTBI

9INH vs. INH 15 mg/kg + RPT 900 mg/wk x 3 m
- 270 vs 12 doses
- DOT for latter
- Efficacy unknown for LTBI
- INH/RPT approved for treatment of active TB
TBTC Study 26

- INH/RPT x 3 months vs 9INH for TLTBI
- 8,000 patients enrolled
  - Extended for pediatric and HIV enrollment
  - Followup phase
- Pooled adverse event rate low
  - Expected ≤0.1% to 0.6% hepatitis
- Non-inferiority trial
- Hepatitis sub-study
- Hypersensitivity sub-study
- Agreement to refer DILIN-eligible patients
**TBTC Studies 27/28**

- HRZE (n=286) vs MRZE (n=218)
- Transaminase elevation of 3 xULN with symptoms or 5 X ULN about 3-4%
- No difference between MRZE and HRZE arms
Study 27/28 liver enzyme elevations

• Mild liver enzyme elevation (n=7, 1.4%)
  ● Bilirubin >1.5xULN (n=4, 0.8%)
  ● AST >3xULN without symptoms (n=2, 0.4%)
  ● Both bilirubin >1.5xULN and AST >3xULN (n=1, 0.2%)

• Hepatotoxicity (n=17, 3.4%)
  o AST >3xULN + symptoms (n=2, 0.4%)
  o AST >5xULN no symptoms (n=10, 2%)
  o AST >5xULN + symptoms (n=5, 1%)
  o No AST elevations > 5xULN
TBTC Study 29: RIF vs RPT

5 days per week: $HR_{10}ZE$ vs $HP_{10}ZE$

- **Primary Objectives**
  - antimicrobial activity
  - safety/tolerability

- prospective, multicenter, open-label clinical study

- 219 patients per arm
MDR/XDR TB studies

- TBTC S30: OBT+ linezolid or plac x 4 m
- Tibotec TMC207
- Otsuka OPC 67683
- RESIST-TB consortium --nascent
TB Biomarker research

- TBTC
  - S29: banking baseline and 1m
  - S30: baseline, monthly x 4m
- ReMOX
  - Banking
- GC Biomarkers for TB
  - Response to rx, contacts, controls
TBTC Initiatives

- Include children
- Include HIV
- Biomarker Working Group
  - Surrogate marker quest
- MDR TB Working Group
- Standardizing Adverse Event Reporting
Finishing up S26 LTBI trial
New LTBI trial not expected for awhile
Treatment trials focused on active TB
- Necessarily international focus
- Include HIV
- Treatment shortening regimens pursued