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EDITORIAL

Current leprosy multi-drug treatment duration for MB patients (12 months) produces good clinical outcomes over many years

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There have been recent discussions in the leprosy world by people concerned that the current 12 months multi-drug treatment (MDT) regimens for multibacillary leprosy patients are inadequate and contribute to poor control of the disease. We argue here that recent studies show that the current regimens are good for treating the infection in individual patients and do not need extending. Patients with an initial high BI do not need longer treatments.[1,2] Clinicians and patients should have a long time frame for patient improvement which can be years after treatment has finished. The WHO sponsored multi-drug regimens were introduced in 1982 and have been regularly altered since then.[3,4] Initially patients with MB leprosy were treated until their slit skin smears were negative. In 1994 the WHO Expert Committee recommended fixed duration treatment of 24 months for MB patients. This was reduced to 12 months in 1998.[5,6] These decisions were not supported by data from prospective drug trials. Fortunately, the relapse rate in leprosy has been very low, with about 1% of patients relapsing with a new study from Brazil showing a low relapse rate after treatment with 12 months MDT with a 12 year follow up.[1,7,8] An early study in Ethiopia had a zero relapse rate after 24 months treatment.[9] Patient outcomes after leprosy multi-drug treatment can be assessed by three measures: (1) Clinical improvement of the lesions, (2) Fall in the Bacterial Index and (3) relapse rate.

Clinical improvement of skin lesions is variable. This is partly due to the ongoing inflammation in the lesions which is part of the clinical disease. Some patients' skin lesions resolve

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completely, others, often those with borderline tuberculoid leprosy, can have persisting lesions with hypopigmentation. The lesions in lepromatous leprosy patients may take years to improve. These variations in patient skin lesion improvement have been documented by Manickam et al.[10] in their prospective open study of Uniform Multi-drug therapy (UMDT) consisting of 6 months of standard triple therapy (dapsone and clofazimine daily and rifampicin monthly) in India and China (2091 PB and 1298 MB patients). They classified skin lesions into three groups: inactive, improved and static, and followed patients for five years; lesions of MB patients were classified into the three groups respectively, as follows:10.4%. 84.9%, and 4.7% at treatment completion; 72.4%, 26.8%, and 0.8% at three years; and 80.7%, 18.2%, and 1.1% at five years. Patients can be reassured that their skin lesions will improve over 4 years, but some will have persisting lesions. This is an important clinical message and patients can be given hope that their skin will improve. The relapse rate was low, four MB patients relapsed giving a rate of 0.07/100 person years.

Leprosy patients' bacterial index continues to fall long after their initial treatment with MDT, because of the slow immunological clearing of bacteria in lesions. There are 3 studies in which the continuing fall in the BI has been measured, in the Philippines,[11] Brazil[1] and Bangladesh.[12]

Balagon et al. treated high BI patients with a fixed dose regimen (rifampicin, dapsone, clofazimine) given for 24 months. The patients' BIs continued to fall without further antibacterial treatment.[11] In Brazil a large prospective study of UMDT was done comparing outcomes after patients (n = 613) with a high BI were given either 6 or 12 months of rifampicin, dapsone and clofazimine. The BIs of Brazilian patients were measured and the BIs in both PB and MB groups continued to fall after 6 months of treatment. The rate of fall in the two groups was not significantly different. A very small number of patients in both groups had increases in their BI.[13] Butlin et al. did a prospective observational study of patients in Bangladesh given 6 months or 12 months MDT.[12] Of the patients who were smear positive at the beginning of the study the proportion becoming smear negative was 21% at 24 months, 80% at 60 months and 100% at 96 months post treatment.

Regarding relapse/re-infection, in the Brazilian study, the relapse rate in the UMDT group was 2.6 per 1000 patients per year of follow up (95% CI [0.81, 6.2] per 1000) during the active follow-up period, meaning that 0.26% of patients relapsed every year on average. The authors performed a sensitivity analysis, and estimated the rate using follow-up person years, which results in an overestimation of relapses. The estimated rate of relapse for the UMDT group was 4.46 per 1000 people per year and for R-MDT 0.44 per 1000 people per year. In the UMDT group the overestimated relapse risk, in ten years, is 4.4%.[1] In Bangladesh the relapse rate was zero at 96 months. Three patients then developed positive skin smears after 97 mo.[2] Only one of these was a confirmed relapse. He was retreated successfully with standard MBMDT, as he did not have drug resistance. These data confirm that the response of smear positive patients to MDT is good with the majority of patients becoming smear negative. There was a single late relapse patient, and the relapse rate was 2.6/1000 per year.

These three studies show that the clinical response to MDT is excellent, patients have a slow fall in their BI and a low relapse rate occurring after many years. Molecular typing done in the Brazilian UMDT study shows that some of apparent relapses were due to re-infection. This would not be prevented by longer MDT.[14]

The newly published study from a Brazilian reference centre where patients (713) were treated with MDT 12 doses and followed for 12 years (mean). There were 10 relapse cases

giving a rate of1.16 relapse cases per 1000 person-year (95% CI = 0.5915–2.076). The accumulated riskwas 0.025 in 20 years.[8]

This is an important finding and clinicians can be reassured by this. Further treatment is not needed unless the patient has a properly documented relapse with a rise in the BI's in their slit skin smear tests. Patients can be reassured that they will respond to treatment. These good responses show that treatments with additional agents such as *Mycobacterium indicus pranii* are not needed.[15] We need better means of identifying the small number of patients who relapse after many years, probably through education.

These patients were followed in careful clinical trials. In the field, compliance to leprosy MDT is poor. One study in North India registered a default rate of 28.8%, with a rate of 34.0% for MB patients in particular.[16] One study in Hyderabad, India, found that only 50% of patients who were attending clinics had dapsone metabolites in their urine or indicated their compliance with leprosy treatment on a questionnaire.[17,18]

Patient education is important, and patients need to be warned that their lesions may takes years to improve. The few late relapses that occur with leprosy treatment is another reason for ensuring that patients know to come back to leprosy clinics when they have new symptoms or lesions.

Monitoring adverse effects caused by MDT has been done poorly. Rifampicin rarely causes renal failure.[19] Dapsone is associated with significant haemolysis that has not been regularly monitored and can be fatal.[20] A systematic review of dapsone-associated adverse effects showed that dapsone hypersensitivity syndrome and haemolysis associated with dapsone are under-reported.[21] Monitoring patients' haemoglobin before and after starting treatment would detect this. Clofazimine causes increased skin pigmentation, which can be a distressing adverse effect of treatment with negative impacts on self-esteem and adherence to treatment. Clofazimine-induced skin pigmentation may disclose the diagnosis of leprosy to others, which may lead to stigmatization. Kumar and colleagues found that 9.8% of patients taking MB MDT stopped their medication because of clofazimine pigmentation, showing that it is a significant problem.[22]

Studies done over a long time period such as Butlin's can yield important clinical information. More observational studies should be done in leprosy endemic areas especially of the high BI patients. Slit skin smears were not done in the Manickam UMDT study even though having positive slit skin smears is a cardinal sign of leprosy. This means that the outcome of relapse cannot be assessed in that study. Having a good slit skin smear service for patients needs to be re-established both to help confirm the diagnosis of leprosy and to detect relapse. Monitoring for leprosy associated adverse drug effects needs to be established and put into practice. The leprosy road map 2021–2030 has indicated that this should now be part of patients monitoring.

Future trials should focus on reducing the adverse effects associated with dapsone and clofazimine, so using combinations like rifampicin/ofloxacin/minocycline (ROM) should be assessed as a single monthly regimen.[23] A recent systematic review confirmed that the ROM combinations give equivalent outcomes in the treatment of leprosy.[24]

Assessing better bactericidal regimens with new drugs such as bedaquiline should be started.[25,26]

Validation of clinical scales for skin lesion progress would be an important piece of work. This was done to develop the ENLIST severity scale with scale development, refinement and proper testing before the scale was used.[27] Testing of other new tools such as the *M. leprae* viability test could also be part of this study[28] as suggested by David Scollard.[29]

In conclusion, the current drug regimens can be used and are effective in treating the infection. Clinicians and patients need to understand that improvement is slow and may take years. Leprosy is a slow disease to develop, and improvement is also slow. A long time frame is needed. The scientific evolution of the treatment of leprosy needs to be evidence based, otherwise we run the risk of returning to "treatment for life".[1,30] On the way to having a single treatment and shortening the treatment time, the current 12-month treatment for MB patients is effective for most patients. Exceptions should not be made the rule.

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