National Surveillance for Severe Adverse Events Associated with Treatment for Latent Tuberculosis Infection

Lilia Manangan, RN, MPH
Krista Powell, MD, MPH
Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination

Background

• About 4% of U.S. population has latent tuberculosis infection (LTBI)

• Targeted testing & treatment for LTBI is a key component of TB elimination

• 6 to 9 months of isoniazid (INH) has been mainstay of treatment

• Toxicity concerns and long duration have limited use of INH to cure LTBI

INH-Associated Liver Injury

• Idiosyncratic reaction, independent of dosing

• No specific diagnostic criteria (diagnosis of exclusion)

• Heterogeneous definitions across studies

• Estimated incidence: 1 per 1,000 patients initiating treatment
Rifampin-Pyrazinamide (RZ)

• April 2000: Guidelines for targeted testing & treatment published
  – Introduction of RZ as an alternative, short-course regimen

• 2001–2003: Excess morbidity (liver injury) & mortality compared to recipients of INH
  – 48 adverse events (11 deaths)

Adverse Event Surveillance

• August 2003: Revised recommendations to exclude RZ regimen for LTBI treatment

• September 2003: Division of TB Elimination work group on adverse events

• January 2004: Initiation of national surveillance project for severe adverse events (SAEs) with any LTBI regimen

• October 2004: SAE protocol determined to be non-research, post-marketing surveillance

• November 2004: Office of Management & Budget (OMB) Notice in the Federal Register on the proposed data collection

• April 2008: SAE for data collection form approved by OMB
Surveillance System Objectives

• Quantify the frequency SAEs associated with LTBI treatment

• Characterize the clinical features of affected patients

Methods

• SAE definition: Any drug-associated reaction resulting in a patient’s hospitalization or death after at least 1 treatment dose for LTBI

• Standardized reports submitted to CDC by state health departments
  – Demographic info, treatment regimen & duration, evaluation results, outcome

• CDC available for on-site investigations

Results

• 17 SAEs reported during 2004–2008*
  – 15 adults (ages: 19–63 years)
  – 2 children (ages: 11 & 14 years)

• All patients had received INH & experienced severe liver injury
  – 5 liver transplantations (1 child)
  – 5 deaths (1 transplant recipient)

* CDC conducted on-site investigations for 10 SAEs.
Patient Characteristics (N=17)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years)</td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>2</td>
</tr>
<tr>
<td>15–35</td>
<td>5</td>
</tr>
<tr>
<td>&gt;35</td>
<td>10</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
</tr>
<tr>
<td>Black</td>
<td>1</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>8</td>
</tr>
<tr>
<td>Female gender</td>
<td>11</td>
</tr>
</tbody>
</table>

Timing of SAE Diagnosis During INH Therapy for LTBI Treatment & SAE Outcome†

- Survival
- Transplant
- Death

Month of INH therapy at SAE diagnosis

† Figure excludes one patient who received intermittent therapy for 17 months and survived.
* Patient died following liver transplantation.

Patient Characteristics (N=17)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>104</td>
</tr>
<tr>
<td>Range</td>
<td>28–499*</td>
</tr>
<tr>
<td>Period from INH initiation to onset of SAE-related symptoms</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>109</td>
</tr>
<tr>
<td>Range</td>
<td>26–502*</td>
</tr>
</tbody>
</table>

* Includes 1 patient who received intermittent treatment (>9 months).
On-Site Investigations of SAEs (N=10)

• All patients had indications for treatment

• All patients were prescribed INH within recommended dosage, took as prescribed

• Prescribers followed American Thoracic Society (ATS)/CDC monitoring guidelines
  – At least monthly clinical evaluations for all
  – 2 patients selected for monthly lab testing
  – 5 patients had baseline testing (all normal)

Results from On-Site Investigations, by Case Characteristics (N=10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE diagnosed by provider other than prescriber of INH</td>
<td>7</td>
</tr>
<tr>
<td>SAE diagnosis prompted by symptoms (not lab abnormalities)</td>
<td>10</td>
</tr>
<tr>
<td>Findings upon SAE diagnosis</td>
<td></td>
</tr>
<tr>
<td>Jaundice*</td>
<td>10</td>
</tr>
<tr>
<td>Abnormal lab values†</td>
<td>10</td>
</tr>
</tbody>
</table>

* 7 patients initially experienced excess fatigue, nausea, or abdominal pain
† Serum aspartate & alanine aminotransferase (AST & ALT)

Results from On-Site Investigations, by Case Characteristics (N=10)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period from SAE symptom onset to INH discontinuation</td>
<td></td>
</tr>
<tr>
<td>≤2 days</td>
<td>1</td>
</tr>
<tr>
<td>3–6 days</td>
<td>1</td>
</tr>
<tr>
<td>≥7 days</td>
<td>8</td>
</tr>
<tr>
<td>Putative risk factors for liver injury</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>HIV infection</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>3</td>
</tr>
<tr>
<td>Concurrent hepatotoxic meds</td>
<td>4</td>
</tr>
</tbody>
</table>
Exclusionary Testing Results (N=10)

<table>
<thead>
<tr>
<th>Test or condition</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis (n=10)</td>
<td></td>
</tr>
<tr>
<td>Pre-existing HCV infection</td>
<td>1</td>
</tr>
<tr>
<td>Negative results</td>
<td>9</td>
</tr>
<tr>
<td>Autoimmune hepatitis (n=5)</td>
<td></td>
</tr>
<tr>
<td>Negative results</td>
<td>5</td>
</tr>
<tr>
<td>Histopathologic liver exam (n=5)</td>
<td></td>
</tr>
<tr>
<td>Nonspecific changes consistent with drug-induced liver injury</td>
<td>5</td>
</tr>
</tbody>
</table>

Case Example 1

- 39-year-old woman
- Morbid obesity, type II diabetes (non-insulin dependent)
- 3 months postpartum
- No history of liver disease
- Started INH for LTBI treatment by public health department
- Baseline laboratory testing within normal limits

Case Example 1 (cont.)

- Routine evaluation by primary care provider 2 months after treatment initiation
- Asymptomatic elevation of liver enzymes 5 times upper limit of normal
- Provider unaware of INH therapy, recommended re-evaluation in 6 weeks
- Patient continued INH until symptoms developed 2 months later
Case Example 1 (cont.)

- Patient continued INH until symptoms
  - fatigue, nausea, vomiting, and abdominal pain, then jaundice
  - Discontinued INH within 72 hours
- Dramatic elevation in liver enzymes, coagulopathy, altered mental status
- Outcome: died after liver transplant
- Diagnosis: liver failure secondary to INH

Case Example 2

- 11-year-old boy
- No pre-existing medical conditions
- No identifiable predictors for liver injury
- Public provider prescribed INH
- 6th month: 3-day febrile illness treated with standard doses of acetaminophen

Case Example 2 (cont.)

- 7th month: severe fatigue, icterus, depression for 1–2 days, then jaundice, vomiting for 1 day
- Stopped treatment within 72 hours of onset
- Progressively worsening liver failure
- Outcome: liver transplantation
- Diagnosis: liver failure due to possible INH toxicity versus autoimmune disease
Discussion

• INH-associated liver injury can occur among patients of any age at any point during treatment even in absence of risk factors
  – Series included 2 children
  – 9 of 17 SAEs occurred beyond 3rd month
• Findings underscore importance of following ATS/CDC guidelines
  – Targeting testing & treatment for LTBI
  – Appropriate monitoring

Discussion

• 7 of 10 SAEs diagnosed by provider other than the one prescribing INH
  – Provider-to-patient communication
  – Provider-to-provider communication
• 8 of 10 patients continued INH despite symptoms, initial symptoms without jaundice for 7 patients
  – Educate patients to stop treatment upon earliest symptoms (can be subtle)

Limitations

• Small case series
• Underreporting common in passive surveillance systems
• LTBI is not a reportable condition in most jurisdictions
• True rate of SAEs remains unknown
Recommendations

- LTBI treatment remains a key component of TB elimination
  - Prevented 4,000–11,000 TB cases in 2002
- True rate remains unknown, but SAEs rare
- 9 months of INH remains mainstay of LTBI treatment
- CDC encourages optimal use of INH by targeted testing & treatment

Reporting SAEs

- Local providers should report to their respective health departments & FDA’s MedWatch
- Local health departments should report to state health departments
- State health departments should report to CDC’s Division of TB Elimination (e-mail: LTBIdruevents@cdc.gov)

References

- CDC. Targeted testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-06)