Treatment of rheumatologic conditions (TNFa Inhibitors) and TB

Dr Dick Menzies
Montreal Chest Institute (MUHC)
McGill University
Relative to a healthy person who is TST positive (or IGRA positive) and who has no risk factors for TB reactivation and a normal chest X-ray, what is the relative risk for development of active TB in a TST positive person who will start on TNF alpha inhibitor?

1. 15 to 20 times higher
2. 5 to 11 times higher
3. 3-5 times greater risk
4. 50 to 100 times higher
Which of the following are at highest risk of developing active tuberculosis if TST or IGRA positive and not treated?

1. Prednisone (or equivalent) at >20mg per day for more than 1 month
2. Methotrexate for >1 month
3. Infliximab - 3 doses
4. Etanercept – 3 doses
In a 40 year old Quebec-born individual about to start TNF alpha inhibitor therapy what test results would NOT warrant treatment for latent TB infection (assuming no major contraindications to such treatment).

1. TST 5mm, QFT (Quantiferon) indeterminant
2. TST 16mm, QFT negative
3. TST 0mm, QFT positive
4. TST 3mm, QFT negative
Which of the following are not considered acceptable therapy for latent TB infection?

1. 4 Months Rifampin taken daily
2. 2 months Rifampin and Pyrazinamide (2RZ) taken daily
3. 6 months isoniazid (INH)
4. 3 months INH and rifampin
Which one of the following is the most important contra-indication of LTBI with INH (choose one)?

1. Age greater than 35
2. Regularly drinks alcohol (1 to 2 drinks per day)
3. Hepatitis C co-infection
4. Abnormal liver enzymes (transaminases) pre-treatment
Hotels for Quebec Rheumatology Conference

2016

2017?
Australia's hotel industry has been rocked by a court's ruling that a prostitute was illegally discriminated against by a motel owner who refused

Hotels for TB meetings!
Conflict of interest statement

• Still nothing, after 25 years of work in the field!
• Although, I do hold research operating grants from Canadian Institutes of Health Research, and have received research grants from the World Health Organization, the International Union against TB, and Health Canada
Overview

- Questions
- Clinical aspects – risk of TB, manifestations
  - With TNFα Inhibitors
  - With other agents – Steroids, MTX, etc
- Pathogenesis (briefly)
- Diagnosis of Latent TB Infection
- Treatment of LTBI – who, when, and what
- Answers, and more questions.
Questions

• Question 1. Relative to a healthy person who is TST positive (or IGRA positive) and who has no risk factors for TB reactivation and a normal chest X-ray, what is the relative risk for development of active TB in a TST positive person who will start on TNF alpha inhibitor?

• Question 2. Which of the following causes the highest risk of developing active tuberculosis if TST or IGRA positive and not treated? (All taken for more than 1 month - Choose one)
  – Prednisone (or equivalent) at >20mg per day
  – Methotrexate for >1 month
  – Infliximab
  – Etanercept
Questions, cont’d

• Question 3. In a 40 year old Quebec-born individual about to start TNF alpha inhibitor therapy what test results would warrant treatment for latent TB infection (assuming no major contra-indications to such treatment). Check all that apply.
  – TST 5mm, QFT (Quantiferon) indeterminant
  – TST 16mm, QFT negative
  – TST 0mm, QFT positive
  – TST 3mm, QFT negative

• Question 4. Which of the following are not considered acceptable therapy for latent TB infection?
  – 4 Months Rifampin taken daily
  – 2 months Rifampin and Pyrazinamide (2RZ) taken daily
  – 6 months isoniazid (INH)
  – 3 months INH and rifampin
Questions, cont’d

- Question 5. Which one of the following is the most important contraindication of LTBI with INH (choose one)?
  - Age greater than 35
  - Regularly drinks alcohol (1 to 2 drinks per day)
  - Hepatitis C co-infection
  - Abnormal liver enzymes (transaminases) pre-treatment
Clinical aspects

• Case history:
  • 34 year old male, originally from India, but in Canada >10 years
  • Severe Crohn’s disease – refractory to multiple and prolonged courses of Steroids
  • Received Infliximab (2 doses)
  • Presented to ER with fever and multiple grossly enlarged lymph nodes (axillary, inguinal, cervical)
  • Biopsy: necrotizing granulomas. AFB negative. Culture grew M Tuberculosis after 3 weeks.
TNF-α Inhibitors

- Infliximab (Remicade)
- Adalimumab (Humira)
- Etanercept (Embrel)
- Certolizumab pegol (Cimzia)
- Golimumab (Simponi)
- Etc…

From Wallis, LID 2008
TB and TNFα inhibitors - 2001

1st report – Keane NEJM 2001

- 147,000 treated with Infliximab → 70 cases of TB
  - Rate 48/100,000
  - 91% of patients from countries with incidence ≤ 20/100,000
  - Median age 57
  - Extra pulmonary TB 56% and 24% disseminated TB
- In U.S: Rate in Infliximab treated 24/100,000
  
  Rate in general population 6/100,000
- 102,000 treated with Etanercept → 6 cases of TB
  
  Rate in Etanercept treated 6/100,000
Risk of TB with TNFα inhibitors – Spain 2003

- The Spanish Society of Rheumatology Database on Biologic Products. (Gómez-Reino; Arthritis Rheum. 2003;48:2122)

- 1540 patients with rheumatologic diseases
  - Infliximab (great majority 86%) or etanercept
  - Compared to patients who received neither:

- 17 cases of TB, all in patients taking infliximab.

- Incidence of TB with infliximab:
  - 1900 per 100,000 patients in 2000
  - 1100 per 100,000 patients in 2001

- General Population in Spain: 21 per 100,000
Comparison of TB incidence with different Agents vs the General Population (Rates per 100,000)

<table>
<thead>
<tr>
<th></th>
<th>U.S. + Europe</th>
<th>Spain</th>
<th>U.S.</th>
<th>U.K.</th>
<th>Portugal</th>
<th>Taiwan</th>
<th>France</th>
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</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>48</td>
<td>1900</td>
<td>1100</td>
<td>54</td>
<td>136</td>
<td>175</td>
<td>-----</td>
</tr>
<tr>
<td>Etanercept</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>39</td>
<td>30</td>
<td>450</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>144</td>
<td>230</td>
<td>616</td>
</tr>
<tr>
<td>Rituximab</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>33</td>
</tr>
<tr>
<td>General Pop’n</td>
<td>&lt; 20</td>
<td>21</td>
<td>21</td>
<td>6</td>
<td>15</td>
<td>20</td>
<td>148</td>
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</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RA/Biologic DMARDs Events</th>
<th>Pys</th>
<th>General population Events</th>
<th>Pys</th>
<th>Weight</th>
<th>Incidence Rate Ratio M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Arkema et al. (24)</td>
<td>37</td>
<td>100000</td>
<td>4</td>
<td>100000</td>
<td>3.5%</td>
<td>9.25 [3.30, 25.95]</td>
</tr>
<tr>
<td>Askling et al. (13)</td>
<td>118</td>
<td>100000</td>
<td>5</td>
<td>100000</td>
<td>4.5%</td>
<td>23.60 [9.64, 57.75]</td>
</tr>
<tr>
<td>Dixon et al. (18)</td>
<td>118</td>
<td>100000</td>
<td>13</td>
<td>100000</td>
<td>8.7%</td>
<td>9.08 [5.12, 16.09]</td>
</tr>
<tr>
<td>Gomez-Reino et al. (17)</td>
<td>416</td>
<td>100000</td>
<td>20</td>
<td>100000</td>
<td>11.6%</td>
<td>20.80 [13.28, 32.57]</td>
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<tr>
<td>Seong et al. (16)</td>
<td>1316</td>
<td>100000</td>
<td>67</td>
<td>100000</td>
<td>18.5%</td>
<td>19.64 [15.37, 25.10]</td>
</tr>
<tr>
<td>Tam et al. (20)</td>
<td>2162</td>
<td>100000</td>
<td>92</td>
<td>100000</td>
<td>19.9%</td>
<td>23.50 [19.08, 28.95]</td>
</tr>
<tr>
<td>Tubach et al. (19)</td>
<td>120</td>
<td>100000</td>
<td>9</td>
<td>100000</td>
<td>6.9%</td>
<td>13.33 [6.77, 26.25]</td>
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<tr>
<td>Wallis et al. (14)</td>
<td>45</td>
<td>100000</td>
<td>6</td>
<td>100000</td>
<td>4.8%</td>
<td>7.50 [3.20, 17.58]</td>
</tr>
<tr>
<td>Winthrop et al. (21)</td>
<td>49</td>
<td>100000</td>
<td>3</td>
<td>100000</td>
<td>2.8%</td>
<td>16.33 [5.09, 52.40]</td>
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<tr>
<td>Yoo et al. (23)</td>
<td>1299</td>
<td>100000</td>
<td>73</td>
<td>100000</td>
<td>18.8%</td>
<td>17.79 [14.06, 22.52]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1000000
Total events 5680 292
Heterogeneity: Tau² = 0.05; Chi² = 18.87, df = 9 (P = 0.03); I² = 52%
Test for overall effect: Z = 26.59 (P < 0.00001)

In the summary table, the relative risk of tuberculosis (TB) with biologics compared to the general population is shown. The incidence rate ratio (M-H, Random, 95% CI) indicates a significant increase in the risk of TB with biologics. The overall effect is highly significant with a Z value of 26.59 and a p-value less than 0.00001.
Risk of TB with TNFα inhibitors – additional risk factors  
(Raval; Ann Intern Med. 2007;147:699)

• The US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS): 2001-2006
• 130 patients with TB after infliximab
• Additional risk factors for TB:
  – Other immunosuppressive drugs (in 89 patients),
  – History of latent or active TB (in 33 patients),
  – Born, or lived in a high TB incidence country (in 25 patients)
Timing of TNF-α to TB

Figure 1. Time from the Initiation of Infliximab Therapy to the Diagnosis of Tuberculosis.
Data were available for 57 patients, most of whom had received monthly infusions of infliximab.

Keane NEJM 2001
Incidence of TB – by TNFα inhibitor vs cDMARD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Registration (entry to study)</th>
<th>1 year (365 days)</th>
<th>2 years (730 days)</th>
<th>3 years (1095 days)</th>
<th>4 years (1460 days)</th>
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<tbody>
<tr>
<td>DMARD</td>
<td>3232</td>
<td>2652</td>
<td>1839</td>
<td>742</td>
<td>213</td>
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<tr>
<td>ETA</td>
<td>3913</td>
<td>3474</td>
<td>3051</td>
<td>2363</td>
<td>1029</td>
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<tr>
<td>INF</td>
<td>3295</td>
<td>2694</td>
<td>1918</td>
<td>1392</td>
<td>918</td>
</tr>
<tr>
<td>ADA</td>
<td>3504</td>
<td>2457</td>
<td>1531</td>
<td>729</td>
<td>247</td>
</tr>
</tbody>
</table>

Adalimumab
Infliximab
Etanercept
Non-Biologic
Timing of TB with TNFa inhibitors (from Wallis LID 2008)

• Time from 1st dose to TB diagnosis:
  – Infliximab range 12 to 32 weeks
  – Median: 16 weeks
  – Etanercept range 18 to 79 weeks
  – Median: 60 weeks
Clinical Manifestations of TB with TNFα inhibitors

• Atypical!
• More likely extra-pulmonary manifestations
  – In 3 studies: 57%, 63%, and 67% had EP-TB
  – Abdominal, Lymph nodes, pleural/pericardial
  – Miliary and meningitis (disseminated) in 20 - 25%
• Pulmonary disease – atypical appearance
  – More likely lower lobe
  – Also less likely cavitary
• Leads to delayed diagnosis, with more morbidity and mortality
Pathogenesis
An Epidemiologist’s understanding of Pathogenesis
OK, Back to Clinical/Epi,
TB and Conventional DMARDs
Cumulative incidence of TB with different agents vs non-RA patients (from Liao PLOS1)
# Risks of TB with conventional DMARD vs Biologics

<table>
<thead>
<tr>
<th>Country</th>
<th>Askling 2005</th>
<th>Dixon 2010</th>
<th>Liao 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Pop’n</td>
<td>Sweden</td>
<td>U.K.</td>
<td>Taiwan</td>
</tr>
<tr>
<td>Rate</td>
<td>49</td>
<td>0</td>
<td>394</td>
</tr>
<tr>
<td>RR: /General Pop’n</td>
<td>3.8</td>
<td>0</td>
<td>2.7</td>
</tr>
<tr>
<td>Biologics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Treated</td>
<td>33,615</td>
<td>3,272</td>
<td>36,162</td>
</tr>
<tr>
<td>Rate</td>
<td>118</td>
<td>95</td>
<td>536</td>
</tr>
<tr>
<td>RR: Biologics /cDMARD</td>
<td>2.4</td>
<td>&gt;10</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**cDMARDs (conventional)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Pys</th>
<th>Events</th>
<th>Pys</th>
<th>Weight</th>
<th>Incidence Rate Ratio</th>
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</tr>
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<tr>
<td>Arkema et al. (24)</td>
<td>14</td>
<td>100000</td>
<td>4</td>
<td>100000</td>
<td>9.4%</td>
<td>3.50 [1.15, 10.63]</td>
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<tr>
<td>Dixon et al. (18)</td>
<td>0</td>
<td>100000</td>
<td>13</td>
<td>100000</td>
<td>1.9%</td>
<td>0.04 [0.00, 0.62]</td>
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<tr>
<td>Gomez–Reino et al. (17)</td>
<td>90</td>
<td>100000</td>
<td>20</td>
<td>100000</td>
<td>22.5%</td>
<td>4.50 [2.77, 7.30]</td>
<td></td>
</tr>
<tr>
<td>Seong et al. (16)</td>
<td>257</td>
<td>100000</td>
<td>67</td>
<td>100000</td>
<td>29.1%</td>
<td>3.84 [2.93, 5.02]</td>
<td></td>
</tr>
<tr>
<td>Tam et al. (20)</td>
<td>242</td>
<td>100000</td>
<td>92</td>
<td>100000</td>
<td>29.9%</td>
<td>2.63 [2.07, 3.34]</td>
<td></td>
</tr>
<tr>
<td>Winthrop et al. (21)</td>
<td>9</td>
<td>100000</td>
<td>3</td>
<td>100000</td>
<td>7.3%</td>
<td>3.00 [0.81, 11.08]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 600000 600000 100.0% 3.17 [2.12, 4.73]

Total events 612 199

Heterogeneity: Tau² = 0.12; Chi² = 16.09, df = 5 (P = 0.007); I² = 69%

Test for overall effect: Z = 5.64 (P < 0.000001)
Relative risk of TB with Biologics vs Conventional DMARDs (Ai; Journal of Rheum: 2015)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>RA/Biologic DMARDs</th>
<th>RA/Non biologic DMARDs</th>
<th>Incidence Rate Ratio M-H, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Pys</td>
<td>Events</td>
</tr>
<tr>
<td>Arkema et al. (24)</td>
<td>18</td>
<td>48228</td>
<td>32</td>
</tr>
<tr>
<td>Dixon et al. (18)</td>
<td>40</td>
<td>34025</td>
<td>0</td>
</tr>
<tr>
<td>Seong et al. (16)</td>
<td>2</td>
<td>152</td>
<td>9</td>
</tr>
<tr>
<td>Tam et al. (20)</td>
<td>4</td>
<td>185</td>
<td>16</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>82590</td>
<td></td>
<td>241119</td>
</tr>
</tbody>
</table>

Total events: 64 57

Heterogeneity: $\chi^2 = 5.41, df = 3 (P = 0.14); I^2 = 45$

Test for overall effect: $Z = 5.12 (P < 0.00001)$
Diagnosis of Latent TB

TST or IGRA?
Or both? Neither?
Diagnosis of LTBI in persons who will start TNFα inhibitors

- Tuberculin skin test
  - Simple, accessible, easy to interpret,
  - Documented value of LTBI treatment if TST +
  - BUT – 2 visits in 48-72 hours, and BCG effect

- IGRA’s (QFT)
  - One visit, but takes 2 weeks to get results (batched)
  - No problems related to effect of prior BCG

- False negative rate – same with TST or QFT
  - So Chest X-ray also – for fibro-nodular changes
### Effect of Disease, Test, and Treatment on IGRA results *(Wong Thorax 2016)*

<table>
<thead>
<tr>
<th></th>
<th>On IST N</th>
<th>Not on IST N</th>
<th>Odds of Pos. IGRA OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All 17 studies</strong></td>
<td>2215</td>
<td>982</td>
<td>0.66 (0.5, 0.8)</td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantiferon</td>
<td>1728</td>
<td>764</td>
<td>0.65 (0.5, 0.8)</td>
</tr>
<tr>
<td>T-Spot-TB</td>
<td>924</td>
<td>448</td>
<td>0.81 (0.6, 1.1)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>988</td>
<td>788</td>
<td>0.75 (0.6, 1.0)</td>
</tr>
<tr>
<td>Other oral imm. Supp.</td>
<td>1189</td>
<td>737</td>
<td>0.68 (0.5, 0.9)</td>
</tr>
<tr>
<td>Anti-TNFα</td>
<td>249</td>
<td>334</td>
<td>0.50 (0.3, 0.9)</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>649</td>
<td>289</td>
<td>0.50 (0.3, 0.8)</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>1169</td>
<td>484</td>
<td>0.67 (0.5, 0.9)</td>
</tr>
</tbody>
</table>
Predictive value of concordant and discordant TST and IGRA reactions

<table>
<thead>
<tr>
<th></th>
<th>The Gambia</th>
<th>Turkey</th>
<th>Senegal</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGRA- / TST-</td>
<td>4.0 (0.8-7.2)</td>
<td>5.1 (0.6-18)</td>
<td>9.8 (3.3-26)</td>
</tr>
<tr>
<td>IGRA+ / TST-</td>
<td>12.4 (0.3-25)</td>
<td>11.7 (0.3-65)</td>
<td>5.9 (0.8-42)</td>
</tr>
<tr>
<td>IGRA- / TST+</td>
<td>9.6 (0.2-19)</td>
<td>7.4 (0.9-27)</td>
<td>4.9 (1.2-20)</td>
</tr>
<tr>
<td>IGRA+ / TST+</td>
<td>8.9 (2.4-15)</td>
<td>22 (10.6-41)</td>
<td>14.7 (8.7-25)</td>
</tr>
</tbody>
</table>
### Summary of recommendations for testing patients before TNFα therapy

*(Iannone, *J Rheumatology* 2014)*

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>IGRA</th>
<th>Both?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Canada TB Standard</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Possibly if 1\textsuperscript{st} test negative</td>
</tr>
<tr>
<td><strong>U.S. (CDC)</strong></td>
<td>Yes</td>
<td>Yes – if BCG</td>
<td>Possibly if 1\textsuperscript{st} test negative</td>
</tr>
<tr>
<td><strong>U.K. (BTS)</strong></td>
<td>Yes</td>
<td>No</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Europe (TBNET)</strong></td>
<td>Not if BCG</td>
<td>Yes – if BCG</td>
<td>Not stated</td>
</tr>
</tbody>
</table>
What is a positive test? Who should be treated?

- TST 5mm or greater (Canadian, US, UK standards)
- Role of IGRA?
  - To identify false positive TST in BCG vaccinated?
  - To add sensitivity, if TST might be false negative?
- What if both TST and IGRA are negative?
  - Will a chest Xray be helpful?
Lets do some math

- Foreign-born – age 45, BCG as an infant
  - From Zimbabwe, arrived at age 20
  - TST is positive (11mm), and IGRA is negative.
  - Chest Xray is normal.
- Using TSTin3D calculator [www.TSTin3D.com](http://www.TSTin3D.com):
  - Likelihood that TST reflects true infection: 92%
  - Annual risk of disease: (0.1% X 17 X = 1.6%)
One more example

• Foreign-born – age 45, BCG in primary school
  – From Russia, arrived at age 20
  – TST is positive (11mm), and IGRA is negative.
  – Chest Xray is normal.
  – Using TSTin3D calculator www.TSTin3D.com:
    – Likelihood that TST reflects true infection: 50%
    – Annual risk of disease: (0.1% X 17 X = 0.8%)

• For both – treatment is indicated given high risk of disease, *even if it may be false positive due to BCG*
Current regimens for treatment of LTBI

What is the evidence?
LTBI treatment – what are the options?

- 9 months of INH – the current standard
- 6 months INH
- 3-4 months INH-RIF
- 3 months once weekly INH & Rifapentine
- 4 months RIFampin
Serious hepato-toxicity from INH treatment  
*(Smith; CMAJ: 2011)*  
Unadjusted risks of hospitalization for hepatic illnesses per 100 patients

<table>
<thead>
<tr>
<th>Age group, yr</th>
<th>LTBI therapy no. of events/patients / 100 patients (95% CI)</th>
<th>Risk difference Treated vs. Untreated / 100 patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Patients without comorbidity</td>
</tr>
<tr>
<td>Total</td>
<td>45/9145 (0.5)</td>
<td>15/6532 (0.2)</td>
</tr>
<tr>
<td>&lt;35</td>
<td>5/4523 (0.1)</td>
<td>5/3765 (0.1)</td>
</tr>
<tr>
<td>36-50</td>
<td>8/2533 (0.3)</td>
<td>4/1898 (0.2)</td>
</tr>
<tr>
<td>51-65</td>
<td>10/1232 (0.8)</td>
<td>2/668 (0.3)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>22/857 (2.6)</td>
<td>4/205 (2.0)</td>
</tr>
</tbody>
</table>
RCT of 4RIF vs 9INH for TB Prevention

Problems with INH - Summary

1. Length - 6 months minimum, 9 months better
   – Results in poor compliance - less than 50% in most programs, although can be 70%.

2. Side effects of hepatitis - can be fatal although this is now rare
   – Also rash, neuropathies

3. Costs - INH is cheap but close follow up is necessary and this is expensive
Why 4 months RIF?

- Animal studies
- One prior RCT
- ATS and CTS recommendations in 2000
- 2RIF-PZA experience
Experimental Study of Short-Course Preventive Therapy in Mice – 2RIF was overlooked

Efficacy of 3 months of Rifampin for the Prevention of TB Patients with Silicosis

6 Months Rifampin Mono-Therapy
(For contacts of INH resistant cases)

(Polesky et al., AJRCCM; 1996: 155: 1735-38)

- Homeless persons in Boston, screened in shelters
- **Extended Outbreak of INH resistant TB**
- 204 Exposed persons with documented TST conversion
- Therapy of LTBI was **not** randomized
- 71 no therapy – **8.6%** active TB
- 38 given INH – **7.9%** active TB (INH Resistant)
- 86 RIF or INH/RIF – **0** active TB
  - 49 Rifampin only – no hepatitis or increased LFT’s
Program Experience with 4RIF and 9INH
Maryland 1999-2004
Page et al. Archives Internal Med. 2006: 166; 1863-70

- Patients offered 4 RIF or 9 INH by provider
- Concurrent study but non-randomized

<table>
<thead>
<tr>
<th></th>
<th>4 RIF</th>
<th>9 INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Starting</td>
<td>1,379</td>
<td>770</td>
</tr>
<tr>
<td>Completing Therapy</td>
<td>987 (72%)</td>
<td>405 (52%)</td>
</tr>
<tr>
<td>Grade 3 to 4 Hepatitis</td>
<td>1 (0.1%)</td>
<td>12 (2%)</td>
</tr>
</tbody>
</table>
Program Experience with 4RIF and 9INH
New Jersey 1999-2004
Lardizabal et al. Chest, 2006: 130;1712-16

Non-concurrent and non-randomized study

<table>
<thead>
<tr>
<th></th>
<th>4 RIF</th>
<th>9 INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Starting</td>
<td>261</td>
<td>213</td>
</tr>
<tr>
<td>Completing Therapy</td>
<td>210 (81%)</td>
<td>113 (53%)</td>
</tr>
<tr>
<td>Grade 3 to 4 SAE</td>
<td>8 (3%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>
A randomized trial to compare 4 months Rifampin vs 9 months INH for the treatment of LTBI

(Or, 13 years in 5 minutes)
The 4v9 Trial
4RIF vs 9INH for LTBI

Phase 1: Compliance and completion
Completed in 2003

Phase 2 – Adverse events and costs
Completed in 2007

Phase 3: Efficacy and effectiveness
Started in 2008, Completion Jan 2017
## RCT of 9 INH vs. 4 RIF – Phase 1

Completion of therapy among randomized participants

<table>
<thead>
<tr>
<th></th>
<th>9 INH (N=58)</th>
<th>4 RIF (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Rx good compliance, N(%)</td>
<td>36 (62%)</td>
<td>50 (86%)</td>
</tr>
<tr>
<td>Completed Rx poor compliance, N(%)</td>
<td>8 (14%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Did not complete Rx, N(%)</td>
<td>14 (24%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>MD stopped b/o Side effects N(%)</td>
<td>8 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>&lt; 90% of doses correct at 1 month, N(%)</td>
<td>20 (34%)</td>
<td>12 (21)</td>
</tr>
</tbody>
</table>

\[1 \text{ P-value} = 0.01\]
RCT of 4RIF vs. 9INH for LTBI – Phase 2
Completion of Therapy

<table>
<thead>
<tr>
<th></th>
<th>4 RIF (N=420)</th>
<th>9 INH (N=427)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed Therapy N (%)</strong></td>
<td>339 (81%)</td>
<td>259 (69%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Patient Non-compliant (Total)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Drop-out</td>
<td>61 (14%)</td>
<td>117 (27%)</td>
<td></td>
</tr>
<tr>
<td>- Intolerance</td>
<td>52 (12%)</td>
<td>82 (20%)</td>
<td></td>
</tr>
<tr>
<td>- Intolerance</td>
<td>3 (1%)</td>
<td>23 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>MD Non-compliant</strong></td>
<td>6 (1%)</td>
<td>12 (3%)</td>
<td></td>
</tr>
</tbody>
</table>
## RCT of 4RIF vs. 9INH for LTBI – Phase 2

### Serious Drug Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>4 RIF (N=420)</th>
<th>9 INH (N=427)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>**All Grades – Total (%) *</td>
<td>16 (3.8%)</td>
<td>24 (5.6%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Grade 3 to 4 - Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hepato-toxicity</td>
<td>6 (1.5%)</td>
<td>17 (4.0%)</td>
<td>.02</td>
</tr>
<tr>
<td>- Hematologic</td>
<td>3 (0.7%)</td>
<td>16 (3.8%)</td>
<td>.003</td>
</tr>
<tr>
<td>- Drug Interaction</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>- Rash</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Grade 1 to 2 - Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rash</td>
<td>11 (2.0%)</td>
<td>7 (1.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>- GI intolerance</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>- Hematologic</td>
<td>2</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

* Severity, type + relationship to study drug by independent blinded 3-member panel
RCT of 4RIF vs 9INH – Phase 3

- Pediatric study – safety and tolerability
  - 845 children enrolled.
  - Completed all follow-up June 2015

- Adult study: Effectiveness and efficacy
  - Started 2009, Completed enrolment Dec 2014
  - 6031 adults enrolled.
  - Follow-up will be completed March 2017
Current (or almost current) recommendations

- World Health: 4RIF or 9INH or 6INH or 3HP
- Can Thoracic: 9INH, 4RIF or 6INH alternates
- Am Thoracic: 2000 – 9INH
- 2016 – 3HP and 4RIF
- What are we using now at Mtl Chest - TB clinic? 4RIF
- In Nunavik? 4RIF. Several US States? 4RIF
“How soon after LTBI treatment is started can TNFα therapy be started?

- Iannone et al, (J Rheumatology 2014) reviewed recommendations from 10 different high income countries:
  - Most recommended waiting 1 months.
  - The remainder recommended after 2 months, with the longer period to allow more time to detect adverse effects from INH.
Relative to a healthy person who is TST positive (or IGRA positive) and who has no risk factors for TB reactivation and a normal chest X-ray, what is the relative risk for development of active TB in a TST positive person who will start on TNF alpha inhibitor?

1. 15 to 20 times higher
2. 5 to 11 times higher
3. 3-5 times greater risk
4. 50 to 100 times higher
Relative to a healthy person who is TST positive (or IGRA positive) and who has no risk factors ...
Which of the following are at highest risk of developing active tuberculosis if TST or IGRA positive and not treated?

1. Prednisone (or equivalent) at >20mg per day for more than 1 month
2. Methotrexate for >1 month
3. Infliximab - 3 doses
4. Etanercept – 3 doses
Which of the following are at highest risk of developing active tuberculosis if TST or IGRA positive?

- Prednisone (or equivalent) at >20mg per day for more than 1 month: 47%
- Methotrexate for >1 month: 4%
- Infliximab - 3 doses: 100%
- Etanercept – 3 doses: 2%
In a 40 year old Quebec-born individual about to start TNF alpha inhibitor therapy what test results would NOT warrant treatment for latent TB infection (assuming no major contraindications to such treatment).

1. TST 5mm, QFT (Quantiferon) indeterminant
2. TST 16mm, QFT negative
3. TST 0mm, QFT positive
4. TST 3mm, QFT negative
In a 40 year old Quebec-born individual about to start TNF alpha inhibitor therapy, what test results are shown:

- **TST 5mm, QFT (Quantiferon) indeterminant**: 8% for First Slide, 8% for Second Slide.
- **TST 16mm, QFT negative**: 10% for First Slide, 3% for Second Slide.
- **TST 0mm, QFT positive**: 10% for First Slide, 0% for Second Slide.
- **TST 3mm, QFT negative**: 78% for First Slide, 90% for Second Slide.
Which of the following are not considered acceptable therapy for latent TB infection?

1. 4 Months Rifampin taken daily
2. 2 months Rifampin and Pyrazinamide (2RZ) taken daily
3. 6 months isoniazid (INH)
4. 3 months INH and rifampin
Which of the following are not considered acceptable therapy for latent TB infection?

- 4 Months Rifampin taken daily: 18% (First Slide) 0% (Second Slide)
- 2 months Rifampin and Pyrazinamide (2RZ) taken daily: 49% (First Slide) 89% (Second Slide)
- 6 months isoniazid (INH): 18% (First Slide) 0% (Second Slide)
- 3 months INH and rifampin: 15% (First Slide) 11% (Second Slide)
Which one of the following is the most important contra-indication of LTBI with INH (choose one)?

1. Age greater than 35
2. Regularly drinks alcohol (1 to 2 drinks per day)
3. Hepatitis C co-infection
4. Abnormal liver enzymes (transaminases) pre-treatment

- Age greater than 35: 59%
- Regularly drinks alcohol: 32%
- Hepatitis C co-infection: 5%
- Abnormal liver enzymes: 3%
Which one of the following is the most important contra-indication of LTBI with INH (choose one)?

- Age greater than 35: 0% (First Slide), 3% (Second Slide)
- Regularly drinks alcohol (1 to 2 drinks per day): 2% (First Slide), 5% (Second Slide)
- Hepatitis C co-infection: 46% (First Slide), 32% (Second Slide)
- Abnormal liver enzymes (transaminases) pre-treatment: 51% (First Slide), 59% (Second Slide)
The answers (to my questions)
Questions - Answers

• Question 1. Relative to a healthy person who is TST positive (or IGRA positive) and who has no risk factors for TB reactivation and a normal chest X-ray, what is the relative risk for development of active TB in a TST positive person who will start on TNF alpha inhibitor?

• 2x
• 17x
• Estimates range from 2 to 20. Consensus is 15-20.

• Question 2. Which of the following causes the highest risk of developing active tuberculosis if TST or IGRA positive and not treated? (All taken for more than 1 month - Choose one)
  – Prednisone (or equivalent) at >20mg per day
  – Methotrexate for >1 month
  – Infliximab
  – Etanercept
Answers, cont’d

• Question 3. In a 40 year old Quebec-born individual about to start TNF alpha inhibitor therapy what test results would warrant treatment for latent TB infection (assuming no major contra- indications to such treatment). Check all that apply.
  – TST 5mm, QFT (Quantiferon) indeterminant
  – TST 16mm, QFT negative
  – TST 0mm, QFT positive
  – TST 3mm, QFT negative

• Question 4. Which of the following are not considered acceptable therapy for latent TB infection?
  – 4 Months Rifampin taken daily
  – 2 months Rifampin and Pyrazinamide (2RZ) taken daily
  – 6 months isoniazid (INH)
  – 3 months INH and rifampin
• Question 5. Which one of the following is the most important contraindication of LTBI with INH (choose one)?
  – Age greater than 35
  – Regularly drinks alcohol (1 to 2 drinks per day)
  – **Hepatitis C co-infection**
  – Abnormal liver enzymes (transaminases) pre-treatment
Thank you (other questions?)

- Merci
- Gracias
- Obrigado
- Awanou
- Nakurmik