4 months Rifampin for the treatment of LTBI

What is the evidence?

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 similar grants from the World Health Organization, the International Union against TB, and Health Canada

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
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, 12 years in 20 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, Completed when my lifetime
**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%)  1</td>
<td>50 (86%)  1</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%)  1</td>
<td>4 (7%)  1</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 P-value = 0.01

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**RCT of 4RIF vs 9INH for LTBI – Phase 2**

Objectives of Phase 2

- **Primary objective**
  - Compare rate of serious adverse events
- **Secondary objectives**
  - Compare compliance and completion
  - Compare costs

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**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>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Therapy N (%)</td>
<td>339 (81%)</td>
<td>259 (60%)</td>
</tr>
<tr>
<td>Patient Non-compliant (Total)</td>
<td>61 (14%)</td>
<td>117 (27%)</td>
</tr>
<tr>
<td>- Drop-out</td>
<td>52 (12%)</td>
<td>82 (20%)</td>
</tr>
<tr>
<td>- Intolerance</td>
<td>3 (1%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>MD Non-compliant</td>
<td>6 (1%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</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>Grade 3 to 4 - Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hepato-toxicity</td>
<td>6 (1.5%)</td>
<td>17 (4.0%)</td>
<td>.003</td>
</tr>
<tr>
<td>- Hematologic</td>
<td>1</td>
<td>1</td>
<td>-</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>Grade 1 to 2 - Total</td>
<td>11 (2.0%)</td>
<td>7 (1.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>- Rash</td>
<td>8</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>- GI intolerance</td>
<td>1</td>
<td>2</td>
<td>-</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 for LTBI – Phase 3**

**Objectives of Phase 3**

- Adults: Primary objective
  - Effectiveness - Incidence of confirmed active TB in all randomized in the 28 months post-randomization
- Adults: Secondary objectives
  - Efficacy - Incidence of confirmed active TB in those who took at least 80% of doses within allowed time
  - Serious adverse events
- Pediatric: Objectives
  - Safety and tolerability
  - Completion/compliance

**RCT of 9 INH vs. 4 RIF for LTBI – Phase 3**

**Study design**

- Design - open label randomized trial.
- “Pragmatic” trial – work in programme conditions.
- Follow-up: active detection of TB within 28 months post-randomization.
- Outcomes – TB and Adverse events – blinded independent review panel.
RCT of 4RIF vs 9INH for LTBI – Phase 3

Study Centres

• 4 in Canada
  – Montreal (Chest), Saskatoon, Edmonton, Vancouver
• International sites
  – Australia (Sydney)
  – Benin (Cotonou)
  – Brazil (Rio de Janeiro - 2 sub-sites)
  – Ghana (Kumasi)
  – Guinea (Conakry)
  – Indonesia (Bandung)
  – Korea (4 sub-sites)
  – Saudi Arabia - Riyadh

Sites in RCT Phase 3

- World map showing locations of study centers

RCT of 4RIF vs 9INH for LTBI – Progress - enrolment

• Study up and running in all sites
• One site never opened
• One very low enrolling site closed
• One low-enrolling site - budget cut in half
• One site – start delayed by a year due to civil unrest (coup / martial law / etc)
• Two new sites identified and opened
•
Cumulative enrolment – Pediatric trial
October 2011 to January 2014 (completed)

Cumulative enrolment – Adult trial:
October 2009 to May 2014 (target 6000)

RCT of 4RIF vs 9INH for LTBI –
Timelines of Phase 3

- Pediatric trial – target 822 children
  - January 15 2014: 845 enrolled
- Adults - Planned enrolment is almost 6,000 persons.
  - By May 31: 5,420 enrolled
  - Enrolment until Dec 1 2014
  - Final follow-up will end in April 2017
- Publication in July 2017!
- Wish us luck
  - (even just to survive!!)
The investigators – at the starting line

After a few years – Note how they dress!!

The investigators in 2013 – the survivors!!
4RIF for LTBI –
Thank you

• Merci
• Gracias
• Obrigado
• Awanou
• Nakurmi

RCT of 4RIF vs 9INH for LTBI –
Budget matters

• Phase 2: $1.1 million
• Phase 3: Adults: $4.8 million
  Children: $1.2 million
  Biomarker: $0.6 million
  In kind/other sources: $1.0 million
  (in-kind includes grants and other support from Australia, Brazil, Saudi Arabia)
• Phase 3 total: $7.6 million for 6,800 enrollees
  = $1118 per participant (although not done yet)