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# Primary results of Clinical Trial for Uniform Multidrug Therapy for Leprosy Patients in Brazil (U-MDT/CT-BR): reactions frequency in multibacillary patients

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*Summary*
*Settings*: Many believe that the regular treatment for multibacillary (MB) leprosy cases could be shortened. A shorter treatment, allowing for uniform treatment for all cases, makes case classification superfluous and therefore simplifies leprosy control.
*Objective*: To evaluate the association of the treatment duration with the frequency of reactions among MB patients.
*Methods*: An open-label randomised clinical trial to compare the present routine treatment with one lasting six months. Patients were recruited between March 2007 and February 2012. We analysed the frequency of first reaction with the Kaplan-Meier method and of recurrent reaction with a Poisson regression, using the treatment group and baciloscopic index level (BI) as independent variables. Logistic regression was used to evaluate the statistical association of different reaction types and the treatment group.

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*Results*: Among those with BI $< 3$, we found a statistical significant difference of reaction frequencies between the treatment groups from 6 to 18 months since the beginning of treatment. This difference disappears at 2 years after the start of treatment. Multiple reactions were associated with the treatment group and with BI $\geq 3$. No specific types of reactions were associated with treatment duration.
*Conclusion*: Although this is the first report of U-MDT/CT-BR, the results presented here support the possibility of use of UMDT in the field.

## Introduction

Leprosy will continue to be a public health problem for several more decades[1,2] despite the proposed elimination of tropical diseases.[3]

In 1981 WHO recommended multidrug therapy (MDT) for leprosy treatment consisting of two drug regimens: the first composed of three drugs - rifampicin, dapsone and clofazimine – for 24 months for multibacillary (MB) cases and the other with a two-drug MDT - rifampicin and dapsone – for 6 months for paucibacillary (PB) cases. In 1997 WHO recommended reducing MB leprosy treatment from 24 to 12 months[4] after the 7th Expert Committee Meeting stated in its final report that 'based on the available information, it is possible that the duration of the current MDT regimen for multibacillary leprosy could be shortened to 12 months' (p. 37).[5]

Leprosy control is based on early diagnosis and effective treatment to reduce the sources of transmission. The current proposed treatment requires the classification of cases as MB or PB. This classification is a problem for general health workers, despite the simplification based on the number of skin lesions. Another operational problem is patient compliance with long-term treatments.[6]

A 6-month uniform regimen for leprosy would make case classification superfluous and would reduce the duration of treatment for MB patients, simplifying leprosy control and allowing for its incorporation into primary health care units.

This paper presents preliminary results of the Brazilian randomised clinical trial for uniform multidrug therapy of MB patients. It presents reaction frequencies in the two study arms. The follow-up duration does not yet allow analysing the relapse rate differences between the two treatment groups.

## Methods

Patients were recruited between March 2007 and February 2012 at two National Brazilian leprosy reference outpatients units: Dona Libânia (Fortaleza, Ceará) and Alfredo da Matta (Manaus, Amazonas).

The study population included newly diagnosed, previously untreated PB and MB leprosy patients, between the ages of 6 and 65. Patients who were on tuberculosis treatment, steroid treatment or presented overt signs of AIDS were not included. The same was applied to patients not residing permanently in the area of the reference unit or those unwilling to comply with follow up medical visits. Patients were classified as PB or MB according to the number of skin lesions.

Open-label, randomised clinical trial design was used for comparing two treatment regimens. R-MDT treatment, the present WHO recommendation, versus U-MDT treatment, a 6-month treatment with rifampicin (monthly), dapsone and clofazimine (daily).

A random list of numbers was prepared using the clinical report form (CRF) numbers. The space in the worksheet containing the randomisation codes was covered with the same material utilised in lottery scratch cards so that the printed numbers were not visible. For MB patients the randomisation number was revealed on the day the patient came for the 6th treatment dose.

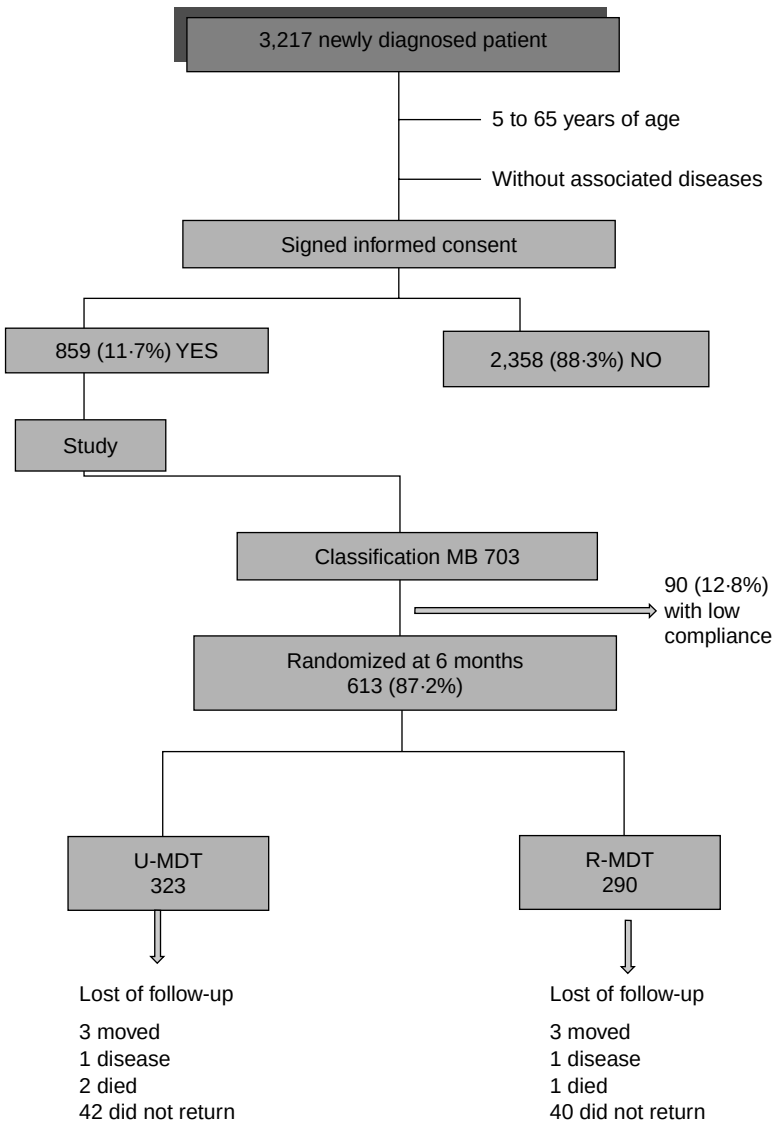


**Figure 1.** Flow diagram of the study.

Patient follow-up included a monthly medical visit in the first year after the beginning of treatment for both treatment groups. In the following years, patients had a yearly medical visit. In addition, all patients were asked to return to the clinic immediately in the case of any abnormalities and received instructions about signs and symptoms of reactions or nerve function impairment.

If a patient developed reactions or nerve function impairment, he/she received the appropriate treatment and remained in the study. All reaction and nerve function impairment episodes were registered. If there was any difficulty in distinguishing between reactions and relapses, an independent and experienced external specialist was consulted.

Reactions were diagnosed clinically by the attending physicians in the reference centre. All the physicians were dermatologists with significant experience in leprosy treatment. Reactions were classified as Type I, II or pure neuritis. Type I reactions included reverse reaction, with or without neuritis. Type II reactions included erythema nodosum leprosum, erythema polymorphus, lymphadenitis, iridocyclitis, orchitis and arthritis with or without neuritis. If the patient presented only neuritis with no other symptoms, then the reaction was classified as neuritis.

In order to compare the baseline characteristic of the groups, 't' tests were used for continuous variables and 'chi square' for dichotomous variables. The reaction frequency in time was analysed using the Kaplan-Meyer survival function comparing the two study groups and stratified by baciloscopic index (BI), less than 3 and 3 or more. The statistical test used was the logrank test. For the survival analysis time, zero was the time at which the treatment

**Table 1.** Baseline Characteristics of the Study Patients According to Treatment Group

| Characteristic | UMDT (323) | | RMDT (290) | |
|---|---|---|---|---|
| Mean age (ys)[b] | 39·63448 | | 40·76471 | |
| *Age group*[a] | | | | |
| 0–9 | 5 | 1·55% | 6 | 2·07% |
| 10–19 | 24 | 7·43% | 26 | 8·97% |
| 40–49 | 68 | 21·05% | 68 | 23·45% |
| 30–39 | 59 | 18·27% | 51 | 17·59% |
| 20–29 | 61 | 18·89% | 51 | 17·59% |
| 50–59 | 72 | 22·29% | 65 | 22·41% |
| more than 60 | 34 | 10·53% | 23 | 7·93% |
| *Sex*[a] | | | | |
| Male | 217 | 67·18% | 193 | 66·55% |
| Female | 106 | 32·82% | 97 | 33·45% |
| Mean BI[b] | 2·49816 | | 2·46761 | |
| *BI Group*[a] | | | | |
| BI $<$ 3 | 205 | 63·47% | 195 | 67·24% |
| BI $\geq$ 3 | 118 | 36·53% | 95 | 32·76% |
| *Clinical Classification*[a] | | | | |
| I | 3 | 0·93% | 2 | 0·69% |
| L | 71 | 21·98% | 59 | 20·42% |
| BT | 93 | 28·79% | 77 | 26·64% |
| BB | 71 | 21·98% | 71 | 24·22% |
| BL | 85 | 26·32% | 81 | 28·03% |

[a] Chi square with $P$ value $<0{\cdot}05$
[b] $t$ test with $P$ value $<0{\cdot}05$

began. For the analysis of multiple reaction episodes multivariable Poisson regression was applied to the data with the logarithm of the number of days of observation as an offset variable. The model fits the logarithm of the incidence of multiple reactions as a function of the intercept, treatment group and BI $\geq 3$ using BI $< 3$ as the reference. Significant statistical results were those with a probability (*P* value) lower than 0·05.

For evaluation of the statistical association of different types of reaction with the treatment and the initial BI, we fitted logistic regressions. The dependent variable was the frequency of each form of reactions in the period of 6 to 18 months after the treatment started, having those with no reaction as the control group.

This study is an independent study coordinated by the Tropical Medicine Centre of the University of Brasilia with the participation of the Institute of Tropical Pathology and Public Health of the University of Goiás. This study was performed under the international (Helsinki) and Brazilian research regulations and was approved by three regional ethical committees from all the states involved and by the National Ethics Commission of Research (CONEP) of the National Health Council (CNS)/Ministry of Health (MS), on February 17, 2006, protocol number 001/06. Written informed consent was required from all the patients prior to their inclusion in the study. For patients aged 6 to 17 years, written parental consent was obligatory. Data confidentiality was strictly guaranteed. Patients were free to leave the study, if they so desired, and opt for the R-MDT regimen outside the study. ClinicalTrials.gov identifier - NCT0066,9643.

Further details about the study protocol can be found in the paper 'Clinical Trial for Uniform Multidrug Therapy for Leprosy Patients in Brazil (U-MDT/CT-BR): Rationale and Design'[7] with open-access at the site http://memorias.ioc.fiocruz.br/ or at http://www.scielo/mioc.

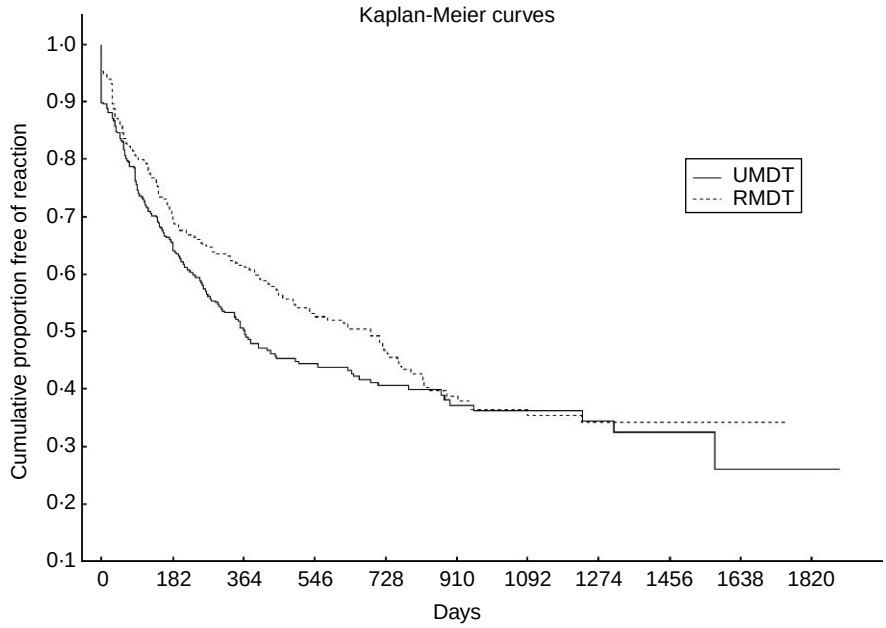


**Figure 2.** The Kaplan-Meier curves comparing UMDT and RMDT.

## Results

Figure 1 shows the participant flow diagram.

Table 1 shows baseline values of some demographic and clinical variables that are similar in the two groups, with no statistical significant difference.

The total person-time observed was 49,8613 person-days, i.e. 1366·063 person-years, with a maximum of 5·20 years of follow up. One relapse, in a patient of UMDT group with initial BI = 4, was observed in 2011, 4·5 years since the beginning of treatment.

Figure 2 presents the Kaplan-Meyer curves showing the free of reaction proportion in each group as a function of time.

At 6 months, when UMDT for the experimental group is completed, the curves separated. Those on UMDT have more reactions than those on RMDT. The biggest difference is found around 1 year (difference of 11·9% at 1·15 years). The curves meet each other around 2 years after the beginning of treatment due to higher first reaction incidence in the control group in the second year after the beginning of treatment. The proportion free of reaction is the same in both groups around 2 years.

Table 2 presents the numbers that generated the graph, i.e., the proportion with and without reaction in each time interval.

It is worth noticing that the number of patients became very small after 4 years of observation, and that introduces an important random variation in the data, turning the end of the curves unreliable (Table 2).

**Table 2.** Life table of Kaplan Meyer Analysis of the first reactions in patients treated with UMDT and RMDT

| Time in days | Time in years | No. Enter the period | No. Censored | No. with reaction | Cumulative percentage of cases reaction free | Cumulative percentage of cases with reaction |
|---|---|---|---|---|---|---|
| UMDT | | | | | | |
| 0 | 0 | 316 | 10 | 120 | 100 | 0 |
| 210·56 | 0·58 | 186 | 39 | 41 | 61·41 | 38·59 |
| 421·11 | 1·15 | 106 | 16 | 8 | 46·29 | 53·71 |
| 631·67 | 1·73 | 82 | 28 | 6 | 42·51 | 57·49 |
| 842·22 | 2·31 | 48 | 9 | 4 | 38·76 | 61·24 |
| 1052·78 | 2·88 | 35 | 15 | 1 | 35·2 | 64·8 |
| 1263·33 | 3·46 | 19 | 8 | 1 | 33·92 | 66·08 |
| 1473·89 | 4·04 | 10 | 8 | 1 | 31·66 | 68·34 |
| 1684·44 | 4·61 | 1 | 1 | 0 | 26·38 | 73·62 |
| 1895 | 5·19 | 0 | 0 | 0 | 26·38 | 73·62 |
| RMDT | | | | | | |
| 0 | 0 | 280 | 8 | 90 | 100 | 0 |
| 210·56 | 0·58 | 182 | 41 | 22 | 67·39 | 32·61 |
| 421·11 | 1·15 | 119 | 11 | 15 | 58·21 | 41·79 |
| 631·67 | 1·73 | 93 | 24 | 17 | 50·52 | 49·48 |
| 842·22 | 2·31 | 52 | 8 | 4 | 39·92 | 60·08 |
| 1052·78 | 2·88 | 40 | 11 | 2 | 36·59 | 63·41 |
| 1263·33 | 3·46 | 27 | 12 | 0 | 34·47 | 65·53 |
| 1473·89 | 4·04 | 15 | 14 | 0 | 34·47 | 65·53 |
| 1684·44 | 4·61 | 1 | 1 | 0 | 34·47 | 65·53 |
| 1895 | 5·19 | 0 | 0 | 0 | 34·47 | 65·53 |

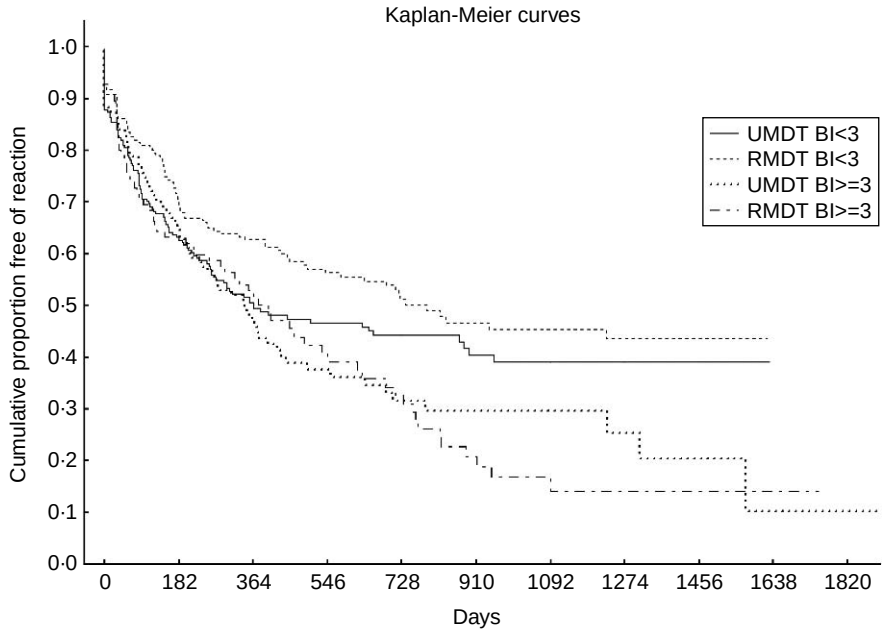


**Figure 3.** The Kaplan-Meier curves comparing UMDT BI $<$ 3, RMDT BI $<$ 3 and UMDT $\geq$ 3 and RMDT BI $\geq$ 3.

Figure 3 shows the Kaplan Meyer curves stratified by BI level, with four subgroups: UMDT and BI $<$ 3; RMDT and BI $<$ 3; UMDT and BI $\geq$ 3; RMDT and BI $\geq$ 3.

The two subgroups with BI $<$ 3 behave very similarly to the complete UMDT and RMDT groups. The groups with BI $\geq$ 3 show a smaller difference in the same period if treated with UMDT or RMDT. After one year, the subgroups with initial BI $<$ 3 presented 39·10% with at least one reaction episode in the RMDT subgroup and 52·91% in the UMDT subgroup. Those with BI $\geq$ 3 presented 53·72% for RMDT and 57·8% for UMDT at the same time interval. Those with a high BI had a higher frequency of first reaction than those with BI $<$ 3 throughout the observation time (Table 3).

The logrank test result for the difference in the entire period of those with BI $<$ 3 was $-1{\cdot}35{,}226$ with $P = 0{\cdot}18$ and for those with BI $\geq$ 3 was $-0{\cdot}32{,}9769$ with $P = 0{\cdot}74$, showing no statistical significance in the two study arms in those subgroups. But if we restrict the comparison to the period of 6 to 18 months after the treatment started, logrank test value was $-2{\cdot}00548$ with $P = 0{\cdot}04$ for those with BI $<$ 3 and $-1{\cdot}22{,}507$ with $P = 0{\cdot}22$ for those with BI $\geq$ 3 highlighting that during this period the curves difference among those with low BI is statistically significant.

Table 4 shows the result of the Poisson regression.

The incidence of recurrent reaction presented a positive association with BI $\geq$ 3 and with UMDT treatment. The estimated parameters are a measure of association and the association between multiple reactions is stronger with BI $\geq$ 3 than with UMDT or RMDT. An interaction term showed statistical significance, meaning that the simultaneous influence of the UMDT group and BI $\geq$ 3 is less than the sum of the effect of each of these variables.

Table 5 shows the distribution of the type of first reaction by MDT group and BI level.

Table 6 shows the result of the logistic regression including age group, sex, BI and study arm as independent variables. The group with BI $\geq$ 3 showed statistical association with the

**Table 3.** Life table of Kaplan Meyer Analysis of the first reactions in patients treated with UMDT and RMDT stratified by BI level

| Time in days | Time in years | No. Enter the period | No. Censored | No. with reaction | Cumulative percentage of cases reaction free | Cumulative percentage of cases with reaction |
|---|---|---|---|---|---|---|
| UMDT BI < 3 | | | | | | |
| 0 | 0 | 205 | 7 | 80 | 100 | 0 |
| 210·56 | 0·58 | 118 | 26 | 23 | 60·3 | 39·7 |
| 421·11 | 1·15 | 69 | 8 | 3 | 47·09 | 52·91 |
| 631·67 | 1·73 | 58 | 19 | 2 | 44·92 | 55·08 |
| 842·22 | 2·31 | 37 | 7 | 4 | 43·06 | 56·94 |
| 1052·78 | 2·88 | 26 | 13 | 0 | 37·92 | 62·08 |
| 1263·33 | 3·46 | 13 | 5 | 0 | 37·92 | 62·08 |
| 1473·89 | 4·04 | 8 | 8 | 0 | 37·92 | 62·08 |
| 1684·44 | 4·61 | 0 | 0 | 0 | 37·92 | 62·08 |
| 1895 | 5·19 | 0 | 0 | 0 | 0 | |
| RMDT BI < 3 | | | | | | |
| 0 | 0 | 195 | 4 | 64 | 100 | 0 |
| 210·56 | 0·58 | 127 | 29 | 10 | 66·84 | 33·16 |
| 421·11 | 1·15 | 88 | 9 | 8 | 60·9 | 39·1 |
| 631·67 | 1·73 | 71 | 22 | 9 | 55·06 | 44·94 |
| 842·22 | 2·31 | 40 | 6 | 1 | 46·8 | 53·2 |
| 1052·78 | 2·88 | 33 | 8 | 1 | 45·54 | 54·46 |
| 1263·33 | 3·46 | 24 | 12 | 0 | 43·97 | 56·03 |
| 1473·89 | 4·04 | 12 | 12 | 0 | 43·97 | 56·03 |
| 1684·44 | 4·61 | 0 | 0 | 0 | 43·97 | 56·03 |
| 1895 | 5·19 | 0 | 0 | 0 | 0 | |
| UMDT BI ≥ 3 | | | | | | |
| 0 | 0 | 118 | 3 | 47 | 100 | 0 |
| 210·56 | 0·58 | 68 | 13 | 18 | 59·66 | 40·34 |
| 421·11 | 1·15 | 37 | 8 | 5 | 42·2 | 57·8 |
| 631·67 | 1·73 | 24 | 9 | 4 | 35·8 | 64·2 |
| 842·22 | 2·31 | 11 | 2 | 0 | 28·46 | 71·54 |
| 1052·78 | 2·88 | 9 | 2 | 1 | 28·46 | 71·54 |
| 1263·33 | 3·46 | 6 | 3 | 1 | 24·9 | 75·1 |
| 1473·89 | 4·04 | 2 | 0 | 1 | 19·37 | 80·63 |
| 1684·44 | 4·61 | 1 | 1 | 0 | 9·68 | 90·32 |
| 1895 | 5·19 | 0 | 0 | 0 | 9·68 | 90·32 |
| RMDT BI ≥ 3 | | | | | | |
| 0 | 0 | 95 | 4 | 36 | 100 | 0 |
| 210·56 | 0·58 | 55 | 12 | 12 | 61·29 | 38·71 |
| 421·11 | 1·15 | 31 | 2 | 7 | 46·28 | 53·72 |
| 631·67 | 1·73 | 22 | 2 | 8 | 35·48 | 64·52 |
| 842·22 | 2·31 | 12 | 2 | 3 | 21·96 | 78·04 |
| 1052·78 | 2·88 | 7 | 3 | 1 | 15·97 | 84·03 |
| 1263·33 | 3·46 | 3 | 0 | 0 | 13·07 | 86·93 |
| 1473·89 | 4·04 | 3 | 2 | 0 | 13·07 | 86·93 |
| 1684·44 | 4·61 | 1 | 1 | 0 | 13·07 | 86·93 |
| 1895 | 5·19 | 0 | 0 | 0 | 13·07 | 86·93 |

frequency of Type II reaction and the frequency of neuritis as first reaction. The frequency of Type I first reaction showed an association only with the sex of the individual.

Among those who had at least two reactions, 99% had the same type of reaction the first and the second time, and among those who had at least three reactions, 58·3% had the same kind of reaction in all the events.

**Table 4.** Parameters Estimates of the Poisson Regression

| | Estimate | Relative Risk | Standard Error | Wald Statistic | *P* value |
|---|---|---|---|---|---|
| Intercept | −6·12 | 0·00 | 0·04 | 20112·37 | 0·00000 |
| BI | 0·34 | 1·40 | 0·04 | 61·56 | 0·00000 |
| Group | 0·09 | 1·09 | 0·04 | 4·23 | 0·03972 |
| BI * Group | −0·14 | 0·87 | 0·04 | 10·49 | 0·00120 |

## Discussion

The main problem when evaluating any new treatment regimen for leprosy is that there are no good and reliable data available for the current treatment regimen. No randomised clinical trial supports the reduction of treatment duration to one year for MB patients. Relapse rates have never been systematically determined, and the same holds true for reactions and nerve function impairment rates, the major causes of the nerve damage that leads to impairments and disabilities in leprosy patients.

Differences in methodology mean that it is difficult to compare available studies. In this study the observation period considered was from the beginning of treatment (time = 0) to the last medical visit attended by the patient that guaranteed accurate information about the patient status at the end of the observation period. The routine examinations including slit skin microscopy and histopathology of skin biopsy also increased the accuracy of the data.

The primary outcome – relapse – is very difficult study due to its low frequency and the long duration of the follow-up needed. There are solid reports that relapses occur up to 5 years after the initial treatment.[8,9] In our study, 69% of our patients were followed for 3 years or less, therefore, our data isn't suitable for relapse analysis.

Our observation differs from a recent open field, non-controlled treatment trial using the same 6-month treatment regimen (UMDT). This paper reported six relapses defined clinically, two patients in the group of those with up to five skin lesions and four among those with six and more lesions, three in the first follow up year, two in the second and one in the third year of follow up.[10] In this study no slit skin smears or histopathology were used

**Table 5.** Distribution of first reaction according to the type by MDT group and BI level

| Group | EN | RR | Neuritis | No Reaction | Total | Qui$^2$ | *P* value |
|---|---|---|---|---|---|---|---|
| BI < 3 | | | | | | | |
| U-MDT | 6 | 64 | 42 | 93 | 205 | | |
| | 2·93% | 31·22% | 20·49% | 45·37% | | | |
| R-MDT | 7 | 66 | 20 | 102 | 195 | 8·084581 | *P* = 0·04430 |
| | 3·59% | 33·85% | 10·26% | 52·31% | | | |
| BI ≥ 3 | | | | | | | |
| U-MDT | 25 | 26 | 26 | 41 | 118 | | |
| | 21·19% | 22·03% | 22·03% | 34·75% | | | |
| R-MDT | 25 | 23 | 19 | 28 | 95 | 1·252878 | *P* = 0·74035 |
| | 26·32% | 24·21% | 20·00% | 29·47% | | | |

**Table 6.** Results of the logistic regression for the occurrence of different types of reactions 6 to 18 months after the beginning of treatment

| | Level of Effect | Odds Ratio | Lower CL 95·0% | Upper CL 95·0% | *p* value |
|---|---|---|---|---|---|
| Outcome: occurrence of reaction Type 1 | | | | | |
| Sex | M | 1·67 | 1·46 | 1·88 | 0·02 |
| | F | 1·00 | | | |
| Age | >19 | 0·88 | 0·54 | 1·21 | 0·70 |
| | 20 + | 1·00 | | | |
| BI | BI ≥ 3 | 1·00 | 0·78 | 1·22 | 0·99 |
| | <3 | 1·00 | | | |
| Regimen | UMDT | 0·92 | 0·70 | 1·13 | 0·69 |
| | RMDT | 1·00 | | | |
| Interaction term | UMDT + ≥ 3 | 0·86 | 0·64 | 1·07 | 0·48 |
| Outcome: occurrence of reaction Type 2 | | | | | |
| Sex | M | 0·89 | 0·55 | 1·22 | 0·72 |
| | F | 1·00 | | | |
| Age | >19 | 0·56 | 0·09 | 1·04 | 0·23 |
| | 20 + | 1·00 | | | |
| BI | ≥3 | 11·32 | 10·98 | 11·66 | 0·00 |
| | <3 | 1·00 | | | |
| Regimen | UMDT | 0·81 | 0·47 | 1·14 | 0·53 |
| | RMDT | 1·00 | | | |
| Interaction | UMDT + ≥ 3 | 0·83 | 0·49 | 1·17 | 0·58 |
| Outcome: occurrence of pure neuritis | | | | | |
| Sex | M | 1·15 | 0·90 | 1·39 | 0·59 |
| | F | 1·00 | | | |
| Age | >19 | 0·74 | 0·36 | 1·12 | 0·45 |
| | 20 + | 1·00 | | | |
| BI | BI ≥ 3 | 2·12 | 1·88 | 2·37 | 0·00 |
| | <3 | 1·00 | | | |
| Regimen | UMDT | 1·48 | 1·23 | 1·72 | 0·12 |
| | RMDT | 1·00 | | | |
| Interaction term | UMDT + ≥ 3 | 0·63 | 0·39 | 0·88 | 0·07 |

meaning that the differential diagnosis between relapse and reaction were based on criteria with low accuracy.

Reactions and disability development are secondary outcomes of the treatment that have clinical relevance. Reactions after MDT are felt by patients as disease resulting in low quality of life.[11] Development of disabilities after the beginning of MDT is also a serious medical event. Kumar *et al.*[12] show the cumulative risk of disability after 4 years of follow-up, estimating that only 10% of patients are free from disability at the end of this period. It is interesting to note that the authors did not find statistical significant differences between those who completed 1 year of treatment and defaulters with less than 6 months of treatment. As these results come from an observational study, we should not forget that compared groups may be biased, because those with a better clinical response to the initial few months of treatment could have a higher probability of non-compliance with the full treatment.

The present study found that the incidence of recurrent reaction is associated with treatment duration and with initial BI. Balagon *et al.*[13] in their observational study comparing reactions of MB cases treated for 1 and 2 years also found association between reaction frequency and treatment duration and with BI > 3. The frequency of reaction reported was

lower than was found by us, but their analysis considered the initial time as the end of each group treatment and not the beginning, as in our study.

The risk of having at least one reaction is the same for the two treatment groups after 2 years, being higher for those with initial BI $\geq 3$. Although the risk of first reaction converges 2 years after the beginning of treatment, the Kaplan Meier curves separate when UMDT ends and the RMDT group are still taking their drugs. The fact that the Kaplan Meier curves converge makes statistical analysis difficult, as the logrank test is more efficient with parallel curves, resulting in lack of statistical significance for the whole curve. However, the restricted test for the period of 6 to 18 months showed that between those with low BI, those in UMDT have the first reaction earlier in time, a difference statistically significant. The consequence of having the first reaction earlier is a higher chance of having more than one reaction in the observation period, as shown in the Poisson regression.

For the analysis of the frequency of different types of reaction we decided to do a logistic regression to explore associations, meaning that we analysed the clinical trial cohort as a case-control study. In this analysis the follow-up time is not included, making the results weaker compared to the life table. This difference in analysis strategy explains the differences between Kaplan-Meyer estimators (Tables 2 and 3) and the actual proportion of reactions (Table 5). The Kaplan-Meyer method estimates the risk of reaction in a defined period of time.

Neuritis and Type II reactions showed association with BI $\geq 3$ but not with treatment duration supporting what was seen in the prospective analysis for the total number of reactions and published by other authors.[14,15] It is worth noting that there is a very strong association between the occurrence of Type II reaction and high BI, odds ratio of 11. We found no association of Type I reaction with BI or treatment duration. The logistic regression pointed to an association with the sex of the patient, which may be a particular characteristic of our data, since this association is not found in other studies.

A recent paper with open field, non-controlled treatment trial using the same 6-month treatment regimen in China[16] presented reaction frequencies and notes that among those taking UMDT the occurrence of Type 2 reaction was higher than reported in the literature, but was smaller than the frequency found in the present study. The Shen *et al.* study and our study differ in criteria in terms of both the exclusion of patients from the analysis and the follow up. Our follow up was done by expert doctors with a standard frequency which could increase the probability of reaction diagnosis if compared to a field study.

Reactions are associated with development of disabilities which is a very important outcome. Further analysis of this study should include severity of reaction and disability development.

Although this is the first report of U-MDT/CT-BR, the results presented here support the possibility of using UMDT. The difference in reaction frequency between treatment groups was more relevant among those with a low BI than those with a high BI which was not expected by the authors. Furthermore, the frequency of first time reactions was not statistically different at 2 years after the beginning of treatment. No specific types of reaction were associated with treatment duration.

Finally, we can all agree that since 1981 the introduction of the associated medications for leprosy has brought considerable advances. However we also know that MDT is far from ideal given its long treatment duration, the cutaneous pigmentation caused by clofazimine, and the side effects of dapsone. On the other hand, there is nothing on the horizon to substitute

MDT in the short-or medium-term,[17] consequently the proposal to achieve elimination in a short time-frame[3] is not a plausible goal.

It should therefore be agreed that as long as this treatment is internationally accepted, it should be provided to the greatest number of patients. In this way, the UMDT may be an opportunity to the extent that there is greater integration of leprosy control activities into primary healthcare services.

The authors declare no conflict of interest.

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