No difference in leprosy treatment outcomes comparing 12- and 24-dose multidrug regimens: a preliminary study

Nenhuma diferença na evolução da hanseníase entre os esquemas terapêuticos de 12 *versus* 24 doses: um estudo preliminar

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Abstract

A comparative study was performed on the initial and final bacillary indexes of 213 multibacillary leprosy patients who received 12 doses (Group 1: 128 patients) or 24 doses (Group 2: 85 patients) of multidrug therapy (MDT/WHO) to measure the effectiveness of the two regimens. All patients were evaluated at treatment baseline, 12 months, and 24 months. The reduction in bacillary levels and mean bacillary indexes at 24 months was similar in the two groups. No statistical difference in reaction rates was observed between the two treatment regimens.

Leprosy; Drug Therapy; Comparative Study

Introduction

As with all diseases that have plagued mankind for millennia, there have been numerous attempts to treat and cure, if not completely eliminate, leprosy. In the early 1940s, the introduction of dapsone and its derivatives paved the way for modern chemotherapy for leprosy, allowing follow-up studies in outpatient clinics for the first time. However, patients with lepromatous leprosy continued to require lifelong treatment. The aims of treatment are to block transmission of infection and eliminate all viable *Mycobacterium leprae* from the body as rapidly as possible.

In 1982, the World Health Organization (WHO) recommended that a standard regimen of multidrug therapy (MDT) consisting of rifampin, dapsone, and clofazimine be administered to multibacillary leprosy patients for a minimum of two years and continued whenever possible until smear negativity had been reached [1]. As of 1994, suggested policy by the WHO Study Group on Chemotherapy of Leprosy was to suspend MDT in multibacillary patients after the two-year period, regardless of the patient's bacillary index at the time [2].

However, operationally, the 24-dose regimen was still considered too long, which finally posed the main impediment to more successful implementation. Based on observations, a reduction in length of treatment (without jeopardizing ef-

fectiveness) might potentially facilitate patient compliance and national program activities.

Operational data supported the hypothesis that a shorter MDT regimen would be sufficient to effectively treat multibacillary leprosy, based on the following reasons: (i) multibacillary leprosy patients with high bacillary indexes are now rare. WHO has recently estimated newly-detected cases with high bacillary indexes (≥ 3) at less than 15%, thereby requiring smaller drug doses than before [3]; (ii) annual relapse rates in multibacillary patients have been reduced to only about 0.2% [4,5]; (iii) according to some studies, the response by multibacillary leprosy patients receiving fewer than the standard 24 doses of MDT was just as favorable as by those receiving 24 doses or more [6]; and (iv) four WHO-sponsored studies to evaluate the efficacy of a variety of drug combinations and treatment periods have found that even though the bacillary load was reduced, a positive bacillary index was maintained at the moment MDT was suspended [7,8]. It has also been shown that MDT could be suspended safely in the presence of a positive bacillary index, as confirmed by mouse footpad inoculation, demonstrating that bacteria are no longer viable under such conditions [9].

At its 17th meeting, the WHO Expert Committee on Leprosy stated that while the recommended 24-month treatment period for multibacillary leprosy remained valid, it suggested further shortening the duration of MDT to 12 months [10,11]. Almost all multibacillary patients are now receiving 12-month MDT, but little information is available on the relapse rate in these patients. Thus, future studies performed under proper conditions should include the monitoring of relapse rates and reactional episodes [12].

In summary, the aim of this study was to evaluate bacillary index reduction in multibacillary leprosy patients after 12 months of MDT, compared to that found after completing a full 24-dose regimen. Evolution of the disability grade and frequency of reactions were also analyzed. Reactional episodes were monitored over a 36-month period.

Material and methods

The aim of this study was to compare the results of 24- and 36-month surveillance periods in two groups of multibacillary leprosy patients receiving MDT, among those treated at the Leprosy Outpatient Clinic of the Oswaldo Cruz Foundation in Rio de Janeiro, Brazil, in order to analyze bacillary indexes and frequency of reactions. All patients were classified as borderline-lepromatous, borderline-borderline, or lepromatous-lepromatous according to the Ridley & Jopling scale [13]. Clinical diagnoses were confirmed by histopathology. Group 1 included 128 multibacillary patients that began 12-dose MDT between 1998 and 2000. Group 2 consisted of 85 multibacillary patients who received the standard 24 doses between 1995 and 1997.

As inclusion criteria, a multibacillary leprosy patient was defined as any untreated leprosy carrier with an above-zero bacillary index confirmed by slit-skin smears from 6 different sites, as recommended by WHO [1]. The same experienced laboratory technicians performed both the slit-skin smear collection and bacillary index for all patients.

In both groups, reactional episodes were monitored throughout the 12, 24, and 36-month study periods. An experienced physical therapist evaluated each patient's disability grade, classified as 0, 1, or 2, based on the criteria described in the *Guia de Controle da Hanseníase* [Leprosy Control Handbook] [14]. The bacillary indexes and disability grades of both groups of patients were evaluated at three different stages: treatment baseline; following 12 doses (corresponding to end of treatment for Group 1 and middle of treatment for Group 2); and following the standard 24-dose regimen in Group 2, corresponding to one year after end of treatment in Group 1. To reiterate, reactional episodes were monitored constantly throughout the 12, 24, and 36-month periods, i.e., for Group 1, during the 2 years after discharge from treatment, and for Group 2, for a minimum one-year period after end of treatment.

All patients included in the study were duly informed and voluntarily signed a written consent form authorizing their participation and enabling them to receive appropriate medical care for all aspects of their disease whenever necessary.

Statistical analysis used Epi Info 3.01 (Centers for Disease Control and Prevention, Atlanta, USA). Results of contingency tables were studied using the chi-square (χ^2) test, with a 95% confidence level.

Linear regression analysis was used to compare participants' initial bacillary indexes with their post-24-month bacillary indexes. Since this comparative study did not adopt an experimental model that randomly distributed the individuals in the two groups, multiple regression analysis was adopted to control the effect of cases' initial attributes regarding treatment regimen and final bacillary indexes.

The associations were analyzed between reactional episodes and the following categorized

variables: group (therapeutic regimen); initial bacillary index (< 1.5 and ≥ 1.5); age (< 40 and ≥ 40); gender; number of skin lesions (< 20 and ≥ 20); and edema. Risk of reaction was analyzed for each treatment regimen and other patient characteristics, considering each variable singly and in combination, using univariate and multivariate logistic regression models.

Results

Groups 1 and 2 were similar in age, frequency of physical disability, and distribution of clinical forms of the disease, but dissimilar in gender composition and mean number of skin lesions. Mean bacillary index in Group 2 was slightly higher than in Group 1, but not statistically significant at p = 0.05 level (Table 1).

Mean bacillary index was similar in the two groups at treatment baseline (2.27 and 2.64, respectively); after 12 months (1.56 and 1.75, respectively), corresponding to treatment discharge for Group 1 and middle of treatment for Group 2; and again very close after 24 months (1.03 and 1.06), corresponding to the 12-month period during which Group 1 received no specific medication and was under surveillance and Group 2 had just completed treatment (Figure 1). The mean monthly reductions in bacillary index in Groups 1 and 2 were 3.3% and 3.8, respectively.

Coincidentally, at the end of 24 months, the bacillary indexes of 30 patients from each group (31.9% of Group 1 and 35.3% of Group 2) were zero, so that no significant statistical difference was finally found between the two regimens (p = 0.75).

Table 2 shows the results of a multiple linear regression model using bacillary index-24 as the dependent variable. No association was found between treatment regimen and bacillary index-24 after controlling for the other study variables.

As for the number of reactional episodes during the 12, 24, and 36-month treatment/surveillance periods, at the end of 12 months, 71.9% of Group 1 and 75.3% of Group 2 had experienced reactions during the same period (12 months) (p = 0.69). Meanwhile, at the end of 24 months, the reaction rate in Group 1 (one year without treatment) was 56.3%, while the rate for Group 2 (still taking specific medication) was a similar 62.4% (p = 0.47). However, at the end of the 36-month period, the rate had increased slightly to 63.1% for Group 1 and 55.3% for Group 2 (p = 0.37). In conclusion, no statistically significant difference was observed between the two groups in terms of reaction rate (Figure 2).

Table 3 shows the association between reactions during the 24 months and other study variables. Logistic regression showed that edema and number of initial skin lesions were predictors of future reactions. Treatment regimen was not directly related to reaction rate.

As for reactional episodes and initial bacillary index, 70.3% of patients with bacillary indexes ≥ 1.5 presented erythema nodosum leprosum (ENL) and 13.5% had reverse reactions, while among those whose bacillary indexes < 1.5, 13.4% had ENL and 73.2% had reverse reactions. For patients with initial bacillary indexes of < 1.5 versus ≥ 1.5, isolated neuritis was observed in 13.4% and 16.2%, respectively.

Disability grade was 0 in 53.1% of Group 1 at diagnosis, 57.8% after 12 months, and 56.1%

Table 1

Patient characteristics at diagnosis, Groups 1 and 2.

Characteristics	Class	Group 1 (12 doses)	Group 2 (24 doses)	p
Age (mean)	All	37.0	38.3	0.59
Gender	Male	75.0% (96)	60.0% (51)	0.02
	Female	25.0% (32)	40.0% (34)	
Skin lesions (mean)	All	16.0	18.3	0.02
Disability grade	0	53.1% (68)	61.2% (52)	0.50
	1	19.5% (25)	16.5% (14)	
	2	27.3 (35)	22.4% (19)	
Clinical form	Borderline-Borderline	32.8% (42)	35.3% (30)	0.60
	Borderline-Lepromatous	31.3% (40)	35.3% (30)	
	Lepromatous-Lepromatous	35.9%(46)	29.4% (25)	
Bacillary index (mean)	All	2.27	2.64	0.08

Figure 1

Mean reduction in bacillary indexes in Groups 1 and 2 measured at diagnosis and at 12 and 24 months.

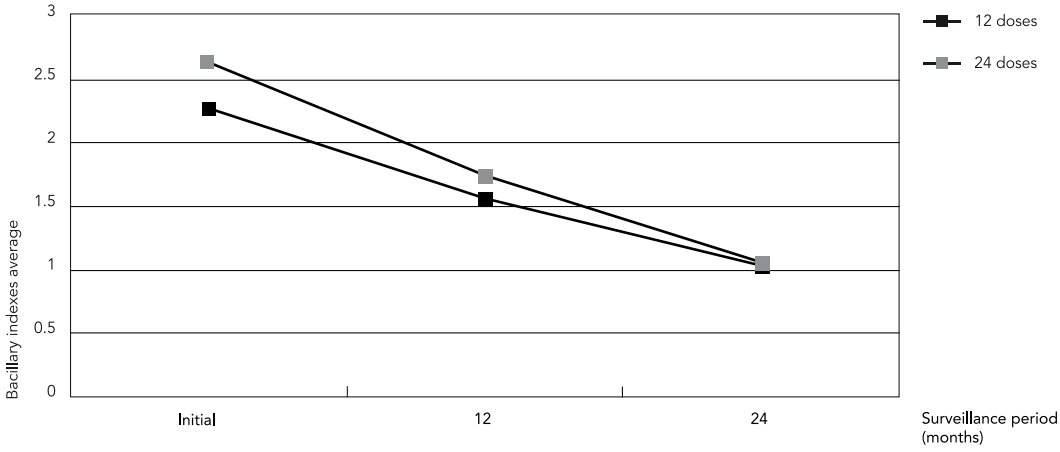


Table 2

Analysis of the association between BI-24 and treatment regimens, controlling for patient characteristics at treatment baseline.

Variables	Univariate analysis			Multivariate analysis		
	b	Standard error	p	b	Standard error	p
Group	-0.148	0.169	0.383	0.033	0.128	0.794
Initial bacillary index	0.529	0.042	0.000	0.527	0.044	0.000
Age	0.000	0.005	0.949	0.004	0.004	0.264
Sex	0.479	0.176	0.007	0.103	0.138	0.456

after 24 months. In Group 2 patients, the proportions were 61.2%, 70.6%, and 62.4%, respectively. Again, with regard to disability grade, no statistically significant difference was observed between the two treatment regimens ($p = 0.5$, $p = 0.25$, and $p = 0.33$) (Figure 3). Importantly, no relapses were recorded during the study.

Discussion

This study compared the clinical outcomes of 12-dose versus 24-dose MDT regimens in two groups of pre-selected multibacillary leprosy patients, especially regarding bacillary index variations during the course of treatment and after discharge.

However, to exactly determine how many months of MDT are needed to achieve maximum results for multibacillary leprosy patients still remains controversial, because regardless of initial bacillary index, a significant number of patients remained smear-positive at the end of both regimens [7,8,15,16]. Operationally, reducing the length of treatment without jeopardizing the outcome has become a necessity in order to facilitate implementation of MDT in remote rural areas where medical care is often scarce and frequently inaccessible to most patients.

Moreover, the immune system of multibacillary patients is grossly deficient in its ability to mount an effective defense against *M. leprae*. Consequently, clearance of bacilli from the body is a slow process. To further complicate matters,

Figure 2

Percentage of reactional episodes at diagnosis and after 12 and 24 months for the two treatment regimens.

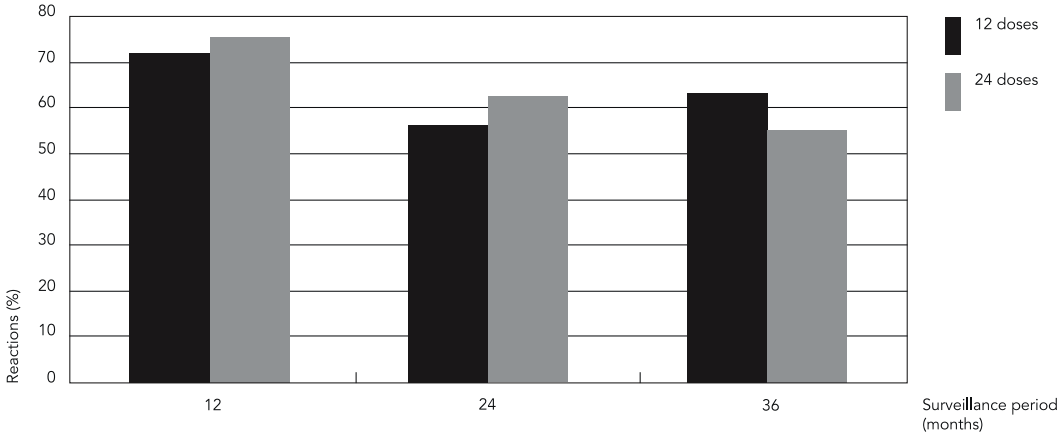


Table 3

Association between reactional episodes and treatment regimens, controlling for patient characteristics at treatment baseline.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Group	0.778	0.440-1.374	0.387	0.637	0.331-1.223	0.176
Initial bacillary index	2.153	1.188-3.903	0.011	1.196-	0.606-2.362	0.606
Age	0.669	0.378-1.182	0.166	0.637	0.339-1.197	0.161
Gender	1.767	0.969-3.222	0.063	1.420	0.728-2.767	0.303
Skin lesions	3.148	1.609-6.158	0.001	2.524	1.192-5.343	0.016
Edema	3.086	1.709-5.572	0.000	2.919	1.539-5.537	0.001

conventional slit skin smear examination has been found to have its own limitations [17].

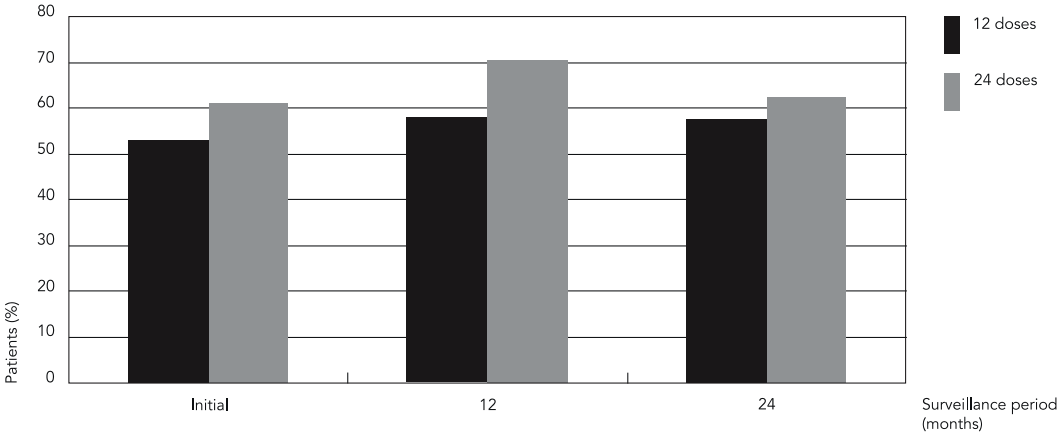
Groups 1 and 2 were similar in almost every respect, except for the slightly higher proportion of males in Group 1 and the fact that, although not statistically significant, initial bacillary index in Group 2 was slightly higher than in Group 1. Interestingly, various studies have shown that the bacillary load of most patients now routinely classified as multibacillary is significantly lower than in the past, and only one-sixth of multibacillary patients have bacillary indexes ≥ 3 [3].

In the present study, the evolution of bacillary indexes corroborated other findings in the literature, to the extent that while bacillary indexes remained positive at the end of treatment, they gradually declined during follow-up [15,18]. The two groups also followed a similar pattern of bacillary index reduction, including similar bacillary index rates after two years. The Group 1 bacillary indexes continued to gradually and steadily decrease even after treatment had ended, indicating that bacterial load continued to decline, tending to confirm that bacillary clearance is not affected by prolonging drug intake.

It was also demonstrated that the final bacillary indexes in both groups were directly related to the bacillary index values recorded at treatment baseline. In a study comparing patients receiving 24-month MDT to those receiving MDT until negative bacillary indexes were reached, Girdhar et al. [19] reported that after two years of MDT, a significant percentage of multibacillary patients was still smear-positive,

Figure 3

Percentage of patients without disabilities (disability grade = 0) at diagnosis and after 12 and 24 months for the two groups.



especially those with high baseline bacillary indexes.

Reaction rates were similar to those reported elsewhere for multibacillary patients treated with 24-dose MDT [20]. The results of the present study agree with those of Kaur et al. [21], who showed that reactions were more frequent up to 6 months of therapy and then gradually decreased. No statistically significant differences were observed between the two groups.

It is generally accepted that the effectiveness of any leprosy treatment should be measured primarily in terms of both relapse and disability rates during and after MDT. Obviously, deformities and disabilities are of great importance, since they simultaneously represent every patient's main concern and a significant public health care issue for society as a whole. Relapse rates are often considered less important, to the extent that they can be successfully treated. Again, as regards disability grade, no variation was observed during the course of this study. However, the total period was considered insufficient to adequately evaluate the appearance and development of disabilities, and no definitive conclusions could be drawn. A five-year follow-up study of both groups has thus been launched to address this issue.

Resumo

Foi realizado um estudo comparativo de dois grupos de pacientes definidos de acordo com o esquema terapêutico, a fim de se avaliarem os índices baciloscópicos: PQT/12 doses (Grupo 1: 128 pacientes) e PQT/24 doses (Grupo 2: 85 pacientes). Todos os pacientes foram avaliados no início do tratamento, aos 12 meses, e novamente aos 24 meses. Ao final dos 24 meses, observou-se uma redução das médias dos índices baciloscópicos, semelhantes nos dois grupos. Não houve diferença estatística na avaliação da freqüência de quadros reacionais nos dois esquemas terapêuticos.

Hanseníase; Quimioterapia; Estudo Comparativo

Contributors

A. M. Sales participated in the patient follow-up, elaboration of the database, data entry, and preparation of the manuscript. P. C. Sabroza contributed to the elaboration of the database, data analysis, and preparation of the manuscript. J. A. C. Nery participated in the patient follow-up, elaboration of the database, data entry, and preparation of the manuscript. N. C. Dupprè participated in the elaboration of the database and supervision of sample collection for laboratory tests. E. N. Sarno contributed to the preparation of the manuscript.

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