Short-course chemotherapy for multidrug-resistant tuberculosis

or

the difficulty in accepting paradigm shifts

[Chimiothérapie de courte durée dans le traitement de la tuberculose multi-résistante ou la difficulté à accepter un changement de paradigme]

Cotonou, 15 janvier 2012

Hans L Rieder, UICTMR
Culture Conversion of Pulmonary Tuberculosis in Patients with Susceptible Organisms, Receiving SM-INH-PAS

Crofton J. Am Rev Tuberc 1958;77:869-71
Drug-susceptible tuberculosis is curable with a three-drug combination of isoniazid, streptomycin, and para-aminosalicylic acid in 18 months (observational study in Edinburgh, Scotland)

*Crofton J. Am Rev Tuberc Pulm Dis 1958;77:869-71*

“... it is clear that the bacilli are not eradicated ... as a direct consequence of the chemotherapy... ...Triple-drug regimens have little place, as judged both on theoretical grounds and from experience in actual trials...”

*McDermott W. Bull World Health Organ 1960;23:427-61*
Drug-susceptible tuberculosis is curable with a three-drug combination of isoniazid, rifampicin, ethambutol in 9 months (clinical trial in France)

*Brouet G, Roussel G. Rev Fr Mal Respir 1977;5(Suppl 1):5-13*

“... Short-course chemotherapy for tuberculosis – a story of flawed studies...”

*Buechner HA. Am Rev Respir Dis 1981;124:655-6*
Multidrug-resistant tuberculosis that is not XDR is curable with a 9-month, fourth-generation-based fluoroquinolone regimen (observational study in Bangladesh Damien Foundation project areas)


“...an intensive phase of at least 8 months’ duration ... a total duration of at least 20 months is recommended ...”

“... a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”

Max Planck
The Regimen Cascade

8- or 18-mo INH-throughout regimen:
- 2 S-H-PAS / 16 H-PAS
- 2 S-H-R-Z / 6 H
- 2 E-H-R-Z / 8 E-H
≥ 90% effective

6- or 8-mo RMP-throughout regimen:
- 2 S-E-H-R-Z / 6 E-H-R-Z
- 2 S-E-H-R-Z / 6 R-H
- 2 E-H-R-Z / 4 H-R
≥ 90% effective

9- to 12-mo FQ-throughout regimen:
- 4(+) K-G-T-C-H-E-Z / 5 G-C-E-Z
≥ 90% effective

Complex! Toxic! 21-mo regimen – poor effectiveness (50%)
Definition for non-success and success

Adverse treatment outcome (non-success)
- Death from any cause while on treatment
- Bacteriological treatment failure
- Transfer to another jurisdiction (0 cases in the series)
- Absconding from treatment
- Recurrent tuberculosis, not proven to be re-infection

Successful treatment outcome
- Completion or preferably relapse-free cure up to 2 (update: 5) years subsequent to treatment cessation

The (minimum) 9-month regimen for MDR in Bangladesh (220 €)

Kanamycin

Prothionamide

Isoniazid

Gatifloxacin

Ethambutol

Pyrazinamide

Clofazimine

4-month intensive phase prolonged if still smear-positive after 4 months

Fixed 5-month continuation phase

# Fluoroquinolone generations

<table>
<thead>
<tr>
<th>Generation</th>
<th>Selected examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cinoxacin, oxolinic acid (mostly obsolete and withdrawn)</td>
</tr>
<tr>
<td>2</td>
<td>Ofloxacin, ciprofloxacin, norfloxacin</td>
</tr>
<tr>
<td>3</td>
<td>Levofloxacin, sparfloxacin</td>
</tr>
<tr>
<td>4</td>
<td>Gatifloxacin (removed by FDA), moxifloxacin</td>
</tr>
</tbody>
</table>


(Mean age: 78yrs)
Minimum inhibitory concentrations for 243 *M tuberculosis* strains by gatifloxacin, moxifloxacin, and levofloxacgin

Effect of fluoroquinolone choice on spleen clearance of *M. tuberculosis* in the murine model in an AK-ETH-PZA regimen

Mutations in *katG* gene

- High-level resistance

Mutations in *inhA* gene

- Low-level resistance

Isoniazid resistance

INH useless, strains often susceptible to thioamides

INH useful, strains often resistant to thioamides

**Pharmacokinetics of Isoniazid, Fasting vs High-Fat Meal**

Time (hours)

<table>
<thead>
<tr>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>


**Specificity in detecting isoniazid resistance, SNRL network**

<table>
<thead>
<tr>
<th>Percentage category</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing round</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


MIC *katG* mutation

MIC *inhA* mutation

MIC wild strain
In vitro effect of ethambutol at 1/4 of its MIC on increasing the effect of a weak companion drug

Effect of clofazimine addition on lung clearance of *M. tuberculosis* in the murine model in an AK-MOX-EMB-PZA regimen

Adverse event-free MDR treatment outcome, adjusted for age and sex, Bangladesh, 2005 to June 2011 (estimated by Cox proportional hazard model)

- Ofloxacin susceptible (n=446): 88.2%
- Ofloxacin resistant (n=59): 68.3%

Aung KJM, Van Deun A, Rieder HL. Unpublished data, 29 Nov 2012
Treatment results among patients with MDR tuberculosis, excluding death and default, by initial ofloxacin resistance

<table>
<thead>
<tr>
<th>Initial ofloxacin result</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Cured</td>
<td>368</td>
<td>82.3</td>
</tr>
<tr>
<td>Completed</td>
<td>22</td>
<td>4.9</td>
</tr>
<tr>
<td>Died</td>
<td>24</td>
<td>5.4</td>
</tr>
<tr>
<td>Absconded</td>
<td>31</td>
<td>7.0</td>
</tr>
<tr>
<td>Failed</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>Relapsed</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td>446</td>
<td></td>
</tr>
</tbody>
</table>

Damien Foundation Projects, Bangladesh, unpublished data, January 2013
Proportion failing or relapsing among 59 patients with MDR and ofloxacin resistance, by pyrazinamide resistance

<table>
<thead>
<tr>
<th>Per cent failure or relapse</th>
<th>Pyrazinamide-resistant</th>
<th>Pyrazinamide-susceptible or no test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7 of 19</td>
<td>2 of 40</td>
</tr>
</tbody>
</table>

Odds ratio: 11.1 (2.0-61)

Damien Foundation Projects, Bangladesh, unpublished data, January 2013
Conclusions

Regimen effectiveness

- Zero relapse among 446 without fluoroquinolone resistance: Nine months is overkill, the regimen could be shortened further
- Regimen is remarkably sturdy in the presence of low-level fluoroquinolone resistance
- Pyrazinamide may be a key drug, at least among patients with initial fluoroquinolone resistance
- The tuberculosis community discovers clofazimine...

➤ If you plan to use the “Bangladesh regimen”, don’t fiddle with it!

Research questions and challenges

- Duration of aminoglycoside (toxicity!) with currently 4 months minimum – are there patients in whom it can be stopped earlier?
- Bedaquiline instead of thioamide / isoniazid?