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EDITORIAL

Safer and newer antimicrobial drugs for leprosy – time to test monthly ROM in an adequately powered randomised trial?

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In the last decade many leprologists around the world have been advocating the development and testing of new antimicrobial treatments for leprosy but limited new clinical data have emerged.[1,2] Global guidelines have been published in which the World Health Organization (WHO) now recommends rifampicin, dapsone and clofazimine for all individuals diagnosed with leprosy.[3]

We propose that a large randomised controlled trial of fixed duration (12 doses) antimicrobial therapy for *Mycobacterium leprae* infection, with monthly rifampicin 600 mg,

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ofloxacin 400 mg and minocycline 100 mg (ROM) compared with standard WHO multi-drug therapy (MDT) (rifampicin, clofazimine and dapsone), be conducted in adults with multi-bacillary (MB) leprosy. Robust evidence of efficacy of ROM from a well-designed clinical trial could simplify treatment, improve adherence and reduce the serious adverse effects, including mortality, associated with dapsone and clofazimine.

M. leprae infection has been treated with a two or three drug combination of rifampicin, dapsone and clofazimine since 1982. Rifampicin is the cornerstone of WHO MDT and is bactericidal against *M. leprae* when taken on a monthly basis in the WHO MDT regimen.[4–6] MDT has high cure rates of 99%, confirmed in observational studies with large follow-ups lasting over a decade in Bangladesh.[7,8] The reported relapse rate for participants taking 12 months MB MDT was zero in the Uniform Multidrug Therapy Regimen for Leprosy Patients (U-MDT) trial in Brazil.[9]

The undoubted success of MDT in treating *M. leprae* infection has overshadowed the adverse effects associated with dapsone and clofazimine. Individuals with leprosy have not been studied or monitored systematically with respect to adverse effects and laboratory monitoring is not routinely done in many settings. The Global Leprosy Programme has recognised the need for improved pharmacovigilance and held a meeting about adverse effects caused by drugs used in leprosy in November 2021. National programme managers reported significant adverse effects associated with MDT. We need better adverse effect monitoring of dapsone and clofazimine in patients taking MDT to improve management and promote adherence. Lack of adherence to the dapsone and clofazimine components of WHO MDT has been suggested as a risk factor for the development of rifampicin resistance.[10]

The effect of dapsone on *M. leprae* is bacteriostatic. There are dose-dependent adverse effects associated with dapsone therapy, such as methaemoglobinaemia, bone marrow aplasia and haemolytic anaemia. Haemolysis affected 90% of individuals in a prospective nested study of sixty participants in the U-MDT trial, 15% had abnormal liver function tests, and 10% had epigastric pain and nausea.[11] In a prospective study in India of 176 patients taking MDT, Singh found that 45% of patients had an adverse effect to MDT, with 73 having an adverse effect to dapsone, including 46 with gastro-intestinal manifestations and haemolysis. Nine patients had to stop one of the drugs because of severe complications.[12]

Dapsone Hypersensitivity syndrome (DHS) starts six weeks after commencing dapsone and manifests as exfoliative dermatitis associated with lymphadenopathy, hepatosplenomegaly, fever, and hepatitis, and may be fatal. Shen reported that deaths occurred most commonly in the second month after starting MDT.[13] A retrospective hospital study from Nepal of dapsone adverse effects reported five deaths in 40 individuals diagnosed with DHS.[14]

A systematic review of the adverse effects associated with dapsone in leprosy patients found 114 publications on dapsone adverse effects and 11 reports on DHS with a fatality rate of 11.24%.[15]

Leprosy patients in China and Papua, Indonesia with the HLA-B*13:01 genotype have been shown to be at a higher risk of developing DHS.[15,16] It occurs in 0.5–3.6% of individuals treated with dapsone.[15,17] Agranulocytosis, hepatitis, and cholestatic jaundice occur rarely with dapsone therapy.[18–20] The role of dapsone to treat leprosy should be reappraised.

Clofazimine is a red dye with a weakly bactericidal action against *M. leprae* and its role in MDT is to prevent the development of drug resistance to rifampicin. High drug concentrations are found in the intestinal mucosa, mesenteric lymph nodes, and body fat. The commonest adverse effect is skin discoloration, ranging from red to purple-black, with the degree of discoloration depending on the dosage. The pigmentation usually fades within 6–12 months

of stopping clofazimine, although traces of discoloration may remain for up to four years. The skin discoloration associated with clofazimine is distressing, stigmatising and discloses the diagnosis to those who are aware of this adverse effect.

Few studies report the extent of adverse effects seen with clofazimine. Deps found 18 of 194 patients in a retrospective study had clofazimine skin reactions.[21] Singh reported 24% of those treated with MB MDT had clofazimine adverse effects, 30% had gastro-intestinal adverse effects, two had a severe skin reaction and one case of haematemesis. The authors did not report the frequency of the skin discolouration and ichthyosis caused by clofazimine but described them as common but "minor" adverse effects, because they were not a cause for stopping the drug.[12] Other adverse effects include: dry eyes; eye discolouration, discoloration of body fluids, visual impairment, hair colour changes, photosensitive reactions and splenic infarction.[22]

Clofazimine is said to protect against the development of erythema nodosum leprosum (ENL) but there is little evidence to support this. A prospective double-blind study has been done comparing 100 patients randomly allocated to either 100 mg daily clofazimine or placebo for 12 months after completion of 12 months MBMDT. The outcome measures used were ENL severity scores, total steroid intake, incidence of new ENL episodes and duration of episodes. None of the differences were statistically significant.[23]

Leprosy antimicrobial regimens without dapsone have been studied including six or 12 doses of monthly ROM. Ofloxacin and minocycline have bactericidal activity against *M. leprae*.[24] There is evidence that other agents such as rifapentine, moxifloxacin and bedaquiline may have more potent bactericidal effects.[25,26]

A systematic review conducted in 2010 assessed six studies comparing ROM with WHO MDT, although only two compared monthly doses of ROM.[27] A second systematic review conducted in 2018 identified one further study of monthly ROM compared to WHO MDT in paucibacillary (PB) patients.[28] Kumar *et al.* randomly allocated 268 patients to either ROM or MDT, for six months with cure rates of 99% for the ROM-6 (ROM given at 4 weekly intervals), and 97% for the PB-MDT group.[29] Ten individuals relapsed over the 5–8 year follow up, showing that ROM and PB-MDT have similar cure and relapse rates. The rate of adverse effects was much lower in those receiving ROM, which is a significant benefit. A small cohort of 19 individuals with MB leprosy (although only one was slit-skin smear positive) who completed 12 monthly doses, improved and did not require further antimicrobial therapy.[18]

Only two small studies have been conducted using multiple doses of ROM in individuals with lepromatous leprosy (LL). Villahermosa *et al.* conducted a study in the Philippines that compared 21 individuals with borderline lepromatous leprosy ($n = 8$) and LL ($n = 13$). These participants were given either observed monthly ROM ($n = 10$) or WHO MB-MDT ($n = 11$), for 24 months.[30] The participants who received ROM had a mean bacterial index (BI) of 4 (range 2.7–5.1) at entry to the study, which fell to 1.18 (range 0–3.5) at the end. The participants allocated to WHO MB-MDT had a similar decline in BI. Skin lesions improved, as did the histological appearance of skin biopsies during treatment. Another small study with 20 participants conducted in Brazil had a similar design, allocating participants, most of whom had LL leprosy, to either 24 monthly doses of ROM or WHO MB-MDT for 24 months. Both groups had a similar fall in BI (3.5–2.5) as well as similar clinical and histological improvements.[31] In the study by Villahermosa *et al.*, the BI continued to fall after the completion of antibiotic treatment and no relapses were recorded during the subsequent 64 months. No toxicities were recorded in patients receiving ROM, whereas all patients on WHO MB-MDT developed clofazimine pigmentation.

Many patients do not complete MDT. There have been few systematic studies of adherence to MDT. One study in North India registered a non-adherence rate of 28.8%, with a rate of 34.0% for MB patients; similar rates were reported in Cebu, Philippines.[32,33] A study from Hyderabad, India, found that only 50% of patients who were attending clinics had dapsone metabolites in their urine or indicated their adherence with leprosy treatment on a questionnaire.[34,35]

The challenges of adverse effects and lack of adherence support the need for alternative antimicrobial treatment such as ROM. The U-MDT study in Brazil in newly diagnosed MB patients comparing 12 months MDT with 6 months MDT had four main outcomes: bacillary index trend, relapse rates, frequency of reactions and disability progression. A trial with similar design comparing 12 months MB-MDT with ROM could be undertaken.[9,36]

A large multi-centre randomised controlled trial using an equivalence study design comparing twelve months MDT and twelve-monthly doses of ROM (ROM-12) for individuals newly diagnosed with MB leprosy, could be designed. This would determine whether the treatments are similar. We predict that the clinical improvement and relapse rate would be similar for the two groups but that those receiving ROM would experience fewer adverse effects and have higher rates of treatment completion. The primary outcomes of the trial should include cure and relapse rates as well as frequency of adverse events and acceptability of treatment.[36] This is challenging because it requires lengthy periods of follow-up. The U-MDT trial had a follow-up period of seven years. The trial would provide an opportunity to systematically assess improvement in skin lesions, incidence of reactions, long term outcomes in nerve function impairment and disability progression after completion of antimicrobial therapy. Collaboration with individuals who have received antimicrobial treatment for leprosy would guide important person reported outcome measures. WHO MDT is provided by donation and cost effectiveness analyses would be important evidence to guide policy decisions. It is hard to envisage significant challenges in operationalising monthly antibacterial therapy for leprosy, but this would need to be assessed.

We recognise that fluoroquinolones in daily doses, are associated with rare, severe adverse effects and caution must be used in the elderly, individuals with pre-existing neuropathy and those taking corticosteroids all of which may be relevant in individuals diagnosed with leprosy.[37] Dyspigmentation associated with minocycline has not been reported in monthly dose regimens outlined above although it has been when taken daily.[38] Fluroquinolones and minocycline are recommended by WHO for the treatment of drug resistant leprosy.[3] Consideration also needs to be given to the treatment of leprosy during pregnancy, in women who are breastfeeding and children in whom these drugs are contraindicated.

Monitoring for adverse effects of MDT is important, but there are antimicrobials available with better adverse effect profiles, greater acceptability and more bactericidal activity against *M. leprae* than both dapsone and clofazimine. Individuals affected by leprosy deserve access to the safest and most effective antimicrobial therapy available. The leprosy community should place the assessment of safe and effective antimicrobial regimes on the research agenda. There is a debate to be had about the components of such new regimes.[10] Moxifloxacin, which has a longer half-life than ofloxacin, could be used as the fluoroquinolone component as proposed in the PEP++ research study for chemoprophylaxis, although in that study it was eventually replaced by clarithromycin, which has a safer profile for use in children.[39] Bedaquiline is currently being assessed with respect to efficacy and safety in individuals with MB leprosy in Brazil.

Finally, we must recognize the benefits that MDT has brought to individuals affected by leprosy. Nevertheless, it is time to gather evidence about newer safe, acceptable and effective antimicrobial regimes to prevent exposure of individuals with leprosy to the distressing and life-threatening adverse effects of dapsone and clofazimine.

Conflict of interests

We have no conflicts of interest to declare.

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