The Use of the 12-Dose Isoniazid-Rifapentine Regimen for Latent TB Infection in the United States

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2013 CTCA Educational Conference
May 30, 2013

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- 9 months of daily isoniazid
- 9 months of twice weekly isoniazid
- 6 months of daily isoniazid
- 4 months of daily rifampin
- 12 doses of weekly isoniazid and rifapentine
  - up to 900 mg isoniazid
  - up to 900 mg rifapentine
  - Known as 12-dose INH-RPT or 3HP

Characteristics of Rifapentine (RPT)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life (h)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (μg/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt;/MIC&lt;sub&gt;50&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>2.46</td>
<td>0.25</td>
<td>58.44</td>
<td>471</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>15.9</td>
<td>0.12</td>
<td>98</td>
<td>2658</td>
</tr>
</tbody>
</table>

In contrast to Rifampin, Rifapentine:
- Stays in the body 7 times longer
- Kills TB organisms at a much lower concentration

3 Clinical Trials With INH-RPT

- Brazil (Jan 01 —July 03) Schecter et al, AJRCCM 2006
  - 399 Household contacts; INH-RPT vs. 2RZ
  - Excess hepatotoxicity in 2RZ (20 vs. 2 for INH-RPT)
  - 3 TB cases for INH-RPT vs. 1 for RIF-PZA

- South Africa (Sep 02 —Jun 05) Martenson et al, NEJM 2011
  - 1148 HIV-infected persons; 4 arms (INH-RPT, 3HR, 6H, cont. H)
  - Serious adverse events more common in continuous H
  - No significant difference in development of TB among 4 arms

- Prevent TB study, multi-site (Jun 01 —Feb 08) Sterling et al, NEJM 2011
  - 7731 high risk persons in 2 arms
  - DOT INH-RPT vs. SAT 9H
  - INH-RPT by DOT as effective as 9H in preventing TB with higher completion rate; less hepatotoxicity; more hypersensitivity
  - Long term safety monitoring will be important

CDC Recommendations: 12-dose INH-RPT by DOT

- 12 weekly DOT doses of INH-RPT an equal alternative to 9 months of daily self-supervised INH for treating LTBI
- Use in otherwise healthy patients aged ≥12 years with a greater risk of developing TB
  - Those with recent exposure to contagious TB
  - Converting from negative to positive tests for indirect tests for TB infection
  - Radiographic findings of healed TB
  - HIV-infected patients who are otherwise healthy and not taking anti-retroviral medications
  - For children aged 2-11, tolerability and efficacy has not been established. INH-RPT can be considered on a case-by-case basis

- AE monitoring for INH-RPT use in the field needed
  - INH-RPT well tolerated in treatment trials
  - For both INH and RIF-PZA, fatal liver injuries came to attention only after regimens widely adopted

- National Surveillance for Severe Adverse Events (NSSAE)
  - Approach: Passive surveillance system
  - Challenge: lack of denominator data to estimate incidence and risk ratios

MMWR
Fatal and Severe Hepatitis Associated With Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection — New York and Georgia, 2000
Post-marketing INH-RPT Project Objectives
- Monitor for adverse events with 3 month INH-RPT in non-research settings
  - Collect denominator data prospectively
  - Note if certain populations, risk factors or settings are associated with adverse effects (AE) more often
- Assess compliance and treatment completion
- Assess impact of INH-RPT on programs
  - Staffing
  - Costs
- Match patients with TB registry at 2 years

Project Methods
- Multiple volunteer sites implementing INH-RPT carry out “post-marketing surveillance”
- Modifiable data templates to record findings
- Core information collected by all sites
  - Number of treatment starts
  - Symptom review
  - Treatment outcome
- Some sites collect additional information about patient characteristics
- Focus on programmatic issues
- Match patients with local TB registry after 2 years

Recording Adverse Events

Preliminary Data From 15 Sites
- 1102 persons started INH-RPT; 513 completed; 112 stopped; 477 on treatment
- Of 112 that stopped
  - 76 stopped due to an adverse event
  - 36 due to symptoms
  - 13 due to elevated liver function tests (LFT)
  - 36 stopped for other reasons (moved, lost to follow-up, released from facility)
- 8 patients were hospitalized
  - No deaths
  - No serious or permanent sequelae
  - Investigation through NSSAE by independent reviewers
  - Reports reviewed by DTBE experts

As of 11/2012
Of 63 patients:

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, chills, myalgias or fatigue</td>
<td>25 (39.7%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (9.5%)</td>
</tr>
<tr>
<td>Nausea, vomiting, abdominal pain or diarrhea</td>
<td>15 (23.8%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>17 (27.0%)</td>
</tr>
</tbody>
</table>

As of 11/2012


*one patient with underlying HCV and HIV
†one patient hospitalized

Comparison of Rates for Reason Treatment Stopped

<table>
<thead>
<tr>
<th>Reason</th>
<th>Prevent TB Study</th>
<th>Post-marketing Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped due to adverse event</td>
<td>196/3986 (4.9%)</td>
<td>76/1102 (5.7%)</td>
</tr>
<tr>
<td>Serious event (death, permanent sequelae or hospitalization)</td>
<td>64/3986 (1.6%)</td>
<td>8/1102 (0.7%) *</td>
</tr>
<tr>
<td>Fever, chills, myalgias or fatigue</td>
<td>152/3986 (3.8%)</td>
<td>25/1102 (2.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>31/3986 (0.8%)</td>
<td>6/1102 (0.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>131/3986(3.2%)</td>
<td>17/1102 (1.5%)</td>
</tr>
</tbody>
</table>

* 8 hospitalized; no deaths or permanent sequelae

As of 11/2012

Summary

- 12-dose INH-RPT is being adopted rapidly and widely in the U.S.
- Initial field experience is similar to treatment trial experiences
- No deaths or severe organ damage detected
- Clinical trial sub-analyses show—
  - Drug-associated reactions (excluding hepatitis and rash only) are more common with 12-dose INH-RPT regimen
  - Patients with severe and non-severe adverse events recovered rapidly

Drug-associated Reactions from Prevent TB Study

- 7799 patients, 365 with drug reactions
  - 156 with possible hypersensitivity reaction
  - 140 (3.5%) on INH-RPT; 16 (0.4%) on INH
  - 16 with severe adverse event (hospitalized or death)
  - 1 (0.4%) on INH-RPT; 1 (0.03%) on INH

Villarino et al. Drug-associated reactions among persons receiving 3 month regimen of Rifapentine plus isoniazid for treatment of LTBI, CROI 2013

Acknowledgments

- INH-RPT Implementation Group
  - Nora Plugl, Jennifer Stankiewicz, Julia Kwolek, Rose Desautel, Alison Leavitt

- CEPIC Surveillance and Evaluation Branch
  - Mark Stover, Marinane Souza, Ilyas Doss, John Krajden, Benoit Grinberg, Paul Smith, Ana Santos, Gauthier Quere, Antonio Rojas, Aviva Hershowitz, Patricia Vasquez

- CDC Field Services and Evaluation Branch
  - Risa Webb, conductivity, Derrick Felix, Dottem Kress, David LeMieux, Patricia Loughran, Rich Ward

- Surveillance, Epidemiology and Outbreak Branch
  - Susan Day, Kristy Mitten

- Data Management and Surveillance Branch
  - Mark Miner, John Jereb

- Clinical Research Branch
  - Julia Mancuso, Carol McGlothlin, Mary Pendergrass, Tom Miller, Chris Stringer, Susan Bredemeyer, Richard Smith, Diana Fortune, Marco Burgos, John Silverman, Charlie Crane

- Preventive Medicine Branch

* 8 hospitalized; no deaths or permanent sequelae

As of 11/2012


†one patient with underlying HCV and HIV
‡one patient hospitalized

As of 11/2012

Asymptomatic

<table>
<thead>
<tr>
<th>WHO classification*</th>
<th>Total</th>
<th>Grade 1 ALT 51-125</th>
<th>Grade 2 ALT 126-250</th>
<th>Grade 3 ALT 251-499</th>
<th>Grade 4 ALT &gt;500</th>
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</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2*</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>3</td>
<td>1†</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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‡one patient hospitalized