Reactions Following Completion of 1 and 2 Year Multidrug Therapy (MDT)

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Abstract. We evaluated the incidence, severity, and duration of reactional states in 139 multibacillary (MB) leprosy patients in the first 2 years after the completion of the 1 year regimen of multidrug therapy (MDT) currently recommended by the World Health Organization (WHO) and compared those findings with 295 MB leprosy patients treated with the same regimen previously recommended for 2 years. During the first year after the completion of 1 year MDT, patients experienced 1 or more reactional states 27% of the time, the vast majority being lepra type 1 reactions (reversal reactions, RR), whereas patients who received 2 year MDT experienced a reactional state during that time period only 8% of the time ($P < 0.001$). Furthermore, during the first year after the completion of therapy, and during the first 2 years, both the number of reactional states and reversal reactions were significantly ($P \leq 0.004$) more frequent, severe, of longer duration, and more commonly associated with neuritis.

INTRODUCTION

Reactional states in leprosy are varied signs and symptoms of inflammation arising from acute or chronic hypersensitivity brought about by the patient's immunologic response to antigens of *Mycobacterium leprae*. This may occur in the regular course of the disease even without the intervention of treatment. However, this hypersensitivity can also be initiated or aggravated by effective chemotherapy, because of the active destruction of bacilli during treatment, thereby producing an abundance of antigenic material to the immune system. Furthermore, reactions involving frank neuritis or perhaps "silent neuritis" are responsible for many of the debilitating conditions that occur in leprosy.

Two types of reactions can occur—type 1 or reversal reaction (RR) and type 2 reactions or erythema nodosum leprosum (ENL):

Type 1 reactions are promulgated by fluctuations in the cellular immune system and products of *M. leprae*.¹ Clinically, in type 1 reactions, there is erythema and elevation of existing lesions and new skin lesions may also occur. Occasionally, low-grade fever and nerve involvement may accompany these skin lesions. These hypersensitivity reactions occur in roughly one-third of patients with leprosy. Type 1 reactions that occur following a course of antimicrobial therapy are termed RR and are associated with an increasing cellular immune response to mycobacterial antigens, infiltration of reactional sites with interferon-gamma (IFN- γ),² tumor necrosis factor-alpha (TNF- α)-secreting CD4 + lymphocytes,³ and increased cytokine production by peripheral blood lymphocytic cells,⁴ resulting in increased levels of serum cytokines.⁵

Although RR generally occurs early in the course of effective chemotherapy, these type 1 reactions have been reported as occurring at the time of diagnosis between 3% and 6% of the time by most,⁶ whereas others have found these to occur 24%⁷ to 28%⁸ of the time. More recently, Lockwood and others⁹ noted fully 41% with type 1 reactions at the time of leprosy presentation, and Kumar⁷ found that 31% of leprosy patients presented with type 1 reactions, despite having symptoms of leprosy much earlier. In both studies, over 50% of patients with reactions presented with frank neuritis. Most RR are known to occur 6 to 12 months after the initiation of therapy,^{10,11} and in Zaire⁶ type 1 reactions were found to occur in fully 48% of MB patients during the course of leprosy.

Type 2 reactions (erythema nodosum leprosum [ENL]) are seen exclusively in patients with high bacillary loads and in almost half of those with multibacillary (MB) leprosy (borderline lepromatous leprosy [BL] or lepromatous leprosy [LL]). Although ENL may occur before the initiation of antimicrobial therapy, being associated with the release of *M. leprae* antigens from dead and dying bacilli, it generally occurs in the first few years of effective antimicrobial intervention. Type 2 reactions are generally believed to be a consequence of humoral immune mechanisms and are considered to be associated with immune complexes, accompanied by high levels of circulating concentrations of TNF α .⁵ These complexes result from an antigen-antibody reaction involving activation of the complement system¹² and may resemble the Arthus phenomenon,¹³ resulting in systemic vasculitis and panniculitis, which may result in a myriad of manifestations including skin lesions, malaise, neuritis, orchitis, uveitis, and at times, frank glomerulonephritis. Clinically, the skin lesions appear as tender and painful papulonodules, which may be accompanied by nerve involvement and systemic signs and symptoms such as fever, weakness, and joint pains. Alternatively, ENL may also involve Th1 mechanisms including the HLA-DR framework antigen on epidermal keratinocytes¹⁴ (a marker for delayed type hypersensitivity responses) and as compared with LL tissues, increased number of cells staining for IL-2¹⁵ and more cells synthesizing INF- γ .¹⁶

During the majority of the last half of the 20th century MB leprosy patients were treated with life-long dapsone monotherapy. Thus, there was little opportunity to assess reactional states in these patients after the completion of treatment. In the dapsone monotherapy era, ENL was reported to occur in 50% of LL patients and 25% of BL patients,¹² these figures seemingly being generally reduced during MDT therapy, perhaps as a result of the inclusion of clofazimine in the regimen.¹⁷ However, the incidence of ENL in two studies in MB patients while on treatment with MDT in Nepal¹⁸ and North India⁷ was found to be respectively 29% and 47% in LL patients and 8% and 11% in BL patients, while lower in certain field studies, 12% in LL and 4% in BL patients from Ethiopia¹⁶ and 2% of MB patients in Bangladesh.¹⁸ A prospective study of at-risk newly diagnosed hospitalized leprosy patients in the United States found that type 1 reactions occurred in 32% of patients, were common in females, and were not generally recurrent, whereas type 2 reactions occurred in 33% of these patients, were associated with disease onset in the second decade of life, and were often recurrent.

In 1982, the World Health Organization (WHO) recommended the use of a multidrug therapy, consisting of rifampin,

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dapsone, and clofazimine, of 2 years duration or until skin smear negativity for MB leprosy worldwide.¹⁹ However, in 1998²⁰ onward, the regimen was shortened to only 1 year duration because of the perceived excellent efficacy of 2 year MDT and because of concerns that overtreatment was occurring.

There is little published information on reactional states in MB patients following the completion of MDT. However, Saunderson and others²¹ found after fixed duration 2 year WHO MDT that 43 of 300 patients (14%) developed reversal reactions, most in the first year thereafter and 20 of these with first episodes and 23 with recurrences. Saunderson and others,²² also found in this cohort that 24 of these patients, (5%) developed ENL after the completion of MDT, it being associated with a high BI and a LL classification. Furthermore, in a study of 200 patients in Northern Thailand with MB leprosy treated until smear negativity reversal reactions developed in 9% of patients on 6 years of follow-up, most occurring within the first 2 years after completion of therapy.⁸ In this study no instance of ENL after MDT was observed. Kumar⁷ found after 2 year MDT that reactional states were distinctly infrequent. To our knowledge, to date there is no published data on reactional states following the completion of 1 year MDT.

The purpose of this work is to present our experience of the incidence, severity, and duration of reactional states within the first 2 years after the completion of 1 year MDT and compare those findings with those of 2 year MDT. This was made possible because the Leonard Wood Memorial (LWM) has been actively following up MB leprosy patients treated with both 1 and 2 year WHO MDT for clinical and bacteriologic relapse.

MATERIALS AND METHODS

This report presents our experience in MB patients with reactional states occurring during the first 2 years after 1 year MDT and compares those findings of incidence, severity, and duration with those found after 2 year MDT. The protocol for this study was approved by a local human rights committee approved and licensed by the National Institutes of Health, and written informed consent was obtained from all patients monitored in this trial. In this study, patients were considered multibacillary who had a bacteriologic index (BI) in at least 1 of 6 skin smear sites $\geq 2+$. Patients (139) treated with 1 year WHO MDT was diagnosed between 1998 and 2001. Patients (295) treated with 2 year WHO MDT was diagnosed in 1985 and 1992. Patients in this study underwent initially a thorough clinical evaluation, had skin smears obtained from 6 sites (examined by the same highly experienced technologists), and were classified histologically from the findings of a skin biopsy from the most active lesion by a pathologist highly experienced in the methods of Ridley and Jopling. From these, baseline parameters were obtained consisting of age, gender, initial BI (average of 6 skin smear sites), and histopathologic leprosy classification.

Patients were informed of signs and symptoms of reactional states and asked to report at least annually for clinical evaluation. Both cohorts were followed up by the same two highly experienced leprologists. In both treatment groups, patients with mild to moderate reactions were regularly monitored at intervals of 1 to 2 weeks. Severe cases were advised hospitalization. Patients who refused hospitalization were either provided home-based patient care or were advised to report to the clinic at closer intervals. Chronic, stable reactional states

were seen at longer intervals. Prednisone was used as the standard treatment (20–40 mg/day), and the dose was adjusted as to weight, severity of reaction, and patient response.

Comparison of reactional states obtained in the two cohorts were evaluated from data obtained by chart review of the clinical record and included comparisons of reactional states obtained 1 year, 2 years, and in those seen in both years (the vast majority); 1 and 2 years combined after the completion of therapy, and 2 years after the initiation of therapy.

Reversal reactions were considered mild if signs of inflammation were only confined to the original lesions, and moderate if new lesions also appeared with or without nerve involvement. Reactions were considered severe when constitutional signs and symptoms were present with or without ulcers, blebs, or edema. In most severe reversal reactions neuritis was observed.

The ENL reactions were considered mild when there were less than 10 tender papulonodules and moderate if there were 10 to 20 papulonodules with or without slight edema and/or joint pains. Reactions were considered severe if there were more than 20 ENL skin lesions or if papulonodules of ENL were associated with either severe joint pains, edema, high fever, other constitutional signs and symptoms of iritis, laryngitis, orchitis, and other organ involvement.

In some patients with reactions, concomitant neuritis was also noted. Neuritis was defined as pain associated with swelling and tenderness of the nerve with or without nerve function impairment.

Careful review of the clinical records provided the database for the analysis provided in this study. Results for univariate analysis were performed using calculated odds ratios (ORs) and for reactional duration hazard ratios and expressed as *P* values using the method of Fisher. For multivariate analysis the SAS (2004) system for statistical analysis was used, principally procedures LOGIST²³ for linear logistic regression and PHREG²⁴ for proportional hazards regression. Logistic regression was used for the dichotomous responses, incidence, and dichotomized severity of reactions. Proportional hazards regression was applied to duration of reactions, which exhibited heavy-tailed distributions and for which some values were truncated (right-censored). Independent proportions were compared using χ^2 or Fisher exact tests, according to standard criteria. Agreement between two proportions on the same sample was tested by the McNemar test.

RESULTS

Baseline parameters for patients treated with 1 year MDT and 2 year MDT, including median age, sex, and histopathologic classification were quite similar (Table 1). Additionally,

TABLE 1
Patient profiles at the initiation of MDT*

	1 Year MDT	2 Year MDT	<i>P</i> value
<i>N</i>	139	295	
Mean age	28.2 $\pm$ 13.2	27.3 $\pm$ 13.5	0.7
Initial BI	3.9 $\pm$ 0.9	3.5 $\pm$ 1.1	0.0003
Male/female	108/31	234/61	0.3
Histopathologic classification:			
BT – BB/BL/LL	4/72/63	18/143/134	0.3
BL/LL	72/63	143/134	0.7

*MDT = multidrug therapy; BI = bacteriologic index; BT = borderline tuberculoid leprosy; BB = mid-borderline leprosy; BL = borderline lepromatous leprosy; LL = lepromatous leprosy.

TABLE 2
Incidence of reactions after completion of therapy*

Year 1												
1 Year MDT regimen						2 Year MDT regimen						
Leprosy type	No of cases	Reversal reaction			ENL		Reversal reaction			ENL		Total reaction (%)
		Skin only	Skin + nerves	Total (%)	Skin only	Skin + nerves	Skin only	Skin + nerves	Total (%)	Skin only	Skin + nerves	
BT	0	—	—	—	—	—	—	—	—	—	—	—
BB	4	—	—	—	—	—	—	—	—	—	—	—
BL	72	19	6	25 (35)	—	—	13	0	13 (9)	—	—	13 (9)
LL	63	13	0	13 (21)	4	0.3	8	3	11 (8)	5	1	17 (13)
Total	139	32	6	38 (27)	4	3	21	3	24 (8)	5	1	30 (10)
Year 2												
1 Year MDT regimen						2 Year MDT regimen						
Leprosy type	No of cases	Reversal reaction			ENL		Reversal reaction			ENL		Total Reaction (%)
		Skin only	Skin + nerves	Total (%)	Skin only	Skin + nerves	Skin only	Skin + nerves	Total (%)	Skin only	Skin + nerves	
BT	0	—	—	—	—	—	—	—	—	—	—	—
BB	4	—	—	—	—	—	—	—	—	—	—	—
BL	69	4	3	7 (10)	—	—	10	0	10 (9)	—	—	10 (9)
LL	58	5	0	5 (9)	4	3	5	0	5 (5)	5	1	11 (10)
Total	131	9	3	12 (9)	4	3	15	0	15 (6)	5	1	21 (9)
Both Year 1 and 2												
1 Year MDT regimen						2 Year MDT regimen						
Leprosy Type	No of cases	Reversal reaction			ENL		Reversal reaction			ENL		Total Reaction (%)
		Skin only	Skin + nerves	Total (%)	Skin only	Skin + Nerves	Skin only	Skin + nerves	Total (%)	Skin only	Skin + nerves	
BT	0	—	—	—	—	—	—	—	—	—	—	—
BB	4	—	—	—	—	—	—	—	—	—	—	—
BL	69	16	7	23 (33)	—	—	19	0	19 (17)	—	—	19 (17)
LL	58	15	0	15 (26)	6	4	13	3	16 (15)	6	2	24 (23)
Total	131	31	7	38 (29)	6	4	32	3	35 (15)	6	2	43 (18)

hospital staff, medical resources, patient weight, and standard of living were largely stable for the two cohorts. In both cohorts who received 1 year MDT and 2 year MDT the mean bacteriologic index derived from six skin smear sites was high, respectively 3.9 ± 0.9 and 3.5 ± 1.1 , this initial bacteriologic index being higher in patients who received 1 year MDT ($P = 0.0003$). Furthermore, a BI > 3.0 , which was found in 66 of 326 patients, resulted in a reactional state in the first year after the completion of therapy at a significantly greater rate (20%) as compared with that found in the 9 of 108 patients with a BI < 3 (8%), $P = 0.005$, underscoring the importance of the multivariate analysis performed herein to assess differences in reaction outcomes following the two durations of MDT. Of the 22 BT and BB patients in the two cohorts, none developed a reaction during the 2 years after the completion of therapy studied herein, reactions being confined to patients with BL and LL leprosy (Table 2). Reversal reactions were found far more frequently than ENL in both cohorts (Table 2), reversal reactions accounting for almost 80% of the total reactional states encountered.

Though the incidence and severity of ENL was greater in patients treated with 1 year MDT but likely, because of the infrequency of ENL encountered, these were not statistically significantly different between the two cohorts (Tables 2 and 3). However, the duration of ENL was found longer following 1 year MDT in 2 instances—1 year after the completion of therapy (hazard ratio 0.14; $P < 0.02$) and 2 years after the initiation of therapy (hazard ratio 0.22; $P = 0.03$). Although not statistically significant (hazard ratio 0.45; $P = 0.1$), the duration of ENL in patients seen in both the first and second year after the completion of therapy in the cohort receiving 1 year MDT was longer, average duration 26 weeks, than in those treated with 2 year MDT, average duration 15 weeks (Table 4).

In the first year after the completion of 1 year MDT both total reactions and reversal reactions were encountered frequently and were often moderate or severe (Tables 2 and 3).

In these patients during this time period 38/139 (27%) experienced one or more reversal reactions, while 7/139 (5%) had ENL. Reversal reactions and ENL were found to be moderate or severe, respectively in 24/38 of patients (63%) and in 6/7 patients (86%) of the time (Table 3). By contrast, in the first year after the completion of 2 year MDT only 24/295 (8%) experienced reversal reactions and 6/295 (2%) ENL (Table 2); these were generally mild (RR 21/24 [88%] and ENL 4/6 [67%]), Table 3. Furthermore, the duration of both total reactions and reversal reactions were found longer after 1 year MDT (Table 4).

Table 5 presents our statistical analysis of incidence of both total reactions and reversal reactions during all time periods studied, Table 6 those findings for severity, and Table 7 those observations on duration. It is noteworthy that in the first year after the completion of treatment, the incidence of both total reactions and reversal reactions were significantly more frequent in the cohort treated with 1 year than the cohort treated with 2 year MDT ($P < 0.0001$) whether performed by univariate or multivariate analysis (OR respectively for total reactions 4.23 and 3.84 and reversal reactions alone 4.25 and 4.08). Significant covariants ($P < 0.05$) were greater age in decade for RR and initial BI. For total reactions, it is further noteworthy that in the first year after the completion of therapy the frequency of moderate to severe total reactions and reversal reactions were greater after 1 year MDT ($P \leq 0.0004$), whether obtained either by both univariate or multivariate analysis (ORs respectively for total reactions 10.0 and 10.2 and reversal reactions 12.0 and 13.1). For reactional severity no significant baseline covariants were found. Furthermore, in the first year after the completion of therapy the duration of both total reactions and reversal reactions were significantly longer ($P \leq 0.04$) after 1 year than 2 year MDT, whether calculated by univariate or multivariate means (hazard ratios 0.43–0.58), Table 7. The BI was a significant cofactor ($P = 0.04$) in total reactional duration, but not a significant cofactor in RR duration.

TABLE 3
Severity of reactions after completion of therapy*

Year 1							
1 Year MDT regimen				2 Year MDT regimen			
Severity of reaction	No. of cases (%)	Type of reaction		Severity of reaction	No. of cases (%)	Type of reaction	
		Reversal reaction cases (%)	ENL cases (%)			Reversal reaction cases (%)	ENL cases (%)
Mild	15 (33)	14 (37)	1 (14)	Mild	25 (83)	21 (88)	4 (67)
Mod-Severe	30 (67)	24 (63)	6 (86)	Mod-severe	5 (17)	3 (13)	2 (33)
Total	45	38	7	Total	30	24	6
Year 2							
1 Year MDT regimen				2 Year MDT regimen			
Severity of reaction	No. of cases (%)	Type of reaction		Severity of reaction	No. of cases (%)	Type of reaction	
		Reversal reaction cases (%)	ENL cases (%)			Reversal reaction cases (%)	ENL cases (%)
Mild	11 (58)	8 (67)	3 (43)	Mild	18 (86)	14 (93)	4 (67)
Mod-Severe	8 (42)	4 (33)	4 (57)	Mod-severe	3 (14)	1 (7)	2 (33)
Total	19	12	7	Total	21	15	6
Both Year 1 and Year 2							
Severity of reaction	No. of cases (%)	Type of reaction		Severity of reaction	No. of cases (%)	Type of reaction	
		Reversal reaction cases (%)	ENL cases (%)			Reversal reaction cases (%)	ENL cases (%)
Mild	17 (35)	16 (42)	1 (10)	Mild	36 (84)	33 (94)	4 (50)
Mod-Severe	31 (65)	22 (58)	9 (90)	Mod-Severe	7 (16)	2 (6)	4 (50)
Total	48	38	10	Total	43	35	8

* MDT = multidrug therapy; ENL = erythema nodosum leprosum.

TABLE 4
Duration of reactions after completion of therapy*

Both Year 1 and 2							
1 Year MDT regimen				2 Year MDT regimen			
Reaction type	Leprosy type	No. of cases	Average duration of reaction	Reaction type	Leprosy type	No. of cases	Average duration of reaction
RR		25	9.64 wks	RR		35	5.46 wks
	BL	14	10.49 wks		BL	19	5.74 wks
	LL	11	8.53 wks		LL	16	5.13 wks
ENL		9	26.1 wks	ENL		8	15.0 wks
Total		34		Total		43	

* MDT = multidrug therapy; RR = reversal reactions; BL = borderline lepromatous leprosy; LL = lepromatous leprosy; ENL = erythema nodosum leprosum.

Furthermore, in patients seen in both year 1 and 2 after MDT reactional states were again mostly reversal reactions and in the cohort treated with 1 year MDT both total reactions and reversal reactions were more frequent, severe, and of longer duration. Additionally, in patients seen in both year 1 and 2 after MDT both total reactions and reversal reactions were more frequent in the cohort treated with 1 year MDT, respectively 48/131 (37%) and 38/131 (29%) than 2 year MDT, respectively 43/238 (18%) and 35/238 (15%), $P < 0.0004$ (unadjusted and adjusted OR 3.1–4.2), Tables 2 and 5. Bacteriologic index was found to be a significant cofactor for the frequency of total reactions in patients seen both 1 and 2 years after the completion of therapy (Table 5), whereas during this study period age in decade was a significant cofactor for reversal reactions. During this study period patients who received 1 year MDT had moderate to severe total and reversal reactions more frequently, respectively 31/48 (65%) and 22/38 (58%), than those who received 2 year MDT 7/43 (16%) and 2/35 (6%) – ($P < 0.004$; unadjusted OR 7.8–14.3), Tables 4 and 6. The duration of active reversal reactions in patients treated with 1 year MDT during this study period averaged 10 weeks and ENL 26 weeks (Table 5). By contrast, after the completion of 2 years MDT reversal reactions averaged duration of only 5 weeks and ENL 15 weeks (Table 5). In patients seen in both year 1 and 2 after the completion of therapy both total reactions and reversal reactions were significantly longer ($P \leq 0.01$) in the cohort treated with 1 year MDT (both unadjusted hazard ratios and first order adjusted ones being 0.5–0.6), Table 7. For reactional duration no significant pretreatment parameters were found significant (Table 7).

Two years after the initiation of therapy and the completion of therapy the incidence of total reactions and reversal reactions were generally significantly greater in the cohort treated with 1 year than the cohort receiving 2 years MDT

(Tables 2 and 5). Although not consistently statistically significant, during these study periods generally the severity of both total reactions and reversal reactions were greater in patients treated with 1 year MDT than 2 year MDT (Tables 3 and 6). During these study periods no difference in duration of total reactions and reversal reactions were noted between the two cohorts studied (Table 7).

The incidence of neuritis (pain, nerve swelling, and tenderness with or without nerve dysfunction) was evaluated for all patients followed for 2 years after the completion of therapy (Table 8). In addition, Table 8 details which peripheral nerves were involved. Neuritis was more frequent in the first 2 years following MDT in those treated for 1 year, 11/131 (8%) than in those treated for 2 years, 5/238 (2%) $P < 0.004$.

DISCUSSION

This report presents to our knowledge the first major study of reactional states in MB leprosy patients in the first 2 years after the completion of 1 year MDT. These were found to occur frequently, were generally reversal reactions, often of significant severity and long duration. All were of greater magnitude than in published studies of longer duration MDT^{7,8,21,22} and our own experience with 2 year MDT. Insofar as reactional states in leprosy are the result of an immune response to products of *M. leprae*, and in treated patients *M. leprae*, albeit mostly non-viable, and its constituents may remain in tissues for several years, it is not surprising that the reactions they invoke decrease after longer durations of treatment.

The observation that almost half of our MB patients treated with the currently recommended 1 year WHO MDT and 18% of those treated with 2 year WHO MDT developed reactions within the first 2 years after the completion of treatment is, of course, of considerable concern. Furthermore, the frequency

TABLE 5
Statistical analysis: incidence*

Variable (yr after end Rx)	N	Unadjusted		1st order adjustmet		Significant covariants		
		MDT odds ratio	P	MDT odds ratio	P	Variable	Odds ratio	P < 0.5
RR (1)	434	4.25	< 0.0001	4.08	< 0.0001	Age in decade	1.22	0.047
All reac (1)	434	4.23	< 0.0001	3.84	< 0.0001	PreBI	1.49	0.007
RR (2)	309	2.16	0.084	2.26	0.073	–		
All reac (2)	309	2.77	0.0059	2.50	0.015	–		
RR (1&2)	309	3.15	0.0002	3.10	0.0004	Age in decade	1.25	0.03
All Reac (1&2)	309	4.17	< 0.0001	3.81	< 0.0001	PreBI	1.51	0.003
RR (1–2 yr MDT;								
2–1 yr MDT)	366	1.64	0.23	1.56	0.29	–		
All reac (1–2 yr MDT;								
2–1 yr MDT)	366	2.37	0.014	2.06	0.042	PreBI	1.50	0.08

* MDT = multidrug therapy; RR = reversal reactions.

TABLE 6
Statistical analyses: severity*

Variable (Yr after Rx)	N	Unadjusted		1st order adjusted	
		MDT odds ratio	P	MDT odds ratio	P
RR (1)	62	12	0.0004	13.06	0.0008
All reac (1)	75	10	< 0.0001	10.18	0.0001
RR (2)	24	7	0.12	11.68	0.14
All reac (2)	36	5.25	0.041	5.72	0.053
RR (1&2)	60	11	0.0041	14.31	0.0036
All Reac (1&2)	77	7.81	0.0002	8.98	0.0003
RR (1-2 yr MDT; 2-1 yr MDT)	33	3.5	0.18	4.49	0.16
All reac (1-2 yr MDT; 2-1 yr MDT)	45	4.38	0.038	4.45	0.056

* No significant baseline covariants were found. MDT = multidrug therapy; RR = reversal reaction.

of neuritis after the completion of 1 year MDT is more frequent than after 2 year MDT, nerve damage is the major cause of the deformity and disability found in leprosy patients. In any event, these present observations have very important implications for our consideration of the relative efficacy of these two regimens.

It is noteworthy in our study that RR was much more frequent after MDT than ENL. This might be because ENL generally occurs during the rapid killing of bacilli from effective chemotherapy, and like other antigen-antibody complex diseases, occurs particularly in a state of antigen excess.²⁵ The greater problem we encountered with ENL in the cohort treated with 1 year MDT could have, at least partially, be a consequence of the lesser concentration of clofazimine found in the tissues of these patients after the completion of therapy because clofazimine is known to accumulate in tissues and ameliorate ENL. On the other hand, type 1 reactions occur in patients even with a lower bacterial burden and occur frequently before therapy, without necessitating the rapid bacterial death associated with effective antimicrobial therapy.

In this study, initial BI was significantly higher in patients treated with 1 year MDT than 2 year MDT. Furthermore, on several occasions an elevated BI was found to be a suggestive or significant predictive covariant for an increased incidence and duration, but not severity, of both total reactions and reversal reactions. However, because there were no significant differences in baseline values of those treated with 1 year as opposed to 2 year MDT except for initial BI, and the unadjusted and particularly the adjusted OR for incidence of total reactions and reversal reactions were often significant and not substantially different, it appears unlikely that the

differences in BI had a meaningful effect on the relative frequency of reactional states between the cohorts treated with 1 year and 2 year MDT.

Certainly reactional states are a consequence of immune reactions induced by *M. leprae*. Because BI alone does not appear to predict the greater reactional state encountered herein by the cohort receiving 1 year MDT rather than 2 year MDT, what does? We suggest that those differences are related to reversal reactions precipitated by *M. leprae* degradation products induced by the death of bacilli but not yet removed from the tissues, these moieties being found in tissues in higher concentrations in patients treated for a lesser duration.

In the dapsone monotherapy era, patients at the tuberculoid pole were treated for 5 years and at the lepromatous pole for a lifetime, and there was no opportunity to experience reactions in lepromatous patients after the completion of therapy. However, after 2 year MDT it has been reported in some MB patients that reversal reactions occur in 1% to 9%^{7,26-28} of patients and ENL in 3% of patients, generally mild.⁷ Our experience with the incidence of reactions in MB patients after 2 year MDT is higher and very similar to that found in Ethiopia^{21,22} after fixed duration 24 month MDT and in Thailand⁸ after therapy until smear negativity, but greater than in India⁷ following 2 year MDT and MDT continued until smear negativity. Our present experience with reactions following 1 year MDT, the first such report shows that in the Philippines reactions, particularly reversal reactions, are more frequent than found previously by longer durations of MDT.

The successful treatment of patients with leprosy involves appropriate antimicrobial therapy, treatment of reactional states, prevention and treatment of disabilities, and culturally sensitive psychosocial interventions. All are critical to attaining a salutary outcome and maintaining the patients' continued integration in society. Since the widespread adoption of WHO MDT, first at least 2 years and now 1 year for MB patients, antimicrobial therapy has largely been standardized worldwide, leaving those other areas to the care and attention of leprosy services. The success of WHO MDT for individual patients has to date largely been measured by a decrease in the prevalence of leprosy and its high cure rate.²⁹ Except in MB patients, these goals have been successfully achieved, except that MB patients and especially those with high bacterial burdens run a substantial risk of ultimately relapsing,³⁰⁻³³ most commonly many years after the completion of therapy. This current study raises an altogether different concern, showing that reactional states following the completion of WHO MDT, particularly 1 year WHO MDT, may be substantially

TABLE 7
Statistical analyses: duration

Variable (Yrs after Rx)	N	Unadjusted 1 yr MDT hazard ratio	P	1st order adjusted 1 year MDT hazard ratio	P	Covariants		
						Variable	Hazard ratio	P < 0.1
RR (1)	62	0.581	0.044	0.561	0.035			
All reac (1)	75	0.487	0.004	0.453	0.002	Initial BI	0.756	0.04
RR (2)	24	1.25	0.58	0.917	0.85			
All reac (2)	36 (2)	1.01	0.98	1.15	0.71			
RR (1&2)	60	0.534	0.011	0.527	0.010			
All reac (1&2)	77 (2)	0.555	0.007	0.557	0.007			
RR (1-2 yr MDT; 2-1 yr MDT)	33	1.066	0.86	1.034	0.93	Initial BI	0.648	0.01
All reac (1-2 yr MDT; 2-1 yr MDT)	45 (2)	0.585	0.091	0.625	0.15	Initial BI	0.646	< 0.01

* MDT = multidrug therapy; RR = reversal reaction; BI = bacteriologic index.

TABLE 8

Incidence of neuritis within 24 months from the World Health Organization-multidrug therapy (WHO-MDT) completion

	1 year MDT regimen		2 year MDT regimen	
Nerve(s) involved	No. of pts.		No. of pts.	
Facial nerve	1*		0	
Ulnar nerve	3**		2	
Median nerve	0		0	
Ulnar and median	0		0	
Radial nerve	0		0	
Ulnar and common peroneal	5*		1*	
Common peroneal	2		2	
Posterior tibial	0		0	
Total no. of pts. with neuritis	11	1:11	5	1:47
Total no. of pts. without neuritis	120		233	
Total	131		238	

* = both sides affected.

** = both sides affected in 1 of 3 patients.

frequent, severe, and of long duration. Seasoned leprologists are well aware that reactional states, particularly in the first few years of leprosy treatment, are the major reason for patients to seek medical attention. Because of the high incidence and accompanying neuritis, severity and long duration of reactions, particularly reversal reactions, after the completion of the currently recommended 1 year MDT for MB leprosy, rather than the patient-initiated follow-up recommended by the WHO, we recommend physician-initiated follow-up during the first few years after therapy is completed. Unfortunately, now that MB leprosy is largely treated in the developing world with 1 year MDT, reactional states may continue after the completion of therapy in a context where leprosy expertise is wanting and access to specialized leprosy services is not available.

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