Results from the Clinical Trial of Uniform Multidrug Therapy for Leprosy Patients in Brazil (U-MDT/CT-BR): Decrease in Bacteriological Index

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Summary

Background: Many believe that the regular treatment for multibacillary (MB) leprosy cases could be shortened. A shorter treatment allowing uniformity in treatment for all cases renders case classification superfluous and therefore simplifies leprosy control.

Objective: To evaluate the association between treatment duration and the trend in bacteriological index (BI) decrease over time among patients given Uniform MDT (UMDT) compared to those given regular MDT (RMDT).

Methods: An open-label randomised clinical trial to compare the present routine treatment with one lasting six month. Patient intake was from March 2007 to February 2012. To evaluate the trend of BI as a function of time, a multilevel linear with mixed effects model was fixed to the two study groups and also four groups after stratification by BI, less than 3 and 3 or more.

Results: The BI fall was higher among those taking RMDT, this difference however was not statistically significant.

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Conclusion: The results presented here support the possibility of use of UMDT in the field, but further follow up is still needed for a final conclusion.

Introduction

Leprosy will continue to be a public health problem for several more decades\textsuperscript{1,2} despite the proposed elimination target for neglected tropical diseases.\textsuperscript{3} Leprosy control is based on early diagnosis and effective treatment to reduce the source of transmission. The presently proposed treatment requires the classification of cases as multibacillary (MB) or paucibacillary (PB) which may not be easy for general health workers in the field. A 6 month uniform regimen for leprosy would turn case classification superfluous and would reduce the duration of treatment for MB patients, simplifying leprosy control and its incorporation into the primary health care system.

This short communication presents an update of the results of the randomised clinical trial for uniform multidrug therapy of MB patients published before.\textsuperscript{4} It presents the analysis of the trend in BI reduction over time for each treatment group.

Methods

The study is an open-label, randomised clinical trial comparing two treatment regimens. R-MDT treatment, the present WHO recommendation, versus U-MDT treatment, 6 months treatment with rifampicin (monthly), dapsone and clofazimine (daily). Patients were recruited from March 2007 to February 2012 at two National Brazilian leprosy reference outpatients units and were classified as MB according to the number of skin lesions.

Patient follow-up included once a month medical visits in the first year after the beginning of treatment for both study arms and yearly medical visits thereafter. 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.

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’\textsuperscript{5} with open-access at the site http://memorias.ioc.fiocruz.br/or at http://www.scielo/mioc.

To evaluate the BI trend over time from 180 days from the onset of treatment, a multilevel linear with mixed effects model, i.e., random intercept model, was fixed to the two study groups – UMDT and RMDT – and also four groups after stratification by bacteriological index (BI), less than 3 and 3 or more. Individual linear regression for each patient was fitted through minimum square method. The statistical programme used was Stata/MP 12-1.

This study was performed under the international (Helsinki) and Brazilian research regulations. Data confidentiality was strictly guaranteed. ClinicalTrials.gov identifier – NCT00669643.
Results

The total person-time observed was 780930 person-days, i.e. 2139.5 person-years, with a maximum of 6.66 years of follow up. The big increase in person time of observation compared with the one reported in the previous publication is due to an effort to update information on patients. As published before, one relapse was observed in 2011 and another one was observed in 2013, both in patients in the UMDT group with a high initial BI.

Figure 1 shows individual regressions fitted for each patient of both study groups since the 180th day after the beginning of treatment.

Figure 2 shows the estimate for the fall of BI by day for each group and the 95% confidence interval. Although the fall was higher for those taking RMDT, this difference was not statistically significant.

Discussion

The primary outcome of leprosy treatment is cure and the success of treatment is measured in terms of relapse after completion of adequate treatment. Relapse is not easy to study due to its low frequency and the long duration of follow-up needed. There are reports that relapses occur 5 years after treatment6–8 and our data is not suitable for relapse analysis now. Other authors using different diagnostic criteria for relapse found six relapses before the fourth year of follow up.9 The re-analysis of reaction frequency with the updated data did not show any important difference compared with the analysis published in 2012.

Our analysis of the BI fall considered the values of the same patient in a multi-time level, meaning that the BI decrease as a function of time of each patient is the base for the regression

![Figure 1. Individual regressions of patient of the two study groups on time from the 180th day after the beginning of treatment on R – Relapse case.](image)
coefficient of time estimation, i.e., the parameter that quantifies the linear time trend. Figure 1 shows the BI decrease in time for each patient to illustrate that the rate of fall varies between each patient.

Our model estimates the mean of BI decrease as a function of time and not the decrease of the BI mean for all patients, as happens when a traditional linear regression of BI values against time is estimated. Traditional linear regression of BI of all patients in the same period ignores that BI from an individual patient at 360 days from the beginning of treatment correlates with the BI of this same patient at 180 days.

It is worth pointing out that these two approaches estimate different values for the decrease in time with the traditional regression overestimating it. According to our model, the fall was higher for those taking RMDT, but this difference was not statistically significant, as shown in Figure 2 by the overlap of 95% confidence interval.

Although Figure 1 is presented mainly as a way to make it clear why the multilevel analysis was used, we reviewed all patients with a stable or increasing trend. These trends were mostly statistical variation that resulted from adjusting, only two measures or three measures with opposite trends (plus and minus).

Finally, as we know, since 1981 the introduction of MDT for leprosy has brought considerable advances in leprosy control programmes. However, we also know that MDT is far from ideal given its long treatment duration, the cutaneous pigmentation caused by clofazimine, the side effects of dapsone, and the progression of disability in some MB patients.10 Those are the reasons for developing new randomised studies with new drug regimens.11,12 On the other hand, there is nothing on the horizon to substitute MDT in the

![Figure 2. Estimate and 95% Confidence Interval of the BI fall by day for patients treated with UMDT and RMDT from 180 days on. All patients and stratified by BI level.](image-url)
short-or medium-term, consequently the proposal to achieve elimination in a short time-frame 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 U-MDT may be an opportunity to the extent that there is greater integration of leprosy control activities into primary health care services.

The authors declare no conflict of interest.

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References

1 Scollard DM. Leprosy research declines, but most of the basic questions remain unanswered. Int J Lepr Other Mycobact Dis, 2005; 73: 25–27.