SINGLE LESION LEPROSY PATIENTS MULTICENTRIC COHORT TREATED WITH SINGLE DOSE DRUG THERAPY: FINDINGS ON THREE-YEAR FOLLOW-UP AND PUBLIC HEALTH PERSPECTIVE IN BRAZIL

Coorte multicêntrica de pacientes com hanseníase tratada com terapia de dose única: resultados de três anos de seguimento e perspectiva em saúde pública no Brasil

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ABSTRACT

Single skin lesion, paucibacillary (SSL-PB) leprosy is considered an early disease manifestation. This study evaluated the clinical outcome of a cohort of 259 newly diagnosed SSL-PB treated with one dose of rifampicin, ofloxacin, minocycline (ROM) and followed-up for three-years. Patients were recruited from the North, Central West and Southeast regions in Brazil (1997-2001). The result expected with ROM therapy was disappearance or the reduction of lesion size. Manifestations that required additional
intervention were considered as poor clinical outcome: type-1 reaction (T1R) with or without neuritis, neuritis alone, increase in lesion size and shift from paucibacillary to multibacillary. The incidence of poor clinical outcome was calculated by person-month and with the Kaplan-Meier methods. 61.8% of the participants were females, mean age 32.2, and 67.2% had borderline tuberculoid (BT) or tuberculoid forms. T1R was the predominant event; shift from paucibacillary to multibacillary was rare. 92.0% of the volunteers shown no events during the first year, the same occurring to 80.6% of them after 3 years of clinical monitoring. The probability of remaining event-free was highest among those 40 years old or younger. Poor outcome predominated among BT patients. Extended monitoring of SSL-PB leprosy cases under minimal therapy provided valuable case management information for reference centers.

**KEY WORDS**
Leprosy, Hansen’s disease, drug therapy, cohort study

**RESUMO**
Lesão única paucibacilar (SSL-PB) é considerada manifestação clínica inicial da hanseníase. Este estudo avaliou resultado clínico de coorte de 259 pacientes SSL-PB recém-diagnosticados, tratados com esquema de dose única Rifampicina, Ofloxacina, Minociclina (ROM) e acompanhados por 3 anos (1997-2001) nas regiões Norte, Centro-Oeste e Sudeste. O resultado esperado do tratamento ROM compreende desaparecimento ou diminuição da lesão. O desfecho foi definido como qualquer evento clínico com indicação de terapia adicional: reação tipo 1 (T1R) com ou sem neurite, neurite, aumento de tamanho de lesão e mudança de paucibacilar para multibacilar. Estas manifestações foram consideradas eventos clínicos desfavoráveis, calculados por densidade de incidência (pessoa-tempo) e por Kaplan-Meier. 61.8% dos participantes eram mulheres (32,2 média idade), 67,2% borderline-tuberculoid (BT) e tuberculoido. T1R foi o desfecho predominante; mudança de paucibacilar para multibacilar foi rara. 92,0% não apresentaram eventos desfavoráveis no primeiro ano e 80,6% ao final de três anos de monitoramento clínico. Participantes com idade de 40 anos tiveram maior probabilidade de permanecerem sem evento e evolução clínica desfavorável predominou entre pacientes BT. Monitoramento prolongado de hanseníase lesão-única PB tratados com esquema mínimo forneceu dados importantes sobre manejo clínico para os centros de referência.

**PALAVRAS-CHAVE**
Hanseníase, terapia, estudo de coorte

1. INTRODUCTION

In the last two decades, early case detection and the large-scale implementation of multidrug therapy (MDT) were the World Health Organization’s (WHO) main policy for leprosy control, playing a major role in the declining prevalence trends worldwide (WHO, 2007). The universal adoption of fixed short-course chemotherapy regimens, varying from 6 months for paucibacillary (PB) to 2 years
for multibacillary (MB) patients, has pushed the leprosy elimination at a global level defined as prevalence of less than one case per 10,000 population in many countries. This has been considered a successful strategy to intensify leprosy control efforts and to include leprosy in the political agenda (Lechat, 2001; Jacobson & Krahenbuhl, 1999; Lockwood & Sunetra, 2005). Nevertheless, the incidence of leprosy has been stable or rising on the most endemic countries during the same period, including Brazil (Lockwood, 2002a).

Although the reduction in the duration of leprosy treatment was considered a great achievement, it was still considered long regarding patients’ compliance at in-place healthcare settings and logistically unfeasible for universal implementation (Sales et al., 2007). The WHO-sponsored randomized trial of one dose regimen of rifampicin, ofloxacin and minocycline (ROM) was compared to the standard MDT (6 doses) to treat single lesion in patients with PB leprosy in the late 1990’s. The results suggested that one dose regimen has similar cure rates and less than 1% relapses (Lockwood, 2002b; Single-Lesion Multicentric Trial Group, 1997). The randomized field trial raised some methodological issues, mainly on “case” definition, outcome ascertainment based solely on clinical findings and the relatively short term follow-up (Lockwood, 1997; Katoch, 1998).

Single-dose ROM therapy was recommended under the assumption that the single lesion is an early stage of chronic leprosy, considered as a homogenous clinical entity with low bacterial load and preserved cell mediated immunity, which yield low relapse rates under single-dose therapy or spontaneous cure (Single-Lesion Multicentric Trial Group, 1997). This regimen was universally implemented on the leprosy control program in India. In Brazil, it has been recommended as an alternative strategy for reference centers according to the Leprosy Control Program guidelines (Brasil, 2000).

In previous papers, we showed evidence that most single-lesion paucibacillary patients show histomorphological findings compatible with indeterminate, tuberculoid and borderline tuberculoid forms of paucibacillary disease, and also a few multibacillary cases (Martelli et al., 2000; Costa et al., 2001). There was also evidence that pro- and anti-inflammatory cytokines, detected in the lesions on this group with early leprosy, limits the bacilli load and avoids the immunopathological mechanism of the disease (Stefani et al., 2003). The current article describes three-year monitoring of single-lesion paucibacillary patients treated with single-dose therapy (ROM) within a well-defined cohort of single skin lesion leprosy cases assembled in three Brazilian endemic regions.
2. Patients and Methods

This is a prospective cohort study of newly registered single-lesion paucibacillary (SLPB) patients with three years follow-up. The investigation was conducted in 5 collaborative centers from three endemic Brazilian regions: Central West – Goiânia (Goiás); North – Manaus (Amazonas), Porto Velho and Ariquemes (Rondônia) and Southeast - Rio de Janeiro (Rio de Janeiro). This multicentric cohort was approved by the institutional ethics committee of each site and by the National Ethical Review Board (CONEP - Brazilian Ministry of Health). All volunteers or their legal guardians signed an informed consent form. The study design and baseline findings were previously published (Martelli et al., 2000; Costa et al., 2001) and are briefly described.

Eligibility criteria: Patients were potentially eligible if newly diagnosed with one leprosy skin lesion, negative bacilloscopic smear and had histopathology findings on skin biopsies of tuberculoid (TT), borderline tuberculoid (BT) or indeterminate (I) forms, according to Ridley & Jopling (1966) criteria (Ridley & Jopling, 1966). Children less than 7 years old, pregnant, breast-feeding women and known HIV/AIDS infected cases according to patients’ information or record file were excluded.

259 eligible SSL-PB patients were recruited from November 1997 to December 1998. Patients treated with single dose ROM therapy were seen monthly in the first six months and visits were held every 6 months during a 3-year period until the year 2002. The expected result of ROM treatment is the disappearance of the skin lesion or the reduction in lesion size without other clinical complication. During follow-up, information about occurrence of other perceived dermatological signs, disability measures using monofilaments and a complete dermatological examination with measurement of the initial lesion (in centimeters) were conducted. Nerve function was verified using simple, standardized voluntary muscle tests and sensory tests. Participants were advised to contact the physician anytime if new skin lesions became visible and/or neural pain occurred.

The outcome was defined as any of the clinical manifestations: type-1 reaction with or without neuritis, neuritis alone, appearance of new lesions, increase in lesion size and shift from paucibacillary (PB) to multibacillary (MB). According to the protocol, events that required additional intervention were considered a poor clinical outcome whereas the disappearance or reduction of skin lesion, or no alteration during extended follow-up, were favorable events. Type 1 reactions and/or neuritis were clinically treated with a standard course of corticosteroids (1mg/Kg daily for one to three weeks) with tapering according to clinical evolution. Incident cases of increase in the number or in lesion size, multibacillary type of leprosy were treated accordingly, with multidrug therapy (Brasil, 1998).
3. Statistical analysis

Incidence density of poor clinical outcome was calculated by person-month, with 95% Confidence Interval (CI). Only the first event from any individual contributed to the analysis. The event-free interval was measured from the date of the single dose ROM therapy intake and the occurrence of the initial sign of poor outcome. The Kaplan-Meier-product limit method was used to calculate the cumulative probability of event-free interval. Participants who did not present any event were included in the survival analysis according to the time of follow-up and considered censored. Participants who died from other causes (n=1) or refused to continue in the project (n=2) were also treated as censored. The log-rank test was applied to assess the differences of survival curves among different groups. Fisher’s exact test was used for categorical variable and two-tailed t-test paired and unpaired for continuous variables. The sample size (n=259) was sufficiently large to estimate the incidence rate in 20% during 3-year follow-up within 2.4% of precision of its true value (12% of 20%) with 95% confidence interval (Lemeshow et al., 1990). The statistical analyses were performed using SPSS software for windows (SPSS Inc., Chicago, Illinois, version 13.0).

4. Results

The total of 259 SSL-PB leprosy patients, 160 women (61.8%) and 99 men (38.2%) were analyzed. The baseline and follow-up characteristics are shown in Table 1. The mean age of the entire cohort was 32.4 (SD=16.0) and males were younger than females, 27.9 (SD=15.3) versus 35.1 (SD=15.9), a statistically significant difference (t=3.6 df 257 p<0.001). Histopathological classification of BT and TT comprised two-thirds (67.2%) of the participants. 72.6% of the participants had a positive Mitsuda reading and 17% presented positive anti-PGLI serology. Extended follow-up: Mean follow-up was 31.4 (SD=9.9) for 182 censored patients. Attrition in this cohort was small and the loss of follow-up was considered within the acceptable levels in all sites (15%) (as shown in Table 1).

During a three-year follow-up, 46 out of 259 (17.8%) SSL-PB leprosy patients developed a poor clinical outcome, leading to an overall density incidence rate of 6.9 per 1000 person-months (46 events/6668 person-months). Type 1 reaction was the most frequent event during the follow-up period (16.2%). A higher percentage of these reactions was diagnosed among BT patients (24.0%) when compared with the events among TT (13.4%) and I (9.4%) types, a statistically significant difference (χ²=6.4; df=2; p<0.04). Three patients shown both skin lesions and neuritis and 7 had neuritis as a sole marker of disease progression.

The type 1 reaction was considered mild, treated in the outpatient sector with standard steroids, without any disability recorded during follow-up. There
was a low incidence rate on progression from paucibacillary to multibacillary leprosy (7 per 10,000 patients-month). For the entire cohort the probability of remaining event-free since leprosy diagnosis (Kaplan Meier product-limit method) was 92.0% (± 1.7%) at year 1 and 80.6% (± 2.5%) at year 3 (Table 2). Patients ≥ 40 years old had a cumulative probability of remaining event free of 79.0% (± 4.5%) at year 2 and 70.2% (± 2.5%) at year 3, compared to the probabilities of 89.0 (± 2.4%) and 85.7 +/- 2.8% among the younger age group at same point intervals. Therefore, the probability of remaining event-free throughout the study was higher for patients < 40 years old (log rank test p<0.05). Patients with histopathological classification of BT had higher cumulative probability of disease progression at any point interval than TT and I types. The progression rates differed significantly among histopathologic groups (log rank p=0.03). Other variables analyzed had similar progression rates between the groups (Table 2). Figure 1 shows the Kaplan-Meier curves for the main predictor variables.

Table 1
Baseline and follow-up of the Brazilian Single Lesion Paucibacillary Leprosy cohort.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>259</td>
</tr>
<tr>
<td>Females (%)</td>
<td>160 (61.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td>35 (13.5)</td>
</tr>
<tr>
<td>≥ 15</td>
<td>224 (86.5)</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>87 (33.6)</td>
</tr>
<tr>
<td>BT</td>
<td>87 (33.6)</td>
</tr>
<tr>
<td>I</td>
<td>85 (32.8)</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td></td>
</tr>
<tr>
<td>Censored (sd)</td>
<td>31.4 (9.9)</td>
</tr>
<tr>
<td>Event (sd)</td>
<td>19.6 (2.3)</td>
</tr>
<tr>
<td>Complete - months*</td>
<td></td>
</tr>
<tr>
<td>3-years-follow-up (%)</td>
<td>182 (86.7)</td>
</tr>
</tbody>
</table>

* for 213 censored participants

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Table 2
Single-lesion leprosy cohort. Cumulative probability of remaining event-free according to the study’s variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>% event-free (mean ± SE) at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>Entire cohort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>92.0 ± 1.7</td>
</tr>
<tr>
<td>Age Group</td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>92.4 ± 2.0</td>
</tr>
<tr>
<td>≥ 40</td>
<td>90.0 ± 3.3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>91.6 ± 2.8</td>
</tr>
<tr>
<td>Women</td>
<td>91.7 ± 2.2</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
</tr>
<tr>
<td>BT</td>
<td>87.8 ± 3.6</td>
</tr>
<tr>
<td>I</td>
<td>92.9 ± 2.8</td>
</tr>
<tr>
<td>TT</td>
<td>94.1 ± 2.6</td>
</tr>
<tr>
<td>Lesion size (cm)</td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>92.1 ± 2.1</td>
</tr>
<tr>
<td>5</td>
<td>90.0 ± 3.1</td>
</tr>
<tr>
<td>Anti-PGL 1</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>83.3 ± 5.8</td>
</tr>
<tr>
<td>Negative</td>
<td>93.8 ± 1.7</td>
</tr>
<tr>
<td>BCG scar</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>93.4 ± 2.1</td>
</tr>
<tr>
<td>Yes</td>
<td>90.2 ± 2.8</td>
</tr>
<tr>
<td>Mitsuda test</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>88.5 ± 4.1</td>
</tr>
<tr>
<td>Positive</td>
<td>92.3 ± 2.0</td>
</tr>
</tbody>
</table>
5. DISCUSSION

In this multicentric cohort, single lesion paucibacillary leprosy patients treated with one dose ROM regimen presented high percentage of disappearance of skin lesion and low incidence of multibacillary disease during extended 3-years follow-up. Type-1 reaction was the main adverse outcome in these early leprosy patients clinically monitored after single dose therapy. Leprosy patients with age over 40 years old and those classified as borderline tuberculoid (BT) by histopathology had higher probability to develop an acute clinical event (type 1 reaction) during extended follow-up.

The predominance of favorable clinical evolution in this SSL-PB leprosy cohort seems consistent with type 1 immune response as suggested by the results of laboratory tests performed at baseline. In fact, at diagnosis, patients had negative bacilloscopic skin smear, mainly positive for Mitsuda test, low levels of anti-PGl-1 serology and mainly well formed granuloma compatible with self-limited disease.
and favorable clinical progression (Martelli et al., 2000; Costa et al., 2001). Furthermore, the in situ cytokine profile showed measurable INF-gamma and undetectable IL-4, quantified by real-time, reverse transcriptase PCR in skin biopsies. These findings are also strong evidence, at molecular level, of type I immunity predominance, that is compatible with both resolution of skin lesions and with the type-I reaction observed as outcome in this cohort (Stefani et al., 2003).

In the clinical trial to evaluate the efficacy of single dose ROM regimen performed in India, PB single-lesion patients also presented high percentage of complete disappearance of the lesion (Single-Lesion Multicentric Trial Group, 1997). Several methodological issues were pointed out in previous publications regarding this trial, such as low specificity in case definition, short-term follow-up and the cure criteria adopted (Lockwood, 1997; Katoch, 1998, Ustinowski & Lockwood, 2003). In general, single-lesion patients are paucibacillary, however, there are several case reports presenting single-lesion leprosy patients with multibacillary disease (Job et al., 1989, Ramesh et al., 1991; Ponnighaus, 1996). It is well known that case ascertainment only by clinical and bacilloscopic exam may not exclude other skin diseases or even multibacillary cases leading to overdiagnosis of leprosy. In our study, at the initial screening procedures for the recruitment phase, seven single-lesion patients were excluded by the multibacillary characteristics described by histopathologic readings (Costa et al., 2001). Thus the high specificity in case definition adopted in the current investigation may also explain the low shift from multibacillary to paucibacillary forms during follow-up. A sub-group of SSLPB patients (n=135) in the current study were tested for the presence of M. leprae DNA-PCR in the skin lesion biopsies yielding 44.4% positive results. Also older age (≥ 40 years) ML-PCR positive and lesion size > 5cm were associated with type 1 reaction (Sousa et al., 2007).

In the present investigation, around 16% of PB single-lesion patients under minimal therapy regimen progressed with type-1 reaction and required health care attendance to prevent neural damage and disability. The reversal reactions were considered moderate and treated with steroids in out-patient clinics according to the Brazilian recommendation (Brasil, 2000). This finding suggests that there is early neural involvement in leprosy even among single-lesion early-diagnosed cases corroborating with the hypotheses raised by other authors (Sarno & Pessolani, 2001). Genetic and molecular biology investigations may add valuable information about the precocity of neural involvement in single lesion leprosy.

This cohort of early leprosy showed that patients classified as BT at diagnosis were prone to develop type 1 reaction, in consonance with other studies that evaluated PB leprosy independently of the number of lesions (Rose & Waters, 1991; Lockwood et al., 1993; Lienhardt & Fine, 1994). These acute episodes
during the chronic course of disease are considered events associated with neural
damage and disability (Lienhardt & Fine, 1994; Britton, 1998). In the WHO
ROM single-lesion trial, the frequency of type-1 reaction was considered low
(Single-Lesion Multicentric Trial Group, 1997) in an 18 months follow-up. In the
present cohort, the majority of acute episodes occurred after 18 months of follow-
up, suggesting that there was a clear tendency of increase in these events related
to extended follow-up. These findings are in agreement with the Bangladesh
Acute Nerve Damage Study (BANDS) that showed that borderline patients
were also at risk for developing type – 1 reaction during prolonged follow-up
(Croft et al., 2000).

This multicentric cohort was designed to recruit cases of the single lesion
from major Brazilian endemic regions to ensure a representative sampling. Inclusion
criteria were very strict in order to leave out initial MB patients by using specific
tests results from the cohort. This strategy avoided overestimation on the
progression of PB to MB during the follow-up. Furthermore, it would be unethical
to treat multibacillary patients with single dose ROM therapy under field conditions.
However, several methodological issues must be raised. We judged that cure and
relapse terminology was inadequate to ascertain the factors associated with the
clinical course of early leprosy under one-dose therapy. The outcome definition,
as any clinical event that required additional drug therapy, is essential information,
regarding number of visits and patients management at point of care setting. In
diseases with chronic courses, patients classified on a specific clinical category
may not be a homogenous group, like for instance the single-lesion leprosy patients
in our study comprised different histomorphological forms of the PB disease.

Currently, single dose regimen has universally been implemented only in India
(WHO, 2002). Although, this minimal therapy seems ideal at a public health point
of view, some issues should be raised about the universal implementation in the
horizontal Brazilian Leprosy Control Program. The estimated number of single
lesion among Brazilian leprosy patients has been considered low which makes it
logistically difficult to have another regimen universally implemented in all health
centers (WHO, 2002; Meima, 2004). Furthermore, within the context of single
dose ROM implementation there is still need for management and supervision of
the high-risk group of patients prone to develop acute events.

In conclusion, our results show that there is a predominance of favorable
progression among PB single-lesion patients treated with single dose ROM regimen.
Also there is evidence that BT histopathological classification and older age group
can be considered prognostic factors for disease progression. This study may be
considered the closest as possible to the “natural course of disease progression”
for early diagnosed paucibacillary leprosy cases. Studies on the prognosis of early
leprosy under minimal therapy may add valuable information about the response of different groups to reduced treatment and help to estimate health care needs. The findings of this study also support the current Brazilian Guidelines that recommends single-dose ROM therapy for single-lesion leprosy patients in reference centers considering the case ascertainment and the logistics of drug distribution.

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