

A clinical trial for uniform multidrug therapy for leprosy patients in Brazil: rationale and design

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Leprosy will continue to be a public health problem for several decades. The World Health Organization (WHO) recommends that, for treatment purposes, leprosy cases be classified as either paucibacillary or multibacillary (MB). A uniform leprosy treatment regimen would simplify treatment and halve the treatment duration for MB patients. The clinical trial for uniform multidrug therapy (U-MDT) for leprosy patients (LPs) in Brazil is a randomised, open-label clinical trial to evaluate if the effectiveness of U-MDT for leprosy equals the regular regimen, to determine the acceptability of the U-MDT regimen and to identify the prognostic factors. This paper details the clinical trial methodology and patient enrolment data. The study enrolled 858 patients at two centres and 78.4% of participants were classified as MB according to the WHO criteria. The main difficulty in evaluating a new leprosy treatment regimen is that no reliable data are available for the current treatment regimen. Relapse, reaction and impaired nerve function rates have never been systematically determined, although reaction and impaired nerve function are the two major causes of nerve damage that lead to impairments and disabilities in LPs. Our study was designed to overcome the need for reliable data about the current treatment and to compare its efficacy with that of a uniform regimen.

Key words: leprosy - protocol - clinical trial - uniform multidrug therapy

Despite the proposed elimination of tropical diseases (WHO 2011, 2012), leprosy will continue to be a public health problem for several decades (Scollard 2005, Talhari & Penna 2005). With the increasing decentralisation of control activities, primary public health centres will be responsible for diagnosing and managing patients to achieve programme sustainability (Banerjee et al. 1997, Penna & Penna 2007, Penna et al. 2012).

In 1981, the World Health Organization (WHO) recommended a multidrug therapy (MDT) for leprosy treatment (WHO 1982). The WHO currently recommends that leprosy cases be classified as either paucibacillary (PB) or multibacillary (MB) based on the number of skin lesions. Patients with six or more lesions are classified as MB and treated for 12 months with a MDT that comprises three drugs: rifampicin, dapsone and clofazimine. Patients with fewer than six lesions are classified as PB and treated for six months with a two-drug MDT: rifampicin and dapsone (WHO 1997a).

Since 1989, Brazilian scientists have been calling for a uniform leprosy treatment that would not require disease classification (Penna et al. 2012). Similarly, tuberculosis (TB) can be viewed as a historical example of a

disease that is more infectious and pathogenic than leprosy that has been treated with a combination of drugs since the 1960s. The treatment regimen for all types of patients has changed over the years, but currently, all pulmonary TB patients, both smear-negative ("PB") and smear-positive ("MB") cases, are treated for six months. There is no doubt that this policy increases patient adherence to treatment and improves the performance of health workers in the field (WHO 1997b, 2002).

Analogously, many believe that the regular 12-month leprosy MB course can be shortened for a considerable proportion of, if not all, MB patients. Shortening the treatment in conjunction with increased treatment uniformity could help field programmes, particularly in situations where leprosy control is integrated into general health services. A uniform leprosy treatment regimen would simplify treatment in the field and halve the treatment duration for MB patients. This change may increase the treatment completion rates, given that these rates are consistently better for PB patients compared to MB patients. Previous results from different control programmes (WHO 1994) and research projects (Becx-Bleumink 1992) have demonstrated that relapse rates following MDT were low, approximately 0.2% annually among MB cases with the 24-dose regimen (Jesudasan et al. 1996, Dasananjali et al. 1997, Li et al. 1997). The low relapse rates suggested that there was room to shorten the course of MDT to fewer than the 24 supervised monthly doses of rifampicin plus self-administered doses of dapsone and clofazimine (Vijayakumaran et al. 1996, Li et al. 1997). A 12-month treatment course for MB leprosy

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has been generally recommended by the WHO since 1998 (WHO 1997a). Although some studies suggest that post-MDT relapse rates may be significantly higher in the MB patients who have an initial bacterial index (BI) ≥ 4 (Jamet & Ji 1995), the present leprosy disease group includes few patients with those characteristics. Furthermore, the total number of relapses among these patients would account for a minimal percentage of cases in a control programme (WHO 1997b).

The objective of this clinical trial is to evaluate whether uniform (U)-MDT for leprosy is clinically and statistically equivalent in efficacy to the regular regimen (R-MDT), to determine patient tolerability of the U-MDT regimen among PB patients and to identify the prognostic factors that might influence the U-MDT outcomes.

The current paper presents detailed methodology of the clinical trial and the data obtained from patients thus far.

SUBJECTS, MATERIALS AND METHODS

Study design - An open-label, randomised clinical trial design was used to compare two treatment regimens (R-MDT vs. U-MDT) with monthly patient follow-ups during the treatment period and for the first six months following treatment cessation for the MB patients in the U-MDT study group. This procedure was followed by yearly post-treatment visits for six years. The study population included newly diagnosed, previously untreated PB and MB leprosy patients (LPs) and returning defaulters and relapse cases, provided that the last treatment dose was more than five years prior to enrolment in the study. All of the patients were between the ages of six-65. Patients were excluded if they were receiving TB or steroid treatment, had overt signs of acquired immune deficiency syndrome, were not residing permanently in the area or were unable to visit the clinic every month during the treatment and follow-up periods (Fig. 1).

Study location - A pilot study of 78 patients was conducted at the Federal University of Minas Gerais (UFMG) from November 2004-June 2006 to test all of the study protocols and clinical report forms (CRF). Following adjustments to those protocols, based on the pilot study, patients were recruited from March 2007-February 2012 at two national leprosy reference centres: Dona Libânia (Fortaleza, state of Ceará) and Alfredo da Matta (Manaus, state of Amazonas). A multidisciplinary team composed of 12 physicians (including pathologists and neurologists), nine nurses, five physiotherapists and five biochemists was responsible for patient recruitment and monitoring.

Regular patients - A patient receiving regular PB-MDT or U-MDT treatment is considered a “regular patient” when he/she completes six months of treatment within nine months. A patient receiving regular MB-MDT treatment is considered a “regular patient” when he/she completes 12 months of treatment within 18 months.

Irregular patients - Irregular patients are patients that complete treatment, but do not do so in the required nine or 18 months, as specified above. Instead, irregular patients who receive PB/U-MDT and MB-MDT treatment complete their regimens within 12 and 24 months,

respectively. These patients will be subject to follow-up evaluations, but their “irregular patient” status will be clearly indicated for data analysis purposes in this study.

Defaulters - A patient receiving regular PB-MDT or U-MDT treatment is considered a “defaulter” if he/she does not complete six months of treatment within 12 months. A patient receiving regular MB-MDT treatment is considered a “defaulter” if he/she does not complete 12 months of treatment within 24 months. A patient who does not complete treatment within the required period will be removed from the study.

Screening log - All of the patients who were examined in the reference centres as possible LPs were registered in the screening log (Fig. 2).

Randomisation - The patients were randomised to ensure valid comparisons between the treatment regimens (R-MDT and U-MDT) in each subgroup after being classified into PB and MB based on their number of skin lesions (Fig. 1). A random list of numbers was prepared using the CRF. The randomisation codes on the worksheet were covered with the same material that is utilised for lottery scratch cards; therefore, the printed numbers were not visible. The randomisation numbers for the PB patients were revealed at the beginning of chemotherapy; for the MB patients, the number was revealed on the day the patient arrived for their sixth treatment dose.

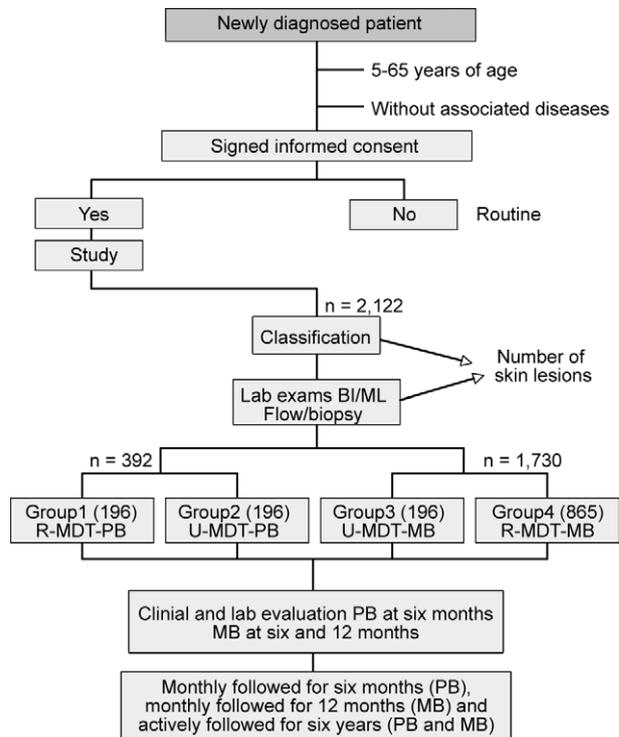


Fig. 1: clinical trial for uniform multidrug therapy (U-MDT) for leprosy patients in Brazil. BI: bacterial index; MB: multibacillary; PB: paucibacillary.

Patient information - The patient characteristics and clinical parameters were recorded and the number of lesions and affected nerves were registered. Slit-skin smears were also taken to identify those patients with high BI and the ML Flow test was used to detect anti-*Mycobacterium leprae* phenolic glycolipid-I (PGL-I) antibodies (Bührer-Sékula et al. 2003, Oskam et al. 2003). As a baseline for all new entries and again for the patients who were suspected of relapse during the follow-up period, punch biopsies were taken for histopathological analyses. The additional test results were considered in the final patient classification that was used in the analysis.

Study groups - The U-MDT PB and U-MDT MB groups consisted of the patients who received the six-month U-MDT regimen, as defined by the WHO protocol, which corresponded to six months of MB-MDT treatment with three drugs.

Control groups - The R-MDT PB and R-MDT MB groups consisted of the patients who received the standard WHO treatment regimens: six months of treatment with two drugs for the PB patients and 12 months of treatment with three drugs for the MB patients.

Reactions and impaired nerve function - If a patient developed reactions or impaired nerve function, he/she received appropriate treatment and remained in the study. All of the reaction and impaired nerve function episodes were registered.

Reaction or relapse - If there was difficulty distinguishing between reaction and relapse (5% of all reactions/relapses) then an independent and experienced specialist was consulted.

Laboratory exams - To evaluate the side effects and toxicities of the three drugs, in addition to the standard clinical examinations, the patients underwent monthly

laboratory testing during treatment to monitor any haematological or hepatic alterations (full blood tests and transaminases).

Treatment - The patients were randomly assigned to one of two study sub-groups according to the standard PB/MB classification (based on the number of skin lesions). The patients returned to the clinic for monthly medical evaluations and to receive new monthly blister packs, which is consistent with the current standard of care in the leprosy control programme in Brazil. Whenever reactions and impaired nerve function occurred in either study group, the affected patients were treated according to standard protocol.

Follow-up during treatment - The patients were monitored monthly for adverse reactions, impaired nerve function or side effects. In addition, the patients were asked to return to the clinic immediately if they experienced reactions or impaired nerve function.

Follow-up after treatment - Slit-skin smears are taken at the end of treatment and during follow-up for the patients who were slit-skin positive at the beginning of treatment. The U-MDT MD study group patients are examined for reactions and impaired nerve function monthly for six months after the end of treatment. The patients are actively monitored for reactions, impaired nerve function and relapses once yearly for six years post-treatment. In addition, the patients were asked to return to the clinic if any adverse reactions or side effects occurred (reactions, impaired nerve function and relapse). If relapse is suspected, slit-skin smears will be taken and serum tested to confirm or support the clinical diagnosis. If a patient is diagnosed as a relapse case, they will be treated according to standard practice: six additional doses for the PB patients and 12 additional doses for the MB patients. The event will be recorded and considered the end point of follow-up for data analysis purposes.

The U-MDT/CT-BR clinical report form and standard operating procedures are available as Supplementary data.

Ethical considerations - The study was performed under international (Helsinki) and Brazilian research regulations regarding human beings and was approved by three regional research ethical committees from the states involved in the study as well as the National Ethical Research Commission. Written informed consent was obtained from all the patients prior to inclusion in the study. For patients aged six-17 years, written parental consent was required. Data confidentiality was strictly guaranteed. The patients were free to leave the study and opt for the R-MDT regimen outside the study (ClinicalTrials.gov identifier: NCT00669643).

Sample - In both treatment groups, the sample size was based on the hypothesis of equivalence for the disease cure, absent relapses or reactions. Given that relapse is the less frequent event, the sample size was based on its estimated frequency. We assumed that the 12-month overall cumulative relapse rate of R-MDT after nine years of follow-up would not exceed 1%; there-

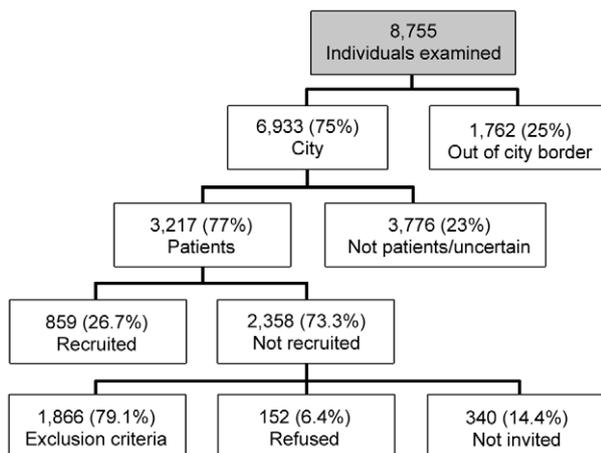


Fig. 2: screening log for recruitment of patients from March 2007-February 2012 in Manaus, state of Amazonas, and Fortaleza, state of Ceará, Brazil.

fore, we set a threshold for the acceptable occurrence of relapse following U-MDT equal to 2.6% (1% ± 1.6%). To ensure 80% power to detect a statistically significant difference in the relapse rates (1% of persons treated according to R-MDT vs. 2.6% for persons treated with U-MDT), a sample size of 1,181 persons was required for each branch of the study. The data analysis will be multivariate to control for other prognostic factors, such as the patients' bacterial loads.

RESULTS

Profile of patient enrolment to date - At the end of February 2012, 858 patients were enrolled in this study: 79% in Fortaleza and 21% in Manaus. Fig. 2 shows the screening log for patient recruitment and Table I shows the distribution by study centre. Table II shows the baseline characteristics (age, sex, the number of nerves affected, the BI and the PGL serologic result) for the enrolled patients in each classification group.

DISCUSSION

There are multiple leprosy care paradigms and the need for a robust, evidence-based response has motivated previous investigation into the viability of uniform treatment for all LPs, independent of their clinical classifications (Lockwood & Suneetha 2005, van et al. 2010, WHO 2010, Penna 2011, Penna et al. 2011). This uniform treatment would be a step forward in controlling a disease that will affect Brazil for the foreseeable future, perhaps with incapacitating consequences (Penna et al. 2009).

The lengthy treatment course has become one of the main obstacles to implementing MDT (Ganapati et al. 1992), particularly in regions where the existing health infrastructure is poor and inaccessible. Leprosy classification is a problem for general health workers who have only received one or two days of training, particularly where leprosy control is fully integrated into health services; the number of areas where this situation occurs will increase in coming years (Barreto et al. 2011). In cultures where

only partial skin examination can be conducted, a classification system that is based on a skin lesion count is difficult to implement consistently (WHO 1997b, 2002).

Recently, an open-field, non-controlled treatment trial was conducted to determine the efficacy of a six-month treatment regimen that consisted of three drugs (rifampicin at 600 mg/month, dapsone at 100 mg/day and clofazimine at 50 mg/day as well as 300 mg/month) for all LPs; the trial was coordinated by the National Institute of Epidemiology of the Indian Council of Medical Research. From November 2003-May 2007, 2,912 patients (India, 2,746, China, 166) were enrolled, with 39% of patients classified as MB solely on the number of skin lesions, 3% of whom had grade 2 disabilities. During the follow-up, only 27 patients (0.9%) developed new lesions, 78% of which were caused by reactions. Six patients had clinically confirmed relapse and 2.9% of patients were lost during the follow-up period. In the study, 85.9% of the patients completed treatment and 19% had inactive skin lesions. In general, the PB patients responded better than the MB patients (27% vs. 6%, $p < 0.001$). In the post-U-MDT follow-up, at the end of the first ($n = 2013$) and second years ($n = 807$), the lesions were inactive in 49% and 46% of patients, respectively [59% (year 1) and 57% (year 2) in PB, 37% (year 1) and 28% (year 2) in MB, $p < 0.001$] (Kroger et al. 2008).

TABLE I

Enrolment status by leprosy type according to World Health Organization criteria based on number of skin lesions and by study centre, uniform multidrug therapy trial, Brazil 2011

Centres	Patients enrolled		
	Paucibacillary (< 6 lesions) n (%)	Multibacillary (≥ 6 lesions) n (%)	Total n (%)
CDERM	126	552	678 (79)
FUAM	59	121	180 (21)
Total	185 (21.5)	673 (78.4)	858 (100)

CDERM: Dermatology Centre Dona Libânia, Fortaleza, state of Ceará; FUAM: Foundation of Tropical Dermatology and Venereology Alfredo da Matta, Manaus, state of Amazonas.

TABLE II
Baseline characteristics of patients enrolled for uniform multi-drug therapy trial, Brazil 2011

Characteristic	Paucibacillary n (%)	Multibacillary n (%)	Total n (%)
Patients enrolled	185 (22)	673 (78)	858 (100)
Age group (years)			
≤ 14	20 (10.8)	37 (5.5)	57 (6.6)
15-64	163 (88.1)	634 (94.2)	797 (92.9)
65	2 (1.1)	2 (0.3)	4 (0.5)
Sex			
Male	62 (33.5)	447 (66.4)	509 (59.4)
Female	123 (66.5)	226 (33.6)	349 (40.6)
Nerve lesions			
0	165 (89.2)	389 (57.8)	554 (64.6)
1	6 (3.2)	95 (14.1)	101 (11.8)
2	8 (4.3)	96 (14.3)	104 (12.1)
≥ 3	6 (3.2)	93 (13.8)	99 (11.5)
Slit skin smear (BI)			
0	174 (94.6)	192 (28.5)	366 (42.6)
0.1 -2.99	10 (5.4)	158 (23.5)	168 (19.6)
≥ 3	0	324 (48)	(37.7)
Not informed	-	-	1 (0.1)
PGL-I serology			
0	155 (83.8)	174 (25.8)	329 (38.4)
1-3	29 (15.7)	327 (48.5)	356 (41.5)
> 4	1 (0.5)	171 (25.3)	172 (20)
Not informed	-	1(0.5)	1 (0.1)

BI: bacterial index; PGL-I: phenolic glycolipid-I.

This non-controlled trial did not include slit-skin smears or skin biopsies, which makes the determination of relapse unreliable. Additionally, because this trial did not include BI, it is not possible to evaluate which group of patients required longer treatment (Ji & Grosset 1990).

The main problem when evaluating any new treatment regimen for leprosy is the lack of reliable data available for the current treatment regimen. The relapse, reactions and impaired nerve function rates have never been systematically determined (Ji 1985) and reactions and impaired nerve function are the major causes of nerve damage that leads to impairments and disabilities in LPs (Ji 1998).

Our study was designed to overcome the need for reliable data about the current treatment regimen and to statistically compare its efficacy with that of a uniform regimen.

This independent study was coordinated by the Tropical Medicine Centre of the University of Brasília (NMT/UnB) with the participation of the Institute of Public Health and Tropical Pathology of the University of Goiás. This study received funding from the Department of Science and Technology and National Council for Scientific and Technological Development (403293/2005-7). It was conceptualised, designed and developed by the NMT/UnB in partnership with the Royal Tropical Institute of Amsterdam and with scientific support from members of the International Federation of Anti-leprosy Association Medical Commission during all phases, except for the pilot study, which was used to test the research forms at the Clinical Hospital of the UFMG. The study has an independent scientific steering committee that included Drs Celina Maria Turchi Martelli, Diana Lockwood, Euzenir Sarno, Ji Bahong[†], Maria Leide Wand-del-Rey de Oliveira, Paulo Roberto Lima Machado, Vijaykumar Pannikar and Sinésio Talhari. Three of these committee members also form the Database Monitoring and Security Committee: Drs Maria Leide Wand-del-Rey de Oliveira, Paulo Roberto Lima Machado and Sinésio Talhari. Their tasks are the following: (i) assessing the field protocol before intake, (ii) assessing the results at the end of the monthly follow-up period, (iii) performing a mid-term evaluation of the results after six years of follow-up and (iv) performing a final evaluation.

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