Brazilian clinical trial of uniform multidrug therapy for leprosy patients - the correlation between clinical disease types and adverse effects

Heitor de Sá Gonçalves[1]/[+], Maria Araci de Andrade Pontes[1], Samira Bührer-Sékula[2], Rossilene Cruz[3], Paulo Cesar Almeida[4], Maria Elisabete Amaral de Moraes[5], Gerson Oliveira Penna[6]

[1]Centro de Referência Dona Libania, Fortaleza, CE, Brasil [2]Universidade Federal de Goiás, Goiânia, GO, Brasil
[3]Fundação Alfredo da Matta, Manaus, AM, Brasil [4]Universidade Estadual do Ceará, Fortaleza, CE,Brasil
[5]Universidade Federal do Ceará, Fortaleza, CE, Brasil [6]Núcleo de Medicina Tropical, Universidade de Brasília, Brasília, DF, Brasil

This study sought to verify the correlation between leprosy types and the adverse effects of treatment drugs. This quantitative, prospective, nested study was developed at the Dona Libânia Dermatology Centre in Fortaleza, Brazil. Data were collected from November 2007-November 2008. During this period, 818 leprosy patients were diagnosed and began treatment. Forty patients with tuberculoid leprosy (TT) were selected. Twenty patients followed a standard therapy of dapsone and rifampicin and 20 were administered dapsone, rifampicin and clofazimine (U-MDT). Twenty patients with borderline lepromatous (BL) and lepromatous leprosy (LL) were also selected and treated with U-MDT. All of the subjects received six doses. With the exception of haemolytic anaemia, there was a low incidence of adverse effects in all the groups. We did not observe any differences in the incidence of haemolytic anaemia or other side effects across groups of patients with TT, BL or LL treated with U-MDT.

Key words: leprosy - multibacillary leprosy - paucibacillary leprosy - adverse effects - therapeutics - leprostatic agents

A turning point in leprosy therapy occurred in 1981 when the World Health Organization (WHO) recommended using multidrug therapy (MDT), with dapsone and rifampicin for six months for paucibacillary (PB) patients (MDT-PB) and 24 months of dapsone, rifampicin and clofazimine for multibacillary (MB) patients (MDT-MB). In 1998, the WHO recommended a fixed duration of 12 months for treating MB patients (WHO 1998). The current WHO recommended treatment regimen for MB patients is 12 600 mg doses of rifampicin once a month, 300 mg of clofazimine once a month plus 50 mg daily and 100 mg of dapsone daily. For PB patients, the regimen is six 600 mg doses of rifampicin once a month and 100 mg of dapsone daily.

Despite the efficacy of the currently recommended leprosy MDT (Cellona et al. 2003, Morel 2004, Penna et al. 2011), there are some limitations, such as a prolonged treatment duration that leads to high drop-out rates, difficulties in general health practitioners classifying the clinical types and wrong diagnoses of the PB and MB types when based solely on the number of lesions (Huikeshoven 1985, Ellard et al. 1988, Dasamanjali et al. 1997). Such difficulties have led several researchers to search for a uniform and shorter MDT (U-MDT) for the different leprosy types (Ji & Saunderson 2003, Talhari & Penna 2005) to replace the current regular MDT (R-MDT) that requires six and 12 months of treatment for PB and MB patients, respectively. Recently, the WHO raised the possibility

that PB and MB patients might be treated for six months (WHO 2002) based on the following factors: MDT has been proven efficacious and safe, there are very few reports of MDT resistance and relapse rates are low (< 1%) (Gelber et al. 2004, Matsuoka et al. 2007, WHO 2009).

Although U-MDT can represent an important advance in disease control, the recognised differences between the multi and PB groups should be considered, such as the bacillary charge (Ji 2001, Ji & Saunderson 2003), histopathological findings (Sarno & Sampaio 1996) and immunological (Goulart et al. 2002) and genetic (Mira et al. 2004, Moraes et al. 2004) profiles. Consequently, there is great concern regarding the possible impacts of U-MDT over several aspects of leprosy treatment, particularly therapy efficacy among MB patients and the incidence of adverse drug reactions in the patients with the PB type.

In 2007, an independent Brazilian study, the Brazilian U-MDT Clinical Trial (U-MDT/CT-Br), was initiated; in the study, dapsone, rifampicin and clofazimine were administered over six months to all leprosy patients (LPs). Here, we present the results of an investigation that was performed in the context of the U-MDT/CT-Br project with respect to comparing the incidence of adverse effects in two situations: (i) PB and MB patients who were treated with the same regimen (U-MDT) and (ii) PB patients who were treated with either the PB (R-MDT) or the MB (U-MDT) regimen. We hope our results will be useful in supporting the decision making process for implementing U-MDT as an efficacious disease control strategy (Penna 2011).

SUBJECTS, MATERIALS AND METHODS

This study is part of an independent study (U-MDT/CT-Br) coordinated by the Tropical Medicine Department of the University of Brasília (UnB) with the participation of the Institute of Public Health and Tropical

Pathology of the Federal University of Goiás; funding was provided by the DECIT/CNPq (403293/2005-7). This study was conceptualised, designed and developed by the Tropical Medicine Department of the UnB in partnership with the Royal Tropical Institute of Amsterdam.

This quantitative, prospective, nested study was developed at the Dona Libânia Center for Dermatology (CDERM) in Fortaleza, state of Ceará, Brazil. The data were collected from November 2007-November 2008. The targeted patients were those with diagnosed leprosy who were treated at the CDERM in the U-MDT/CT-Br study. The U-MDT/CT-Br is an open label randomised clinical trial design that was used to compare two treatment regimens (R-MDT treatment vs. U-MDT treatment) with monthly follow-ups for up to one year post-treatment followed by yearly post-treatment visits for six years. Newly diagnosed, previously untreated PB and MB LPs, returning defaulters and relapse cases (provided that the last treatment dose was more than 5 years prior) ranging from six- 65 years of age were included in the study. Patients who were under tuberculosis treatment, steroid treatment, with overt signs of acquired immune deficiency syndrome or were unable to make monthly clinic visits during the treatment and follow-up periods were excluded. After being classified as either PB or MB based on the number of skin lesions, the patients were randomised and allocated into the trial. A random list of numbers for the study entrance sequence (according to the clinical report forms number) was prepared and the randomisation codes on the worksheet were covered with the same material that is used for lottery scratch cards; therefore, the printed numbers were not visible.

During the study period, 818 patients (all residents of the Fortaleza metropolitan area) were diagnosed with leprosy and began treatment at the centre. Out these patients, 430 were evaluated and 60 who presented with tuberculoid, borderline lepromatous (BL), or lepromatous leprosy (LL) types were selected based on unambiguous, rigorous, clinical, bacteriological and histopathological criteria according to the Ridley and Jopling (1966) classification. These 60 patients were distributed into three groups. Forty PB patients were divided into two sub-groups: (i) 20 patients were treated with MDT-PB treatment and (ii) 20 with the MDT-MB for six months. The 20 MB remaining patients (14 LL and 6 BL leprosy) were treated with MDT-MB for six months. None of the patients were removed from the study. The following exclusion criteria were applied: (i) patient wished to discontinue participation due to unavailability, procedure intolerance or any other personal reason, (ii) non-compliance with the experimental protocol, (iii) violation of the protocol, such as a histological finding that does not confirm leprosy, (iv) severe adverse events and/or signs or symptoms of possible severe toxicity, (v) patient's death during the study period, (vi) any other condition judged by the investigator to be necessary to maintain the health of the volunteer.

The data were prospectively collected during the seven visits, as shown in Table I. The objective of the first visit was to select patients who had never received treatment. On the second visit (day 8 of the study), the

TABLE I

Summary of visit activities

Visits	1	2	3	4	5	6	7
Inclusion criteria and/or patient discontinuation	x	x	x	x	x	x	
Verification of diagnosis of leprosy onset	x	x					
Information of risks and benefits of the study	x						
Signing of informed consent	x						
Filling out clinical report	x	x	x	x	x	x	x
Investigation history of five year-prior treatment	x						
Clinical and dermatological evaluation	x		x	x	x	x	x
Evaluations of leprosy reactions	x	x	x	x	x	x	x
Information on MDT adverse effects			x	x	x	x	x
Clinical peripheral nerves evaluation	x		x	x	x	x	x
Neural pain scale	x	x	x	x	x	x	x
Evaluation of peripheral nerve function	x	x	x	x	x	x	x
Bacilloscopy	x						x
Biopsy for histopathological classification	x						
Clinical evaluation and disability classification	x						x
Classification of leprosy type		x					
Blood collection: complete haemogram, PCR and biochemistry	x		x	x	x	x	x
Recording of exam results		x	x	x	x	x	x
MDT supervised doses		x			x	x	
Evaluation of adverse effects			x	x	x	x	x
Verification of simultaneous drug use	x	x	x	x	x	x	x

MDT: multidrug therapy; PCR: polymerase chain reaction.

clinical classification was performed and the patients received the first supervised treatment dose. On the third visit (study day 9), recent adverse effects were evaluated and the study discontinuation criteria were addressed. On the fourth visit (day 15 of the study), late adverse effects were evaluated and the study discontinuation criteria were addressed. On the fifth visit (day 36), the adverse effects and possible study discontinuation were evaluated and the second supervised treatment dose was administered. The same procedures were performed on the sixth visit (day 148) and the final supervised dose of the treatment was administered. Finally, on the seventh visit (day 176 of the study), adverse effects were again evaluated and the patients were released.

The following adverse effects were monitored in the three groups: decreases in red blood cells (RBCs), haematocrit, haemoglobin, leucocytes and platelets, increases in the medium corpuscular volume, reticulocytes, C reactive protein (CRP), bilirubin, leukocytes and serum activities of lactate dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and alkaline phosphatase and the presence of jaundice, haepatomegaly, epigastric pain, nausea, anorexia, vomiting, abdominal pain, diarrhoea, dizziness, fatigue, headache, methemoglobinaemia, cyanosis, dyspnoea, psychosis, peripheral neuropathy, sulphone syndrome, agranulocytosis, acne, renal failure, flu-like syndrome, cutaneous pigmentation, xeroderma, constipation, acute abdominal pain, weight loss, lower limb oedema and drug-induced skin disorders (Cook 1995, Matsuoka et al. 2007, Harminder et al. 2011).

Statistical analysis - The statistical analysis of the association between the variables (adverse effects of drugs used in the MDT for leprosy) and the study groups (PB MDT-PB, PB MDT-MB and MB MDT-MB) was performed using the non-parametric chi-squared test and the probability ratio. The adverse effects were grouped according to the most likely causative drug.

Ethic - The U-MDT/CT-Br study was performed under the International (Helsinki) and Brazilian research regulations involving humans and was approved by three regional ethical committees from all of the states involved and by the National Ethics 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 obtained. Data confidentiality was guaranteed and the patients were free to leave the study and opt for the R-MDT regimen at any time (ClinicalTrials.gov identifier - NCT00669643).

In addition, informed consent forms specifically prepared for this study were presented to the Ethical Committee on Research of the CDERM and approved by the National Ethics Commission of Research - National Health Council/Ministry of Health, on February 17 2006, protocol 001/06.

RESULTS

Tables II-IV describe the frequency of the adverse effects that were observed in each patient group according to the drug most likely to be the cause of the adverse effect. Haemolytic anaemia was the most frequent adverse

TABLE II

Adverse effects observed, probably related to dapsone and/or rifampicin. Comparison between the paucibacillary (PB) groups on multidrug therapy (MDT)-PB and MDT-multibacillary (MB) treatment

Adverse effect	PB group on MDT-PB n (%)	PB group on MDT-MB n (%)
↓ Red blood cells[a]	13 (65)	19 (95)
↓ Haematocrit[a]	13 (65)	19 (95)
↓ Haemoglobin[a]	12 (60)	18 (90)
↑ MCV[a]	6 (30)	8 (40)
↑ Reticulocytes[a]	13 (65)	19 (95)
↑ LDH[a]	13 (65)	19 (95)
↑ SGOT	3 (15)	3 (15)
↑ SGPT	3 (15)	3 (15)
Epigastric pain	2 (10)	3 (15)
Nausea	3 (15)	2 (10)
Dizziness	2 (10)	0 (0)
Fatigue	3 (15)	2 (10)
Headache	4 (20)	3(15)
↑ Leukocytes	3 (15)	0 (0)
↓ Leukocytes	0 (0)	3 (15)
Abdominal pain	2 (10)	2 (10)
↑ Eosinophils	2(10)	4 (20)

a: statistically significant difference (p < 0.05) in the comparison between groups; LDH: lactate dehydrogenase; MCV: medium corpuscular volume; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

TABLE III

Adverse effects observed, probably related to dapsone and/or rifampicin comparison between paucibacillary (PB) and multidrug therapy (MDT) groups, both treated with MDT-MB

Adverse effect	PB group on MDT-MB n (%)	MB group on MDT-MB n (%)
↓ Red blood cells	19 (95)	20 (100)
↓ Haematocrit	19 (95)	20 (100)
↓ Haemoglobin	18 (90)	18 (90)
↑ MCV	8 (40)	8 (40)
↑ Reticulocytes	19 (95)	20 (100)
↑ LDH	19 (95)	20 (100)
↑ SGOT	3 (15)	2(10)
↑ SGPT	3 (15)	2(10)
Epigastric pain	3 (15)	3 (15)
Nausea	2 (10)	2 (10)
Dizziness	0 (0)	2 (10)
Fatigue	2 (10)	2 (10)
Headache	3(15)	2 (10)
↑ Leukocytes	0 (0)	0 (0)
↓ Leukocytes	3 (15)	3 (15)
Abdominal pain	2 (10)	2 (10)
↑ Eosinophils	4 (20)	3 (15)

LDH: lactate dehydrogenase; MCV: medium corpuscular volume; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

effect, particularly in the groups treated with MDT-MB. Of the PB patients under MDT-MB, 30% presented with a haemoglobin index of < 10 g%, while none of the patients under MDT-PB presented with a haemoglobin index of < 10 g%. Accordingly, we observed a statistically significant difference (p <0.05) between the PB groups on MDT-PB and MDT-MB in the distribution of the haematological alterations of the RBC index. No other statistically significant difference was observed between the groups.

To advance the understanding of the impact of MDT on the RBC index and the severity of haemolytic anaemia, the three groups were compared with respect to their distribution of haemoglobin values (obtained in the 6th month of treatment), as shown in Tables IV, V. Again, statistically significant differences were observed only in the comparison between the PB groups undergoing the MDT-PB and MDT-MB treatments.

DISCUSSION

Of the adverse drug effects that were observed in the three study groups, haemolytic anaemia appeared with the greatest frequency, accompanied by the symptoms classically associated with it, such as headache, fatigue and dizziness. Such data suggest that administering folic acid would serve as a preventive and/or therapeutic measure for all patients undergoing MDT.

The highest incidence of haemolytic anaemia was in the PB (95%) and MB groups (100%) treated with MDT-MB. A comparison to the PB patients who were treated with MDT-PB (65%, p < 0.05) suggests a role for clofazimine in developing these adverse effects (Chan-Tompkins 1995).

Upon analysing the severity of anaemia at the end of the sixth month of treatment, no differences were observed between the MB and PB patients under MDT-MB (25% vs. 30%, respectively) (Table VI), which indicates that the type of leprosy does not impact the severity of haemolytic anaemia. Instead, the statistically significant difference (p < 0.05) among the PB patients undergoing MDT-MB or MDT-PB suggests a possible influence of clofazimine on the severity of haemolytic anaemia (Katoch et al. 1999).

Note that haemolytic anaemia, in addition to being infrequent, did not reach a degree of severity to indicate the suspension of dapsone and/or clofazimine for any of the patients. This observation, in conjunction with the possibility of controlling the condition with folic acid, argues in favour of the viability of MDT/MB for PB patients.

Finally, the adverse effects of dapsone, clofazimine and rifampicin were similar across the PB and the MB groups under MDT-MB, even after considering haemolytic anaemia (95% vs. 100%). Furthermore, none of the other adverse effects were identified at a frequency or severity that would indicate medical intervention. It is important to further highlight the absence of severe adverse effects attributed to dapsone (e.g., methemoglobinaemia, sulphone syndrome and agranulocytosis), rifampicin (renal failure or flu-like syndrome), or clofazimine (semi-occlusion, intestinal occlusion and acute abdominal pain) (Cook 1995). Despite this result, the total number of LPs worldwide using these drugs suggests strict surveillance

of the adverse effects of MDT. In a literature search, we did not identify any studies that found synergistic effects of clofazimine and dapsone in the genesis of adverse effects in LPs. Additionally, there were no large controlled studies of the real prevalence of the adverse effects of R-MDT for comparison with our study.

Although PB and MB LPs presented bacteriological, immunological, histopathological, clinical and genetic differences, no differences in the incidence of adverse effects were observed in this study. Therefore, it is possible that the differences between PB and MB leprosy types have no influence on the pharmacokinetics of dapsone, rifampicin and clofazimine.

TABLE IV

Adverse effects observed, probably related to clofazimine

Adverse effect	PB group on MDT-MB n (%)	MB group on MDT-MB n (%)
Cutaneous pigmentation	2 (10)	1 (5)
Xeroderma	6 (30)	7 (35)
Abdominal pain	3 (15)	3 (15)
Nausea	2 (10)	2 (10)

TABLE V

Haemoglobin index (Hb) at the end of the sixth month of treatment. Comparison between paucibacillary (PB) groups on multidrug therapy (MDT)-PB and MDT-multibacillary (MB) treatment

Hb index (g%)	PB group on MDT-PB n (%)	PB group on MDT-MB n (%)
Hb < 10 [a]	0 (0)	6 (30)
10 < Hb < 11	9 (45)	12 (60)
Hb > 1 [a]	11 (55)	2 (10)

a: statistically significant difference (p < 0.05) in the comparison between groups.

TABLE VI

Haemoglobin index (Hb) at the end of the sixth month of treatment. Comparison between the paucibacillary (PB) and multidrug therapy (MDT) groups, both using MDT-MB

Hb (g%)	PB group on MDT-MB n (%)	MB group on MDT-MB n (%)
Hb < 10	6 (30)	5 (25)
10 < Hb < 11	12 (60)	11 (55)
Hb > 11	2 (10)	4 (20)

REFERENCES

Cellona RV, Balagon MVF, dela Cruz EC, Burgos JA, Abalos RM, Walsh GP, Topolski R, Gelber RH, Walsh DS 2003. Long-term efficacy of 2 year WHO multiple-drug therapy (MDT) multibacillary (MB) leprosy patients. *Int J Lepr Other Mycobact Dis 71*: 308-319.

Chan-Tompkins NH 1995. Toxic effects and drug interactions of antimycobacterial therapy. *Clin Dermatol 13*: 223-233.

Cook GC 1995. Adverse effects of chemotherapeutic agents used in tropical medicine. *Drug Saf 13*: 31-45.

Dasamanjali K, Schreuder PA, Pirayavaporn C 1997. A study on the effectiveness and safety of the WHO/MDT regimen in the northeast of Thailand; a prospective study, 1984-1996. *Int J Lepr Other Mycobact Dis 65*: 28-36.

Ellard GA, Pannikar VK, Jessudasan K, Christian M 1988. Clofazimine and dapsone compliance in leprosy. *Lepr Rev 59*: 205-213.

Gelber RH, Balagon VF, Cellona RV 2004. The relapse rate in MB leprosy patients treated with 2-years of WHO-MDT is not low. *Int J Lepr Other Mycobact Dis 72*: 493-500.

Goulart IM, Penna GO, Cunha G 2002. Immunopathology of leprosy: the complexity of the mechanisms of host immune response to *Mycobacterium leprae. Rev Soc Bras Med Trop 35*: 365-375.

Harminder S, Singh H, Nel B, Dey V, Tiwari P, Dulhani N 2011. Adverse effects of multi-drug therapy in leprosy, a two years' experience (2006-2008) in tertiary health care centre in the tribal region of Chhattisgarh state (Bastar, Jagdalpur). *Lepr Rev 82*: 17-24.

Huikeshoven H 1985. Patient compliance in leprosy control: a necessity in old and new regimens. *Int J Lepr 53*: 474-480.

Ji B 2001. Does there exist a subgroup of MB patients at greater risk of relapse after MDT? *Lepr Rev 72*: 3-7.

Ji B, Saunderson P 2003. Uniform MDT (U-MDT) regimen for all leprosy patients - another example of wishful thinking. *Lepr Rev 74*: 2-6.

Katoch K, Natarajan M, Katoch VM, Singh HB, Bhatia AS 1999. Chemotherapy trial in paucibacillary leprosy using clofazimine. *Indian J Lepr 71*: 311-324.

Matsuoka M, Budiawan T, Aye KS, Kyaw K, Tan EV, Cruz ED, Gelber R, Saunderson P, Balagon V, Pannikar V 2007. The frequency of drug resistance mutations in *Mycobacterium leprae* isolates in untreated and relapsed leprosy patients from Myanmar, Indonesia and the Philippines. *Lepr Rev 78*: 343-352.

Mira MT, Alcaïs A, Nguyen VT, Moraes MO, Di Flumeri C, Vu HT, Mai CP, Nguyen TH, Nguyen NB, Pham XK, Sarno EN, Alter A, Montpetit A, Moraes ME, Moraes JR, Doré C, Gallant CJ, Lepage P, Verner A, van de Vosse E, Hudson TJ, Abel L, Schurr E 2004. Susceptibility to leprosy is associated with PARK2 and PACRG. *Nature 427*: 636-640.

Moraes MO, Pacheco AG, Schonkeren JJ, Vanderborght PR, Nery JA, Santos AR, Moraes ME, Moraes JR, Ottenhoff TH, Sampaio EP, Huizinga TW, Sarno EN 2004. Interleukin-10 promoter single-nucleotide polymorphisms as markers for disease susceptibility and disease severity in leprosy. *Genes Immun 5*: 592-595.

Morel CM 2004. *Multidrug therapy against leprosy. Development and implementation over the past 25 years*, World Health Organization, Geneva, p. vii-viii.

Penna GO 2011. Leprosy: the need to employ evidence-based medicine in control policies around the world. *Lepr Rev 82*: 210-212.

Penna ML, Temporão JG, Grossi MA, Penna GO 2011. Leprosy control: knowledge shall not be neglected. *J Epidemiol Community Health 65*: 473-474.

Ridley DS, Jopling WH 1966. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis 34*: 255-273.

Sarno EM, Sampaio EP 1996. The role of inflammatory cytokines in the tissue injury of leprosy. *Int J Lepr Other Mycobact Dis 64* (Suppl.): S69-S73; discussion S73-S74.

Talhari S, Penna G 2005. Considerations about global policy for leprosy control. *Rev Soc Bras Med Trop 38*: 362-364.

WHO - World Health Organization 1998. *WHO Expert Committee on Leprosy*, WHO, Geneva, 43 pp.

WHO - World Health Organization 2002. *Report on Third Meeting of the WHO Technical Advisory Group on Elimination of Leprosy*, WHO, Geneva, 19 pp.

WHO - World Health Organization 2009. *Report of the Tenth Meeting of the WHO Technical Advisory Group on Leprosy Control*, WHO, New Delhi, 14 pp.