Relapse rate among smear-positive leprosy cases after 12 blister packs and 24 blister packs of multibacillary drug therapy in a tertiary hospital

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ABSTRACT

Background: Several trials on relapse rates on duration of multibacillary regimens have varying results.

Objective: To compare the relapse rate among smear-positive Leprosy patients receiving 12 blister packs of multibacillary drug therapy and 24 blister packs of multibacillary drug therapy.

Method: A review of records of smear positive Leprosy patients seen from 2002 to 2006 was done. Demographic, clinical and therapeutic data were collected. Bacteriologic index was determined from Leprosy Laboratory records.

Results: A total of 391 patients were found to have complete records for review and analysis. Relapse rate was 11.9%(28) for patients who received 12 blister packs and 1.91%(3) for patients who received 24 blister packs and the difference was found to be statistically significant ($p<0.01$). Distribution of relapse was statistically significant according to age ($p<0.01$), bacteriologic index ($p<0.01$) and clinical spectrum ($p<0.01$).

Conclusion: Relapse rates shown among smear positive leprosy patients receiving 12 blister packs vs. those receiving 24 blister packs was statistically higher which differs from previously published studies. Significant predictors were clinical spectrum, bacteriologic index of >3.5, and >4 and number of blister packs.

Key words: *leprosy, relapse rate, bacteriologic index, multidrug therapy*

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INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic disease caused by *Mycobacterium leprae*[1,2]. According to the World Health Organization (WHO) [3], official reports received during 2011 from 130 countries and territories, the global registered prevalence of leprosy at the beginning of 2011 stood at 192,246 cases. In the Philippines, there were 2,041 new cases reported in the same year, 93.92% of which were multibacillary cases.

Bacteriologic index is defined as the density of organisms in the smear, which reflects the bacterial load of the individual[4]. Patients with negative skin smears are classified as paucibacillary and those with positive skin smears are classified as multibacillary. Multi-drug Therapy (MDT) is the standard for the treatment of leprosy. The goals of therapy were to provide a cure, prevent development of bacterial resistance and to prevent widespread transmission of the disease[5]. According to the Action Programme for the elimination

of Leprosy[6] by the WHO, the most important indicator of efficacy of a chemotherapeutic regimen is the rate of occurrence of relapse following successful completion of the scheduled course of treatment. Based on Guidelines for Global Surveillance of Drug Resistance in Leprosy by the WHO (2009)[7], Relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment with WHO recommended MDT. Relapse is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacteriological index (BI) of two or more units at any single site compared to BI taken from the same site at a previous examination.

Several trials assessing relapse rate on shortening duration and modifying multibacillary regimens showed variable results. Twelve months fixed duration of therapy for Multibacillary Leprosy has been accepted by most Leprosy control programmes and is currently being implemented.

The WHO has estimated a risk of relapse of 0.77% for Multibacillary and 1.07% for Paucibacillary patients 9 years after stopping Multidrug therapy[8]. Development of relapse indicates a failure to treat an infection, which translates to increase transmission of the disease. The best way of assessing relapse is through the demonstration of its etiologic agent. Bacteriologic Index (BI) falls with treatment by approximately 0.75 –1.0+ BI units per year[1]. This is used to gauge response to treatment among multibacillary cases and therefore can be used for detecting cases of relapse. Several research projects suggested that relapse rates are high among patients with high bacillary loads and that most of these relapses can occur in the first 3 years after released from treatment.

This study can provide recent data on relapse rates of multibacillary cases to multibacillary drug therapy in patients given 12 blister packs and 24 blister packs, which will serve as a guide for future recommendation.

MATERIALS AND METHODOLOGY

Study Population

A review of records of diagnosed Leprosy patients from January 1, 2002 to December 31, 2006 was conducted at the medical records section of the Department of Dermatology in a Tertiary Hospital. The review included all patients with the following criteria: (1) smear positive, (2) completed 12 blister packs of multibacillary drug therapy within a maximum of 18 months duration and 24 blister packs of multibacillary drug therapy within a maximum of 30 months duration, (3) with follow-up bacteriologic index (a) after receiving 12 blister packs of multibacillary drug therapy and (b) after receiving 24 blister packs of multibacillary drug therapy, (4) received multibacillary drug therapy with follow-up bacteriologic index (c) 1 year after (d) 2 years after and (e) 3 years after being released from treatment.

Study Procedure

Data collected was extracted from the medical records section of the Department of Dermatology. Data on bacteriologic index was cross-referenced for accuracy with the records of Leprosy Laboratory. A data abstraction form for individual patients was completed. The researchers included all smear-positive cases.

The baseline characteristics of the subjects were determined. Each subject was classified according to clinical spectrum based on Ridley-Jopling Classification.

The number of blister packs of multibacillary drug therapy was determined for each patient.

Bacteriologic index (BI) from skin smear examination was recorded on (a) initial examination (b) after 12 blister packs of multibacillary drug therapy and (c) after 24 blister packs of multibacillary drug therapy.

Records of subjects released from treatment after 12 blister packs of multibacillary drug therapy and 24 blister packs of multibacillary drug therapy were reviewed. The BI of these patients a) 1 year (b) 2 years and (c) 3 years after being released from treatment were recorded.

Relapse rate of smear positive leprosy patients completing 12 blister packs and 24 blister packs of multibacillary drug therapy was determined and compared.

STUDY VARIABLES AND OUTCOME MEASURES

1. Multibacillary blister packs given

Multibacillary blister packs consist of a 28-day course of combination of Rifampicin 600mg once a month, Dapsone 100mg daily and Clofazimine 300mg once a month and 50 mg daily.

2. Number of multibacillary drug therapy

12 blister packs of multidrug therapy is defined as 12 blister packs administered within a maximum of 18 months; 24 blister packs is defined as 24 blister packs of multidrug therapy administered within a maximum of 30 months.

3. Bacteriologic index (BI)

Bacteriologic index is based on six sites. Value is obtained by adding the grades from each site and dividing by the number of sites sampled. The grades range from 0+ to 6+, depending on the number of bacilli.

4. Clinical spectrum of patients

Clinical Spectrum refers to the classification scheme identifying five spectrums of leprosy. It uses a combination of clinical, bacteriological index and histopathological aspects.

5. Relapse rate

Based on Guidelines for Global Surveillance of Drug Resistance in Leprosy by the WHO, Relapse is defined as an increase in BI of two or more units at any single site or a total bacteriologic index of 0.33 compared to BI taken from the same site at a previous examination at any time after the completion of a full course of treatment with WHO recommended MDT.

RESULTS

Demographic and clinical data of patients

A total of 391 records of smear-positive cases of Leprosy were reviewed consisting of 288 (73.66%) males and 103 (26.34%) females. Mean age for all patients was 34.11 year (+ 15.10). In the group who completed 12 blister packs, subjects comprised of 166 (70.94%) males and 68 (29.06%) females with a mean age of 33.62 (+ 14.98). For the same group, there were 49 (20.94%) patients who were less than 23 years old, 72 (30.77%) were 23-32 years old, 52 (22.22%) were 33-43 years old and 61 (26.07%) were 43 years old and above. There were 89 (38.03%) classified as Borderline Tuberculoid (BT), 96 (41.02%) as Borderline Leprosy (BL), 38 (16.24%) as Borderline Lepromatous (BL) and 11 (4.70%) patients as Lepromatous Leprosy (LL); 218 (93.16%) had a BI of >3.5 and 16 (6.83%) had a BI of < 3.5; 218 (93.16%) had a BI of <4 and 16 (6.84%) had a BI of >4. In the group who completed 24 blister packs, subjects consist of 122 (77.71%) males and 35 (22.29%) females with a mean age of 34.82. For the same group, there were 33 (21.01%) patients were who less than 23 years old, 40 (25.47%) were 23-32 years old, 40 (25.47%) were 33-43 years old and 44 (28.02%) were 43 years old and above. There were 44 (28.02%) patients classified as Borderline Lepromatous (BB), 57 (36.30%) as Borderline Lepromatous (BL) and 56 (35.67%) as Lepromatous Leprosy; 88 (56.05%) had a BI of < 3.5 and 69 (43.94%) had a BI of > 3.5; 97 (61.78%) had a BI of <4 and 60 (38.22%) had a BI of >4. The baseline characteristics of patients who completed the two regimens are shown in Table 1

Table 1. Baseline characteristics of patients who completed the two regimens

Description	Total	12 blister packs	24 blister packs
Total subjects	391	234	157
Sex			
Male (%)	288 (73.66%)	166 (70.94%)	122 (77.71%)
Female (%)	103(26.34%)	68 (29.06%)	35 (22.29%)
Age (years; Mean (± SD)	34.11 (± 15.10)	33.62 (±14.98)	34.84 (± 15.29)
< 23	82 (20.97%)	49 (20.94%)	33 (21.01%)
23-32	112 (28.64%)	72 (30.77%)	40 (25.47%)
33-43	92 (23.53%)	52 (22.22%)	40 (25.47%)
> 43	105 (26.35%)	61 (26.07%)	44 (28.02%)
Clinical Spectrum			
BT	89 (22.76%)	89 (38.03%)	0 (0%)
BB	140 (35.80%)	96 (41.02%)	44 (28.02%)
BL	95 (24.29%)	38 (16.24%)	57 (36.30%)
LL	67 (17.13%)	11 (4.70%)	56 (35.67%)
Bacteriologic index			
< 3.5	306 (78.26%)	218 (93.16%)	88 (56.05%)
≥ 3.5	85 (21.74%)	16 (6.83%)	69 (43.94%)
Bacteriologic index			
< 4	315 (80.56%)	218 (93.16%)	97 (61.78%)
≥ 4	76 (19.43%)	16 (6.84%)	60 (38.22%)

SD: Standard deviation

The mean age (p=0.43), age groups (p=0.68), and male/female ratio (p=0.13) did not differ significantly between the two groups. The clinical spectrum among the patients (p=0.00) and the bacteriologic indices (p=0.00) were statistically significant.

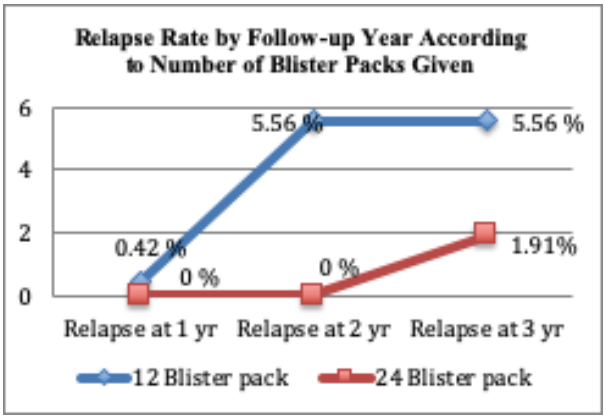
Relapse rate

There were a total number of 30 (7.67%) cases of relapse in both groups. In patients treated with 12 blister packs, there was 1 (0.42%) case of relapse at 1 year, 13 (5.56%) cases at 2 years and 13 (5.56%) cases at 3 years. In patients treated with 24 blister packs, there were no cases (0%) of relapse at 1 and 2 years with 3 (1.91%) cases of relapse at 3 years. These data are shown in Table 2 and Figure 1.

Table 2. Relapse rate by follow-up year according to number of blister packs given

	Total	12 Blister packs	24 blister packs
Total subjects	**391**	**234**	**157**
No relapse	361(92.33%)	207 (88.46%)	154 (98.09%)
Relapse	30(7.67%)	27 (11.53%)	3(1.91%)
Relapse at 1 year	1 (0.28%)	1 (0.42%)	0 (0%)
Relapse at 2 years	13(3.32%)	13 (5.56%)	0 (0%)
Relapse at 3 years	16(4.09%)	13 (5.56%)	3 (1.91%)

Figure 1. Relapse rate by follow-up year according to number of blister packs given



Comparison of baseline bacteriologic index with follow-up bacteriologic index (BI)

A decline in BI reflects adequacy of response to multibacillary drug therapy while an increase in BI shows development of relapse. Thus, the comparison of baseline BI to subsequent measurements was made.

Friedman test was used to determine if variables measured repeatedly over time is significantly different from the baseline of the same population.

In patients who completed 12 blister packs, the mean initial BI was 2.05 (+ 0.80), the mean BI after completion of treatment was 0.30 (+ 0.42), the mean BI 1 year, 2 years and 3 years after being released from treatment were as follows: 0.02 (+ 0.08), 0.10 (+ 0.42) and 0.15 (+ 0.51). The bacteriologic indices in patients given 12 blister packs are shown in Table 3.

Table 3. Comparison of baseline bacteriologic index with follow-up bacteriologic index in patients given 12 blister packs

Bacteriologic Index (BI)	Initial Mean (SD)	12 blister packs Mean (SD)	1 year follow up Mean (SD)	2 years follow up Mean (SD)	3 years follow up Mean (SD)	P value
12 blister packs	2.05 (+ 0.80)	0.30 (+ 0.42)	0.02 (+ 0.08)	0.10 (+ 0.42)	0.15 (+ 0.51)	0.00...

SD-Standard Deviation
P value ≤ 0.05

There was a significant difference (p=0.00) among the mean bacteriologic indices.

In patients who completed 24 blister packs, the mean initial BI was 3.41 (+ 1.10), the mean BI after 12 blister packs was 2.12 (+ 0.81), and the mean BI after completion of 24 blister packs was 0.63 (+ 0.64), the mean BI after 1 year, 2 years and 3 years after being released from treatment were as follows: 0.07 (+ 0.18), 0.00 (+ 0.01), and 0.04 (+ 0.29). There was a significant difference (p= 0.00) among the mean bacteriologic indices as shown in Table 4.

Table 4. Comparison of baseline bacteriologic index with follow-up bacteriologic index in patients given 24 blister packs

Bacteriologic Index (BI)	Initial Mean (SD)	12 blister packs Mean (SD)	24 blister packs Mean (SD)	1 year follow up Mean (SD)	2 years follow up Mean (SD)	3 years follow up Mean (SD)	P value
24 blister packs	3.41 (+ 1.10)	2.12 (+ 0.81)	0.63 (+ 0.64)	0.07 (+ 0.18)	0.00 (+ 0.01)	0.04 (+ 0.29)	0.00...

SD- Standard Deviation
P value ≤ 0.05

Comparison of follow-up bacteriologic index (BI) by number of blister packs

Patients included in the study were given either 12 or 24 blister packs. Bacteriologic index measurement was then repeated at 1 year, 2 years and 3 years.

Kruskall Wallis was used to determine if variables measured repeatedly over time is significantly different between two populations.

The mean initial BI of patients who received 12 blister packs were as follows: initial BI was 2.05 (+ 0.80), 1st year follow-up 0.02 (+ 0.08), 2nd year follow-up 0.10 (+ 0.42) and 3rd year follow-up 0.15 (+ 0.51). For patients who received 24 blister packs, initial BI was 3.42 (+ 1.10), 1st year follow up was 0.07 (+ 0.18), 2nd year follow-up was 0 (+ 0.01) and 3rd year follow-up was 0.15 (+ 0.29), results were all statistically significant when compared to each other (Table 5).

Table 5. Comparison of follow-up bacteriologic index (BI) by number of blister packs

Bacteriologic Index (BI)	12 blister packs	24 blister packs	
	Mean (SD)	Mean (SD)	P value
BI initial	2.05 (± 0.80)	3.42 (± 1.10)	0.00..
BI 1 yr follow-up	0.02 (± 0.08)	0.07 (± 0.18)	0.00..
BI 2 yr ffup	0.10 (± 0.42)	0.00 (± 0.01)	0.05
BI 3 yr ffup	0.15 (± 0.51)	0.04 (± 0.29)	0.00..

SD- Standard Deviation

P value ≤ 0.05

Distribution of relapse by independent variables

Chi-square test was used to determine if the distribution of relapse is significantly different over independent variables. Distribution of the variable was determined according to: (a) sex (b) age group (c) BI of > 3.5 and (d) BI > 4 (e) clinical spectrum and (f) treatment 12 and 24 blister packs of multibacillary drug therapy. Odds ratio was used to express how much more likely the occurrence of relapse is to occur in 1 group more than the other group.

Distribution of relapse according to sex

The prevalence of relapse among male subjects is 9.37% and 3.88% among female subjects. The difference was not statistically significant (Table 6).

Table 6. Distribution of relapse according to sex

	SEX	
Relapse	**Male**	**Female**
Without relapse	261	99
	90.62%	96.12%
With relapse	27	4
	9.37%	3.88%
Chi square		3.13
P value		0.07
Odds ratio		2.56

P value ≤ 0.05

Distribution of relapse according to age

For the age group of the subjects, the proportion of patients who developed relapse were: 6 (7.32%) for patients with ages < 23 years, 7 (6.25%) for patients between 23-32 years of age, 7 (7.61%) for patients between 33-43 years of age, and 7 (6.67%) for patients greater than 43 years of age. There was no significant difference among the different age groups (Table 7).

Table 7. Distribution of relapse according to age group

Relapse	< 23 y/o	23-32 y/o	33-43	>43 y/o
Without relapse	76	105	85	98
	92.68%	93.75%	92.39%	93.33%
With relapse	6	7	7	7
	7.32%	6.25%	7.61%	6.67%
Chi square				0.18
P value				0.98

P value ≤ 0.05

Distribution of relapse according to BI

The prevalence of relapse among subjects with BI < 4 was 6.52% and patients with BI > 4 was 14.49%. There was a significant difference between the two groups. The odds ratio of relapse of any patient with a BI > 4 was 2.42 compared to those with BI < 4. Patients with a BI of > 4 have 2.42 greater odds to relapse than patients with a BI < 4 (Table 8).

Table 8. Distribution of relapse according to Bacteriologic Index > 4

Relapse	Bacteriologic index (BI) ≥ 4	
	Bacteriologic Index < 4	Bacteriologic Index ≥ 4
Without relapse	301	59
	94.48%	85.50%
With relapse	21	10
	6.52%	14.49%
Chi square		4.94
P value		0.02
Odds ratio		2.42

P value ≤ 0.05

The prevalence of relapse among patients with a BI of less than 3.5 was 4.90% and those with a BI equal to higher than 3.5 was 18.82%. The difference between the two groups was statistically significant. The odds ratio of relapse of any patient with a BI > 3.5 was 4.49 compared to those with BI < 3.5. Patients with a BI > 3.5 have 4.49 greater odds to develop relapse compared to patients with a BI < 3.5 (Table 9).

Table 9. Distribution of relapse according to Bacteriologic Index > 3.5

Relapse	Bacteriologic index ≥ 3.5	
	Bacteriologic index < 3.5	Bacteriologic index ≥ 3.5
Without relapse	291	69
	95.09%	81.17%
With relapse	15	16
	4.90%	18.82%
Chi square		17.66
P value		0.00..
Odds ratio		4.49

P value ≤ 0.05

Distribution of relapse according to clinical spectrum

There was no case (0%) of relapse in patients classified as Borderline Tuberculoid (BT), 2 (1.43%) developed relapse in patients classified as Borderline (BB), 17 (17.89%) as Borderline Lepromatous and 12 (17.91%) as Lepromatous Leprosy. There was a significant difference among the different clinical spectrums (Table 10).

Table 10. Distribution of relapse according to clinical spectrum

Relapse	CLINICAL SPECTRUM			
	Borderline Tuberculoid (BT)	Borderline Borderline (BB)	Borderline Lepromatous (BL)	Lepromatous (LL)
Without relapse	89	138	78	55
	100%	98.57%	82.10%	82.08%
With relapse	0	2	17	12
	0%	1.43%	17.89%	17.91%
Chi square				37.83
P value				0.00..

P value ≤ 0.05

Clinical spectrums of patients were grouped into two: (a) BT/BB and (b) BL/LL

The prevalence of relapse among patients with clinical spectrum of BT/BB was 0.87% and 17.90% in the BL/LL group. The difference between the two groups was statistically significant. The odds ratio of patients with a clinical spectrum of BL or LL was 24.74. Patients in the BL/LL have 24.74 greater odds to relapse than patients with clinical spectrum of BT/BB (Table 11).

Table 11. Distribution of relapse according to clinical spectrum

Relapse	CLINICAL SPECTRUM	
	Borderline Tuberculoid (BT)/ Bordeline Borderline (BB)	Borderline Lepromatous (BL) / Lepromatous (LL)
Without relapse	227	133
	99.13%	82.09%
With relapse	2	29
	0.87%	17.90%
Chi square		37.68
P value		0.00..
Odds ratio		24.74

P value ≤ 0.05

Distribution of relapse according to treatment

For the two treatment groups, the number of cases of relapse was 28 (11.96%) for patients given 12 blister packs and 3 (1.91%) for patients treated with 24 blister packs. The difference between the two groups (p=0.00) was statistically significant (Table 12).

Table 12. Distribution of relapse according to clinical spectrum

	TREATMENT	
Relapse	**12 Blister packs**	**24 blister packs**
Without relapse	206	154
	88.03%	98.09%
With relapse	28	3
	11.96%	1.91%
Chi square		13.01
P value		0
Odds ratio		6.97

P value $\leq$ 0.05

Patients given 12 blister packs have 6.97 greater odds of developing relapse compared to patients given 24 blister packs.

DISCUSSION

Demographic and Clinical Data

The mean age among patients (34.11 + 15.10) is very similar to what was found in an earlier study by Maghanoy, et al. The male/ female ratio is 2.8:1 and is consistent to what was done in the earlier study by Maghanoy,et al. The clinical spectrums of the patients were mostly Borderline Tuberculoid and Borderline whereas in the earlier study the cases were mostly in the Borderline Lepromatous and Lepromatous. This may be attributed to the institution's capacity to detect cases at an earlier spectrum.

Relapse rate

Relapse rate in this study for all patients was found to be 7.67%, which is higher than the previously reported study. The said study included 57 patients followed up at 6 years. Whereas, this current study was done on 391 patients seen in this referral institution for the past 5 years.

Clinical Spectrum

Patients classified as Borderline Lepromatous or Lepromatous are 24 times (24X) more likely to develop relapse in patients. This could be attributed to having high bacillary loads at the beginning of treatment.

Bacteriologic index

In the present study, patients with an initial BI > 3.5 have 4.49 times risk of developing relapse and patients with initial BI > 4 are 2.24 times (2.42X) more likely to relapse, which is consistent with an earlier study by Jamet, et al. This could be due to the presence of persisting organisms that have the capacity to survive in the host despite adequate chemotherapy.

Treatment

In the study, the number of cases of relapse was 28 (11.96%) for patients given 12 blister packs and 3 (1.91%) for patients treated with 24 blister packs. Patients who received 12 blister packs have a 6.97 times (6.97X) likelihood of developing relapse compared to patients treated with 24 blister packs. Patients who developed relapse in those receiving 12 blister packs were found to have a clinical spectrum of Borderline Lepromatous or Lepromatous with a high bacillary load. Relapse could be due to insufficient duration of treatment.

CONCLUSION

Smear-positive cases of Leprosy in both 12 blister packs and 24 blister packs of multibacillary drug therapy belong to the BT, BB, BL and LL. Relapse rate of 11.96% was reported for patients treated with 12 blister packs as compared to 1.91% in patients treated with 24 blister packs. Relapse rate in patients treated with 12 blister packs is significantly higher than patients treated with 24 blister packs. Proportion of relapse is significantly greater among clinical spectrum BL/LL; BI > 3.5, BI > 4 and in patients treated with 12 blister packs of multibacillary drug therapy.

RECOMMENDATIONS

Leprosy control programs including community-based settings should include determination of bacteriologic index before initiation of treatment in patients diagnosed with Leprosy. Surveillance of leprosy cases should include yearly skin smear examination while undergoing treatment and after being released from treatment. There is a need for referral centers in local areas with scarcity of trained medical technologists for skin smear examination.

This study recommends that in patients with a bacteriologic index of 3.5 and higher or patients with clinical spectrum of Borderline Lepromatous (BL) and Lepromatous (LL), 24 blister packs of multibacillary drug therapy should be given to decrease the occurrence of relapse.

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