Treatment of Latent TB Infection (LTBI)

Mahesh C. Patel, MD
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Treatment of LTBI

• Mahesh C. Patel, MD
• Associate Professor
• Department of Internal Medicine, Division of Infectious Diseases
• University of Illinois at Chicago
DISCLOSURE

• NO relevant financial relationships

• NO conflicts of interest
OBJECTIVES

• Describe the current guidelines for LTBI treatment

• Describe monitoring recommendations for patients on LTBI treatment
DEFINITION

• Latent TB Infection is INFECTION and **NOT** DISEASE
• Suppressed by host defenses
• Goal should be to identify and treat those with LTBI to reduce risk of reactivation
Ask for any symptoms of tuberculosis in individuals from the risk groups*

Yes

No

TST or IGRA

Positive

Chest radiography

TB and other disease investigations***

Any abnormality

No abnormality

Treat for LTBI

Negative**

Source: WHO
Factors to Consider when Choosing a Regimen

• Drug-susceptibility of presumed source case
• Coexisting medical conditions
• Potential for drug-drug interactions

• Patients in whom adherence is questionable, consider DOT
TREATMENT REGIMENS

- Isoniazid (INH)
  - 6 month
  - 9 month

- INH and Rifapentine (RPT)—12 doses, once weekly

- Rifampin x 4 months
  - (INH and Rifampin x 3 months)
    - Limited data in HIV-UNinfected persons
    - Consider if DOT or RPT not available
### Table 4. Efficacy of various durations of isoniazid therapy compared with placebo: all assigned participants

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of participants entering regimen</th>
<th>Cumulative no. of cases</th>
<th>5-Year incidence&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Percentage reduction</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6990</td>
<td>97&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.3</td>
<td>0</td>
<td>4.0</td>
</tr>
<tr>
<td>12-I</td>
<td>6956</td>
<td>76</td>
<td>11.3</td>
<td>21</td>
<td>3.1</td>
</tr>
<tr>
<td>24-I</td>
<td>6965</td>
<td>34&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.0</td>
<td>65</td>
<td>1.4</td>
</tr>
<tr>
<td>52-I</td>
<td>6919</td>
<td>24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.6</td>
<td>75</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Culture-positive tuberculosis per 1000 persons at risk.

<sup>b</sup> Includes 1 case during the first 6 months of pill-taking.

<sup>c</sup> Includes 2 cases during the first 6 months of pill-taking.

**INH Therapy**

<table>
<thead>
<tr>
<th>Duration</th>
<th>Product</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>Isoniazid</td>
<td>95 (87)</td>
<td>97 (91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>Isoniazid</td>
<td>94 (84)</td>
<td>93 (78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>96 (87)</td>
<td>95 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>52 weeks</td>
<td>Isoniazid</td>
<td>93 (84)</td>
<td>91 (79)</td>
<td>89 (73)</td>
<td>88 (68)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>95 (87)</td>
<td>93 (79)</td>
<td>91 (74)</td>
<td>90 (69)</td>
</tr>
</tbody>
</table>

Isoniazid

• 12 months is probably more efficacious than 6 months

• **BUT**, 6 months has greater adherence and may be more cost effective (and less hepatotoxic)

• So…after extrapolation of this and other trials/data, **9 months** was chosen
INH Issues

- **Hepatitis**: 0.5 to 1 % (fatal in ~ 0.1 %)
  - Risk factors: Increased age, alcohol consumption, underlying liver disease, concurrent use of hepatotoxic agents, ? Viral hepatitis, pregnancy, female gender, IVDU
  - Asymptomatic elevation in LFTs in 10-20%. Hold if LFTs > 3 x ULN with symptoms or > 5 x ULN if asymptomatic

- **Peripheral neuropathy**: 0.2% risk
  - Interferes with metabolism of pyridoxine, so can be prevented with pyridoxine therapy
  - Only recommended if other condition associated with neuropathy like DM, HIV, CKD, EtOHism, pregnancy/breastfeeding
### INH Hepatotoxicity

#### Table 1. Hepatotoxicity rate, adjusted for compliance with therapy, by age groups.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Adjusted incidence hepatotoxicity per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 19</td>
<td>0.8</td>
</tr>
<tr>
<td>20 – 34</td>
<td>2.8</td>
</tr>
<tr>
<td>35 – 54</td>
<td>9.1 (or 17.2*)</td>
</tr>
<tr>
<td>&gt; 54</td>
<td>31.0</td>
</tr>
</tbody>
</table>

Adjusted incidence by age group (criteria from Table 2 applied to age subgroups). References [28-36] were used.

*Reference [29] included in 35 – 54 group (based on mean age of participants = 50). If this study is excluded, rate for 35 – 54 is 17.2.*

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Rifampin

• 4 months of therapy
• Ideally to be used in those who cannot tolerate INH
• Reduction in TB incidence similar to INH
• Low rate of hepatotoxicity and well-tolerated

**ISSUES:**
  • Drug-drug interactions (therefore, be aware in HIV patients on ARVs)
  • Pruritis/Rash in ~ 6 %
  • Hepatotoxicity in 0.6%
INH and Rifapentine (RPT)—12 Dose

• 12-dose once-weekly regimen of INH and RPT = 9 months of INH

• NOT recommended:
  • Children < 2 yo
  • HIV/AIDS on ARVs
  • INH or rifampin-resistant MTb
  • Pregnant women (or those expecting to become pregnant)
INH and RPT Side Effects

• Hepatotoxicity greater in INH only group vs. this combo group, but “hypersensitivity” more frequent in combo group

• Combo therapy also associated with flu-like syndrome and systemic drug reaction (~ 3.5%)
Special Groups

- Contacts of patients with TB
  - Exposed to INH-resistant TB: Use RIF
  - Exposed to MDR TB: Consult expert
  - If previously treated, likely do not need retreatment (except for high risk individuals such as young children and immunosuppressed persons)
Special Groups (continued)

- HIV-infected persons
  - INH x 9 months is gold standard if receiving ARVs
  - Substitute Rifabutin for Rifampin in patients on certain ARVs
  - HIV positive NOT on ARTx can be given 12-dose regimen of INH/RPT
  - May consider treatment of HIV-infected persons with recent exposure to TB even if “TB test” is negative
Special Groups (continued)

- IMMEDIATE treatment of LTBI if HIV-infected or a recent contact
- Delay therapy about 2-3 months post delivery if without other risk factors
- INH daily or twice weekly DOT is preferred (with pyridoxine)
- NO 12-dose regimen
- Increased risk of hepatotoxicity
- OK to breastfeed
Monitoring of patients

- Monthly visit
- EDUCATION!!
  - Signs of hepatitis
  - Adherence to meds
  - Drug side effects (e.g., fever, anorexia, icterus, rash, n/v, RUQ abdominal pain)
- LAB TESTING
  - **Baseline labs NOT routinely necessary**
  - Obtain in patients with liver disease, HIV, pregnancy, hx of liver disease, EtOH users. Potentially for those on other “liver” meds
  - Test symptomatic individuals
Adherence

• Address adherence

• EDUCATION: Why are they taking INH??

• If issues, collaborate with local health dept
  • DOT if high risk
  • Case management
  • Free/Low-cost meds
WHAT TO DO IF THERAPY IS INTERRUPTED?

• Who knows??

• INH regimen (6 or 9 months)
  • If LESS than three months have been missed, probably can RESUME where left off
  • If MORE than three months have been missed, RESTART therapy

• Rifampin Regimen (3 or 4 months)
  • If LESS then two months have been missed, probably can RESUME where left off
  • If MORE than two months have been missed, RESTART therapy
Post-Treatment Follow-Up

• Provide patient with documentation of IGRA/TST, CXR results, medication name and duration of RX

• Discuss signs/symptoms of TB disease (remember, risk decreases by 60-90% after completion of therapy)

• REPEAT CXRs NOT NEEDED unless patient has signs/symptoms of TB disease (even if patient does NOT complete therapy)
OBJECTIVES

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QUESTION

Which of the following is most concerning when using Rifampin?

a) Hepatotoxicity
b) Drug-Drug interactions
c) Bone Marrow Suppression
d) Acute Kidney Injury
e) Neutropenia
Question

INH and Rifapentine 12 dose therapy for LTBI is most appropriate for which of the following patients?

a) 18 month old boy exposed to INH sensitive tuberculosis who now has a PPD skin test showing 22 mm of induration.
b) A pregnant female with a new positive PPD at 34 weeks gestation
c) An asymptomatic HIV positive patient who is well-controlled on his current antiretroviral regimen with a new positive PPD skin test
d) A 42 y/o female with insulin-requiring diabetes mellitus
e) A 24 y/o male medical student exposed to a patient in the hospital with possible rifampin-resistant TB
Questions/Comments??

• Contact Information
  • Mahesh C. Patel, M.D.
  • Office: 312-996-6732
  • Cell: 917-721-5281
  • Email: mp3@uic.edu