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EDITORIAL

Developing new MDT regimens for MB patients; Time to test ROM 12 month regimens globally

DIANA N.J. LOCKWOOD* &
MARIA DA GRACA CUNHA**

**London School of Hygiene & Tropical Medicine, Keppel St, London WC1E 7HT*

***Fundacao Alfredo da Matta, Manaus, Brazil*

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In this editorial we review the data on the use of multi-dose ROM (Rifampicin, Ofloxacin and Minocycline) as an alternative treatment to WHO-MDT (World Health Organisation multidrug therapy) comprising rifampicin, clofazimine and dapsone. There is now sufficient evidence to warrant a large trial of this new regimen. The adverse effects of the current MDT regimen are probably under-estimated and this new regimen would reduce these adverse effects. Ofloxacin and minocycline have been shown to be more bactericidal than dapsone and clofazimine in both mice and clinical trials.^{1–3} The single monthly dosing might improve compliance which is also a major challenge.

In 1997 a randomised double-blind trial comparing single dose rifampicin, ofloxacin and minocycline was published⁴ and rapidly approved by the 7th Expert Committee on Leprosy⁵ in 1998 as treatment for single lesion leprosy. There were methodological problems in the study underpinning this recommendation, and at the time one of us voiced reservations about the new regimen.⁶ However, the regimen has now been used much more widely with studies being done in India and Brazil and there is now substantial experience in using it. A recent systematic review⁷ has assessed all the studies comparing ROM and MDT and found 14 studies that could be included in the review. Four of these compared single dose ROM with WHO-MDT for treating pauci-bacillary leprosy and combining these studies it was found that single dose ROM is slightly less effective than WHO-MDT with a relative risk of 0.91 (95% confidence intervals – 31%) but still has a very high cure rate.

Only two studies have been reported using multiple doses of ROM in lepromatous leprosy (LL). One in the Philippines by Villahermosa *et al.*,⁸ comparing 21 patients with borderline lepromatous and LL who were given either monthly ROM ($n = 10$) or the standard MDT ($n = 11$) which comprised monthly rifampicin (600 mg), and clofazimine (300 mg) with daily dapsone (100 mg) and clofazimine (50 mg) for 24 months. These patients had a mean Bacterial Index (BI) of 4 (range 2.7–5.1) at entry to the study and it fell to 1.18 (range 0–3.5).

Correspondence to: Diana N.J. Lockwood, London School of Hygiene & Tropical medicine, Keppel St, London WC1E 7HT. (e-mail: diana.lockwood@lshtm.ac.uk)

The patients assigned to WHO MB-MDT had similar falls in their BI's. Patients' skin lesions improved (measured by a score) as did the histological appearance on their skin biopsies during treatment. A study done in Brazil⁹ had a similar design, allocating patients to either monthly ROM or MB-MDT. These patients mostly had LL and both groups had a similar fall in BI (3.5 to 2.5) after 24 months of treatment and similar clinical and histological improvements. In the Philippines study the BI continued to fall after the completion of antibiotic treatment and no relapses were recorded during the subsequent 64 months after treatment. No toxicities were recorded in patients receiving ROM, whereas all patients on WHO-MDT developed clofazimine-induced pigmentation. These are important and encouraging studies which should be repeated on a larger scale with a randomised design.

It is encouraging to see that the BI fell during this intermittent monthly treatment. It is probably critical in leprosy chemotherapy to give sufficient antibiotic treatment over a long enough duration. The slow metabolism of *M. leprae* probably requires several hits over a long duration to achieve a sufficient kill. Evidence from other studies showing that ultra- short course duration of multi drug treatment does not produce a lasting bacterial cure, a study done in the Comoros Islands giving 6 weeks of quadruple drug treatment had a relapse rate of 15%.¹⁰ There have also been high relapse rates after the WHO sponsored 4-week course of MDT. In both studies patients were then given 24 months of WHO-MDT treatment.⁸

The three drugs that comprise MDT all have recognised adverse effects. Dapsone has the largest range with skin and haematological adverse effects predominating. There has been little systematic reporting of adverse effects. The early studies on MDT focussed on bacterial cure and relapse rates with no reporting of adverse effects.¹¹ Clinicians are well aware of the problems. Goulart¹² has reported that 37.9% of patients in Minas Gerais, Brazil taking MDT had adverse effects. A retrospective study¹³ from Vitoria, Espirito Sanctu, Brazil using good case definitions found that 45% of patients had adverse effects attributable to MDT with 43.85 having effects attributable to dapsone, 12.3% to Rifampicin and 9.25 to clofazimine. Two patients developed severe leucopenia and one died. A subsequent study from that centre (Deps Lep Rev submitted) found that 24.7% of patients developed haemolytic anaemia after starting MDT, and this was probably an underestimate because not all patients were tested for anaemia. In most centres routine monitoring for adverse effects is not done and so these may be missed. Dapsone hypersensitivity syndrome has also been reported from Nepal¹⁴ where it occurs in 2% patients taking MDT and causes death in 0.25%; it is also increasing in frequency in India.¹⁵

The skin pigmentation caused by clofazimine is troublesome. It accumulates in leprosy lesions and so often highlights lesions on the face and it causes a generalised tanning of the skin and an ichthyosis on the legs. There is little good data on the frequency of this adverse effect. However patients and their communities are well aware of this adverse effect and associate it with treatment for leprosy. Clinicians including ourselves (DNJL, MG) switch patients off the clofazimine component of MDT to reduce these visible adverse effects. The U-MDT trial report commented that patients did not find clofazimine pigmentation troublesome but the authors do not report whether systematic data on skin pigmentation was collected.¹⁶

Compliance is 'the elephant in the room' with our current multidrug regimens. We have very little good routine data on compliance. One study from India¹⁷ showed that in Assam in 2002–2005 35.1% of patients starting on MDT were defaulting whilst in Delhi rates of 60% for defaulting have been reported.¹⁸ In the Philippines a 30% default rate has been reported.¹⁹

Attending a clinic does not ensure compliance and Weiland *et al.* found in India that 33% of patients attending for multidrug therapy did not have urine metabolites in their urine.²⁰

These different factors indicate the need for new approaches and easier regimens for treating leprosy. The monthly ROM schedule has the advantage of being simpler and has fewer side-effects. We propose that a large ROM trial be done comparing 12 months of monthly single dose ROM against 12 months of WHO MB-MDT in multibacillary patients. Patients with a BI over 4 could be randomised to receive either 24 months of ROM or 24 months of WHO-MDT. The trials should incorporate good data collection on clinical improvement, adverse effects, default rates, reactions and neuritis and patient satisfaction. The main outcome measure would be relapse rates and patients would need to be followed for 10 years to pick up late relapses. The research challenge of identifying surrogate markers for relapse could also be addressed in this trial. It is likely that adverse effects would be fewer when a single monthly dose is given but monitoring would be important. Minocycline when used in a daily dose caused pigmentation²¹ so careful checking would need to be done to ensure that this was not happening with a monthly dose. Adequate follow-up involving both active and then passive would be important to detect late relapses. The safety of using of multiple dose ROM in children would need to be supported by a literature review and pharmacokinetic data of minocycline. Ofloxacin is in use as a second line agent for treating typhoid fever in children.²² Giving ROM would be more expensive than using WHO MDT but a single monthly dose would not be prohibitively expensive. There are potential operational advantages since it might be easier to implement monthly supervision with this regimen and so improve detection of reactions and nerve damage. As the drugs have fewer side effects patients will be more likely to comply with the medication even if they do not attend clinic. Innovative approaches such as aiding compliance by the use of SMS messages could be tried. The use of ROM could also help reduce the stigma associated with leprosy; the patients in the Philippines trial commented that they were able to keep their treatment private. The possibilities of using other agents such as rifapentine instead of rifampicin and moxifloxacin instead of ofloxacin should also be considered. Both agents have been shown to be bactericidal against *M. leprae* in mouse models.^{23–24} Moxifloxacin has been shown to be significantly bactericidal in small studies in patients with lepromatous leprosy,^{25–26} and so could be considered as an alternative drug for inclusion in a monthly regimen.

Developing studies using ROM is a potentially exciting way of improving leprosy treatment for patients and helping in the next stage of leprosy control.

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