NEWER DRUGS & POSSIBLE
NEW MULTI-DRUG
REGIMENS FOR LEPROSY

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CURRENT MDT REGIMEN
FOR MB LEPROSY

• Among the three components, only RIF displays powerful bactericidal activity against *M.leprae*, DDS & CLO are modest bactericidal drugs.
• Consists of monthly and daily components. The role of daily component is to eliminate RIF-resistant mutants, but is self-administered.
• Duration of treatment has been progressively reduced, but lacks of solid justifications.
THE NEEDS OF NEW MDT REGIMENS FOR MB LEPROSY

• The current MB regimen is not RIF resistance-proof.

• The duration of treatment remains too long, but it is highly unlikely to further shorten significantly the duration without dramatically modifying the composition.

• A safe and effective alternative regimen should be developed for patients with RIF-resistance or who cannot tolerate RIF treatment.

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Table 1. List of newer drugs with various bactericidal activities against *M. leprae*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Bactericidal activity in <em>mice</em></th>
<th>Bactericidal activity in human</th>
<th>Unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pefloxacin</td>
<td></td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Fluoroquinolone</td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td></td>
<td>++</td>
<td>++</td>
<td>High</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Macrolide</td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Tetracycline</td>
<td>++</td>
<td>++</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Rifamycin</td>
<td>+++</td>
<td>+</td>
<td>High</td>
</tr>
<tr>
<td>R207910</td>
<td>Dihydropyridine</td>
<td>+++</td>
<td>Not done</td>
<td>Not commercially available</td>
</tr>
<tr>
<td>Lincosamide</td>
<td></td>
<td>+</td>
<td>Not done</td>
<td>High</td>
</tr>
</tbody>
</table>

*a Based on the activity of (+) for *mice* and (++) for rifampicin.
NEWER DRUGS

• Moxifloxacin (MXF) and R207910 are as bactericidal against *M. leprae* as RIF, and rifapentine (RFP) is even slightly superior than that of RIF. Unlike in TB, clarithromycin (CLR), a macrolide, is moderately active against *M. leprae*.

• It would be prohibitively expensive if the newer drugs are administered on daily basis, but the costs are manageable if they are administered once monthly.

WE DON’T KNOW THE STERILIZING ACTIVITIES OF THESE NEW DRUGS!

• Progress of clinical trials in leprosy was extremely slow, only 5 of the 8 compounds listed in the Table had been tested in human trials, all were so-called « short-term trials (with duration ≤ 8 weeks) » and mostly in monotherapy.

• The sterilizing activity is the activity in killing the few, slowly metabolizing organisms which survive the initial killing, and is *the deciding factor* determining the duration of treatment.
PRINCIPLES IN DESIGNING NEW GENERATION MDT REGIMENS

• To avoid potential risk caused by presence of unawared resistance to a given compound, the regimen must consist of three components that act by different mechanisms.

• The pre-requisite of a compound to be a component of the monthly administered regimen is that a single dose of monotherapy displays definite bactericidal activity against *M. leprae* and is reasonably tolerated by the patients.

A FULLY SUPERVISABLE, MONTHLY ADMINISTERED REGIMEN FOR RIF-SUSCEPTIBLE MB PATIENT

• **Rifapentine** 900 mg (or, **Rifampicin** 600 mg) – **Moxifloxacin** 400 mg – **Clarithromycin** 1000 mg (or, **minocycline** 200 mg) **once monthly** (under supervision) for **12 months**
AN INTENSIVE REGIMEN FOR PATIENT WITH RIFAMPICIN-RESISTANT LEPROSY

- **Intensive phase**: Moxifloxacin 400 mg – Clofazimine 50 mg – Clarithromycin 500 mg – Minocycline 100 mg daily, supervised, for 6 months;

- **Continuation phase**: Moxifloxacin 400 mg – Clarithromycin 1000 mg – Minocycline 200 mg once monthly, supervised, for an additional 18 months

It is premature to apply either regimen in the routine programmes until its efficacy and safety are firmly established in carefully conducted clinical trials among patients with MB leprosy
CLINICAL TRIALS

• As the first step, the clinical trials should begin with evaluation of the side-effects and preliminary evidence of effectiveness in a small number of patients with MB leprosy.

• If the simplified regimen is reasonably well tolerated and showing early evidence of effectiveness, then the second step should be controlled clinical study, aiming to confirm that the new regimen is effective, with sterilizing activity at least as effective as the current MDT regimen for MB leprosy.

CONTROL CLINICAL STUDY

• Multiple arms.

• Each arm requires at least several hundreds of well characterized MB leprosy patients and will be followed-up at least 7 years after completion of treatment.

• Long-term, multicentre and relatively expensive.