Initial Experiences of Weekly Isoniazid (INH) and Rifapentine (RPT) for Latent TB Infection (LTBI): The Post-Marketing Project

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Treatment Choices for Latent Tuberculosis Infection (LTBI)

- 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
  - DOT only

Characteristics of Rifapentine (RPT)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half Life (h)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (μg/ml)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>AUC&lt;sub&gt;24&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin (10 mg/kg)</td>
<td>2.46</td>
<td>0.25</td>
<td>58.44</td>
<td>471</td>
</tr>
<tr>
<td>Rifapentine (10 mg/kg)</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

J. Grosset '08 IUATLD Keystone
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)

South Africa (Sep 02 — Jun 05) Martisson et al, NEJM 2011
- 1448 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 (TBTC Study 26) 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; higher completion rate; less hepatotoxicity; more "hypersensitivity"
- Long term safety monitoring important

CDC Recommendations: 12-dose INH-RPT by DOT

12 once weekly DOT doses of INH-RPT is equivalent 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
- Contacts
- Converters
- Those with radiographic findings of healed TB
- HIV-infected patients who are otherwise healthy and not taking anti-retroviral medications
- For children aged 2–11 INH-RPT can be considered on a case-by-case basis

LTBI Treatment and a History of Adverse Events

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

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
Post-marketing INH-RPT Project Objectives
Monitor for adverse events with 3 month INH-RPT in non-research settings
• Track number of patients started on regimen
• 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
• Observational measurement of effectiveness
• Surveillance for drug-resistant TB after LTBI treatment

Post-Marketing Surveillance Project Sites
• 18 sites using the regimen, 22 sites contributed to project design and forms
• DOT used for all sites
• Project period: January 2012 through December 2013
• Original target: 4000 patients
• Fewer patients started on INH-RPT due to — staff shortages, drug-resistant TB outbreaks, drug shortages, unable to get state approval of regimen, and waiting to get local IRB approval

Findings to Date
Preliminary Results
Snapshot Through May 27, 2013

1,422 persons started
1,288 eligible to complete treatment
1,061 (82%) completed
220 (17%) did not complete
100 (46% of 220) because of other reasons (index case with INH-resistant TB, lost to follow-up)
120 (54% of 220) because of symptoms or abnormal transaminase levels

As of 5/27/2013

Severe Adverse Events

Severe AE: any patient who was hospitalized or died while on LTBI therapy (NSSAE definition)
14 reports of hospitalizations
- 6 on-site CDC investigations complete
- 4 investigations in progress
- 4 have not been initiated
- No deaths
- No serious or permanent medical sequelae
Coordination with national NSSAE project under Krista Powell and Lilia Manangan
Preliminary Comparison Between TBTC Prevent TB Study and Post-marketing Project for Treatment Discontinuation Rates by Reason, 16 Sites

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Prevent TB, Study 26</th>
<th>%</th>
<th>Post-marketing Project</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued due to adverse event</td>
<td>196/3986</td>
<td>4.9†</td>
<td>120/1288</td>
<td>9.5†</td>
</tr>
<tr>
<td>Hepatotoxicity *</td>
<td>18/4040</td>
<td>0.4</td>
<td>8/1288</td>
<td>0.6</td>
</tr>
<tr>
<td>Rash only</td>
<td>31/4040</td>
<td>0.8</td>
<td>14/1288</td>
<td>1.1</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>56/3986</td>
<td>1.4</td>
<td>14/1288</td>
<td>1.0</td>
</tr>
<tr>
<td>Death</td>
<td>4/3986</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Defined as ALT 3xULN for symptomatic persons and 5xULN for asymptomatic persons
†These rates from Prevent TB Study 26 and Post-marketing Project are not directly comparable due to differences in definition

Post-marketing Project: Data from 7 Sites with Enhanced Data Collection

Patient Demographics Profile
Post-Marketing Project, 7 sites (n=1,183)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Number</th>
<th>%</th>
<th>Race*</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>608</td>
<td>51.4</td>
<td>White</td>
<td>497</td>
<td>38.6</td>
</tr>
<tr>
<td>Female</td>
<td>969</td>
<td>48.1</td>
<td>Black</td>
<td>538</td>
<td>45.5</td>
</tr>
<tr>
<td>Missing Gender</td>
<td>6</td>
<td>0.5</td>
<td>Native American</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>171</td>
<td>14.5</td>
<td>Asian</td>
<td>147</td>
<td>12.4</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>993</td>
<td>83.9</td>
<td>Pacific Islander</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>Missing Ethnicity</td>
<td>19</td>
<td>1.6</td>
<td>Unknown Race</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Missing Race</td>
<td>7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Includes Hispanic and non-Hispanic

As of 5/27/2013
Patients Who Interrupted or Discontinued INH-RPT Due to Adverse Events by Symptom*, 7 Sites (n=1,183)

119 patients had 135 instances of stopping or interrupting treatment due to symptoms

As of 7/17/2013

*patients can have more than one symptom

“Other” Reasons Reported for Patients Who Interrupted or Discontinued INH-RPT, 7 Sites (n=1,183)

71 “other” reasons among 135 instances of stopping or interrupting treatment because of symptoms*

> 15 instances of headache
> 19 instances of elevation in liver transaminase levels
> 3 pregnancies

The following reasons were reported in ≤2 events:

- Swollen lips
- Swollen tongue
- Difficulty breathing
- Menstrual irregularities
- Blurred vision
- Dry mouth
- Platelet drop from 212 to 85
- Gastrointestinal bleeding
- Hip pain
- Change in taste sensation
- Body ache NOS
- Muscle tightness
- Low blood pressure
- Swollen lymph nodes
- Eye Pain
- Weakness
- Itching
- Chest pain
- Confusion

Characteristics of AEs Associated with Interruption or Discontinuation of 12-dose INH-RPT, 7 sites (n=234)

As of 5/27/2013

<table>
<thead>
<tr>
<th>Non-severe (n=225)</th>
<th>Severe (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset &lt;2 hrs.</td>
<td>61 27 0 0</td>
</tr>
<tr>
<td>2-48 hrs.</td>
<td>104 46 5 56</td>
</tr>
<tr>
<td>&gt;48 hrs.</td>
<td>27 12 1 11</td>
</tr>
<tr>
<td>Unknown onset</td>
<td>33 15 3 33</td>
</tr>
<tr>
<td>Duration &lt;24 hrs.</td>
<td>58 26 5 56</td>
</tr>
<tr>
<td>Duration &gt;24 hrs.</td>
<td>107 48 1 11</td>
</tr>
<tr>
<td>Unknown duration</td>
<td>60 27 3 33</td>
</tr>
</tbody>
</table>
Number of Doses Associated with Interruption or Discontinuation of 12-dose INH-RPT, 7 sites (n = 234)

Location Specific Findings

Homeless Contacts Receiving 12-Dose INH-RPT for LTBI Treatment, Two Post-marketing Project Sites

- Mississippi – 48 homeless contacts
  - 39 (81%) completed treatment
  - 9 (18%) did not complete INH-RPT
    - 1 (2%) because of an adverse event
- Kane County – 35 homeless contacts
  - 11 (31%) still in treatment
  - 24 completed (of 24 eligible to complete)
  - None stopped or lost to follow-up

As of 5/27/2013
Foreign-born Students Receiving 12-Dose INH-RPT for LTBI Treatment, Four Post-marketing Project Sites

Kansas – 37 students
- 35 (95%) completed
- 2 (5%) discontinued INH-RPT because of adverse events

Minnesota – 12 students
- 11 (92%) completed
- 1 (8%) discontinued INH-RPT because of adverse event

UC San Diego – 23 students
- 6 in treatment
- 15/23 (65%) completed
- 2 (12%) because of adverse events

Arkansas – 26 students
- 25 (95%) completed
- 1 (4%) discontinued because of an adverse event

As of 5/27/2013

Virginia’s Experience During the Post-marketing Project

- Information available for 68 persons
  - SEND IN THE COMPLETED DOT LOG SHEETS!
- 56 of the 68 completed – 82% completion rate!
- 12 stopped for various reasons
  - 6 for adverse reactions
  - 5 lost to follow-up
  - 2 “other” reasons
- Very important
  - No deaths
  - No hospitalizations

Virginia’s Experience During the Post-marketing Project

Adverse Event Reports
- Adverse event reports submitted on 11 clients
  - 3 HP discontinued on 6
    - 1 changed to INH to finish treatment for TBI
    - 4 discontinued treatment altogether
- Symptom onset
  - < 2 hours – 2 (18%)
  - 2 - 48 hours – 4 (36%)
  - > 48 hours – 4 (36%)
- Symptom duration
  - < 1 day – 3 (27%)
  - ≥ 1 day – 6 (54%)
- 5 continued 3 HP regimen after evaluation
Virginia's Experience During the Post-marketing Project

Symptoms for Which Treatment Stopped

- Six patients stopped treatment due to adverse events
- Reported symptoms for stoppage included:
  - Rash/hives – 4 patients
  - Nausea/vomiting – 3 patients
  - Appetite loss – 1 patient
  - Diarrhea – 1 patient
  - Abdominal pain – 1 patient
  - Sore muscles – 1 patient

*patients can have more than one symptom

Summary

- Initial field experience is similar to treatment trial experiences
- High completions rates, notably in difficult populations
- Rashes and nausea most common reasons for stopping
- No deaths or severe organ damage detected nationally
- No deaths or hospitalizations in Virginia

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