

ORIGINAL ARTICLE

Clinical analysis of multibacillary leprosy patients after 1-year fixed World Health Organization recommended multidrug therapy at Yangon General Hospital, Myanmar

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ABSTRACT

This study included 200 randomly selected multibacillary leprosy cases who had completed 1 year of fixed World Health Organization recommended multidrug therapy (WHO-MDT) without prior dapsone (DDS) monotherapy. The time interval after release from treatment varied from a few months to 8 years. All cases were clinically reviewed in 2006 by comparison with their old clinical records. Reactions, particularly reversal reactions, occurred frequently among patients who had completed MDT within the last 3 years. It was difficult to distinguish relapse cases and late reversal reactions in skin smear-negative multibacillary cases. Based on bacteriological and histological analyses, one patient was confirmed to have relapsed 1 year after release from treatment. The overall relapse rate was 0.5%. No drug resistance mutations were detected by polymerase chain reaction or dot blot hybridization. The present study indicates that it is important to follow up patients for several years after completion of MDT in order to detect possible lepra reactions and relapses.

Key words: reactions, relapse, rifampicin (RFP), World Health Organization recommended multidrug therapy (WHO-MDT).

INTRODUCTION

The World Health Organization recommended multidrug therapy (WHO-MDT) regimen was widely introduced for leprosy control in Myanmar in 1988. In cases of multibacillary (MB) leprosy, MDT consists of three drugs: rifampicin (RFP; 600 mg/month), dapsone (DDS; daily), and clofazimine (CLF; 300 mg/month and 50 mg/day). It was initially started as a 2-year protocol and later modified to 1-year fixed regimens. Due to its shorter course and intensive public health efforts, leprosy was eliminated in early 2003 (WHO elimination level: registered prevalence rate of <1 case/10 000 population). From 1988–2005, a total of 5661 cases had been released from treatment

after completion of MDT at the Central Special Skin Clinic (CSSC) in Myanmar.¹ Among them, 1100 patients were released from treatment with 1 year of fixed WHO-MDT following its introduction in 1997. All patients who had completed treatment were kept under passive surveillance which identified some cases with lepra reactions and only a few relapse cases among the self-reported patients. However, an exploration of clinical problems among the cases after completion of the 1-year fixed WHO-MDT had not been conducted. The aim of this study was to evaluate MB patients who had completed the 1-year fixed WHO-MDT regimen at CSSC, Yangon General Hospital, Myanmar, and to identify potential clinical problems.

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METHODS

Four hundred randomly selected MB cases who had been released from treatment for period of a few months to 8 years were requested for follow-up assessment. These patients had completed 1 year of fixed WHO-MDT without prior dapsone (DDS) monotherapy at CSSC. This study received informed consents from all patients and the study protocol was approved by the Ministry of Health, Myanmar.

Of the original 400 patients selected, 200 cases participated in the study while the others could not be reached mostly due to incorrect or unstable addresses. Each case was clinically reviewed to determine details of clinical presentation and slit skin smears were taken to identify the current bacterial status. The previous clinical and treatment records for each individual patient provided the baseline for evaluation of the present condition. Body charting was done to record new lesions and their nature and distribution. In suspected patients, histopathological examinations were conducted with routine and special stains to determine the nature of cellular infiltrates and the presence of acid-fast bacillus (AFB), and also to support Ridley–Jopling classification. Final evaluations were made with overall analysis of clinical and laboratory findings.

In the present study, relapse was defined by WHO criteria.² In brief, reoccurrence of the disease was inferred by the appearance of new skin lesions or an increase in the extent of lesions and by evidence on a skin smear of an increase in the bacterial index (BI) of two or more units and/or presence of viable bacilli (morphological index, MI) at any time after completion of a full course of treatment. Polymerase chain reaction (PCR) or animal testing was used to determine the presence of bacterial drug resistance in detected or suspected relapse cases according to the methods reported previously.³

RESULTS

Characteristics of the patients

The study included 200 cases (140 males, 60 females) with an age range of 9–87 years and a mean of 40.8 years (Table 1). The majority were adults. Half of the patients resided in suburban areas while one-third were from urban areas. The rest lived in

Table 1. Epidemiological characteristics of the patients

	<i>n</i>	%
Age		
0–15 years	5	2.5
16–50 years	123	61.5
>50 years	52	36.0
Gender		
Male	140	70
Female	60	30
Residence		
Urban	62	31.0
Suburban	106	53.0
Other areas	32	16.0
History of leprosy contact (present/past)		
Yes	37	18.5
No	163	81.5

Table 2. Intervals between completion of multidrug therapy and present evaluation

Periods after release from treatment	<i>n</i>	%
Within 1 year	26	13.0
1–2 years	49	24.5
2–3 years	33	16.5
Over 3 years	92	46.0

other townships in nearby divisions. Only 37 patients (18.5%) gave a history of leprosy contact.

Background of clinical status

All patients successfully completed a 1-year course of WHO-MDT for MB at CSSC. The intervals between treatment completion and present assessment varied from a few months to eight years (Table 2). Approximately half of the patients had completed MDT more than 3 years previously while a few patients (13.0%) were within 1 year of treatment release.

All were of the MB type and consisted of borderline tuberculoid (BT; 36.0%), mid-borderline (BB; 9.5%), borderline lepromatous (BL; 45.5%) and lepromatous leprosy (LL; 9.0%) (Table 3). Skin smears were positive in 131 (65.5%) patients at diagnosis. The majority (76.5%) had good drug compliance and completed 12 doses of MDT within 1 year. Drug compliance was fair in 31 patients (15.5%) who finished the MDT course within 16 months. Sixteen of the patients took irregular treatment.

According to clinical records, lepra reactions were very common and occurred in more than two-thirds

Table 3. Background clinical status and treatment compliance

	<i>n</i>	%
Types of leprosy		
BT	72	36.0
BB	19	9.5
BL	91	45.5
LL	18	9.0
BI status at diagnosis		
Negative	69	34.5
Positive	131	65.5
Compliance with MDT		
Good	153	76.5
Fair	31	15.5
Poor	16	8.0

BB, mid-borderline; BI, bacterial index; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous leprosy; MDT, multidrug therapy.

Table 4. Timing of lepra reactions

When reactions occurred	<i>n</i>	%
During MDT		
Reversal reaction	134	67.0
ENL	16	8.0
Total	150	75.0
At some point after release from treatment		
Reversal reaction	81	40.5
ENL	19	9.5
Total	100	50.0
At present assessment		
Reversal reaction	17	8.5
ENL	11	5.5
Total	28	14.0

ENL, erythema nodosum leprosum; MDT, multidrug therapy.

of patients during MDT and in half of the patients at some point after release from treatment (Table 4). Most reaction episodes occurred during MDT treatment up to a few months after cessation of MDT. The majority of reactions were reversal reactions (type 1) (67.0% during MDT, and 40.5% after completion of MDT). Erythema nodosum leprosum (ENL; type 2) reactions were seen in a few patients (8.0% during MDT, and 9.5% after release from treatment). Depending upon the severity and type of reactions, all patients with reactions were adequately treated with either prednisolone or clofazimine (CLF) or a combination of both.

Table 5. Skin and neural manifestations at follow up

	<i>n</i>	%
Skin lesions		
No skin lesion	90	45.0
Hypopigmented lesions	69	34.5
Skin color/dark brown/mixed colored lesions	19	9.5
Reddish skin lesions	21	10.5
Erythematous annular lesions	4	2.0
Infiltration (mostly mild and regressing)	38	19.0
Nodules (mostly mild and regressing)	7	3.5
Appearance of new lesion(s)	2	1.0
Extension of previous skin lesion(s)	7	3.5
Neural involvement		
Acute neuritis	10	5.0
Extension of previous neural lesion(s)	3	1.5

Table 6. Prevalence of reactions in relation to duration of time after release from treatment (*n* = 28)

Time gap after release from treatment	No. of patients with reactions	%
Within 1 year	12	6.0
1–2 years	10	5.0
2–3 years	3	1.5
>3 years	3	1.5

Present clinical status

Skin and nerve involvements of each patient were carefully assessed and compared to previous clinical findings. Initial skin lesions had completely disappeared at the time of the follow-up examination in nearly half of the patients (48.5%) (Table 5). Residual hypopigmented lesions were frequently observed (34.5%). Regarding active skin signs, reddish skin lesions (10.5%), infiltration (19.0%), nodules (3.5%), erythematous annular lesions (2.0%), onset of new lesion(s) (1.0%) and extension of previous skin lesions (3.5%) were observed (Table 5). In some patients clinical manifestations with more than one active sign were present.

With regard to nerve involvement, acute neuritis was seen in 10 patients (5.0%) while three patients (1.5%) had worsening or extension of previous neural involvement. Some of these patients had both active skin and nerve manifestations.

Additionally, reversal reactions and ENL were observed in 17 patients (8.5%) and 11 patients (5.5%), respectively (Table 4). These reactions were generally prevalent among the patients in the first 3 years after release from treatment (Table 6).

Table 7. Overview of patients at follow up

Clinical status	<i>n</i>	%
Inactive stage	172	86.0
Active stage		
Reaction	27	13.5
Relapse with reaction	1	0.5

Slit skin smears were taken from all patients and the results were compared with those taken at the time MDT was completed. It was found that the level of BI decreased in 90 patients (45.0%), while it was unchanged in 109 patients (54.5%). All patients who were initially negative in the skin smear assessment (69 patients, 34.5%) at the beginning of MDT were included in the latter group. One particular patient had an increased BI together with 1% morphological index (MI). Skin biopsies of the suspected relapse cases revealed regressive stages in most instances.

Overview

In conclusion, most cases (86.0%) were clinically quiescent (Table 7). Those presenting active skin and/or neuronal pathology were generally found among the patients who had complications arising from late reversal reactions or ENL. Among some lepromatous cases who had completed MDT recently, frequent findings of mild infiltration and nodules were generally in regressive states and were not regarded as active signs. While several cases were suspected of relapse, all except one failed to meet relapse criteria. Based on clinical, histological and bacteriological results, only one case (0.5% of total study population) was defined as relapsing with ENL and a full history was undertaken (see following).

Clinical history of the relapse case

A 22-year-old patient of LL type with widespread infiltrated papulonodular lesions, who initiated MDT in April 2004, was initially BI (≥ 4) and MI (1%). Drug compliance was fair and 12 doses of WHO-MDT for MB leprosy regimen were completed in June 2005. During MDT, mild reversal reactions occurred frequently and two courses of steroid were administered. At completion, BI was still 4 or more but MI was absent. Mild infiltrations and dactylitis were still

obvious and mild reversal reactions were also still present. After ceasing MDT, a low dose of steroid was continued to control reaction for several months. On his first annual follow-up visit (May 2006), he presented marked infiltration and numerous ENL with BI of 5 or more and MI 1%. Histopathological examination revealed the active phase of lepromatous leprosy, predominantly infiltrated with immature macrophages. Thus, a diagnosis of early relapse was made and MDT was restarted together with prednisolone and clofazimine. Slit skin smears were also subjected to PCR, which failed to reveal a mutation in drug-resistant genes. The case had no history of contact with active leprosy.

DISCUSSION

In this study, lepra reactions were, as is well known, common findings during MDT and at some times after release from treatment. At the time of present assessment, only a few reaction cases were prevalent. It was often difficult to distinguish relapse and reactions in some active cases, particularly when skin smears were negative. A study performed in India also found that differentiating relapse cases from reversal reactions could be difficult on both histological and clinical grounds.⁴ A study in China which included 425 cases 5 years after completion of fixed-duration MDT also revealed that reactions occurred more frequently during the first 6 months of MDT, decreasing gradually thereafter, and disappeared in the fourth year of surveillance.⁵ Seventy-seven patients treated with WHO-MDT for MB leprosy regimen for 12 months and additionally with four doses of *Mycobacterium w* vaccine were followed up for 3 years in a study in India. They found that reactions occurred more frequently after 6 months of therapy and that their frequency gradually decreased over a period of time but continued even 2 years after release from treatment.⁶ Thus, the present study confirmed that lepra reactions are similarly observed in Myanmar and that more attention needs to be paid even after treatment.

Because different criteria of relapse were applied in different study designs, relapse results could not be directly compared. For example, in a study conducted in Tamil Nadu, India, MB relapse was defined as an increase in the BI of 1 or more with or without

clinical evidence of activity and the relapse rate was 2.2% or 0.23/100 person years at a mean follow up of 9.26 ± 2.98 years/patient for 46 newly detected MB patients (BI, ≥ 3) who had completed a 2-year WHO-MDT.⁷ In the China study, the relapse rate for 35 MB patients with an initial BI of more than 4 with 5 years of surveillance was 0.24/100/year.⁵

In this study, one MB case showed severe ENL and was diagnosed as relapse 1 year after release from treatment. This patient suffered from frequent reversal reactions during MDT, and steroids had been administered during and after MDT therapy. Therefore, it is speculated that prolonged administration of steroid resulted in suppression of cellular immune reaction against *Mycobacterium leprae*. Such a change in immune reaction might be the cause of the transition from reversal reaction to the development of ENL. The incubation period of relapse of this case was shorter than the results of other studies that were conducted on patients following 2 years of WHO-MDT. In the Thailand study, mean relapse interval was 3–4 years,⁸ and 4–7 years in China.⁹ In a study in southern India, three cases relapsed with histoid nodules 12–15 years after release from treatment.¹⁰ In another Indian study, however, among three relapses of initially high BI, one occurred in the second year and the other two in the third year of follow up.⁶ With respect to a study in Mumbai, India, the mean interval between cessation of treatment and occurrence of relapse was significantly lower among the patients who had completed 12 months of MDT (6.8 years) compared to 24 months of MDT (9.4 years).¹¹ When a total of 58 cases of relapse were analyzed in a study in India, the majority of relapses occurred in the first 3 years after release from treatment.¹² The time interval between release from treatment and relapse ranged from 6 months to 13 years and the mean was 3.8 years in an Indian study.¹³ Also, a Belgian study found that early relapses occurred within 3.5 years of cessation of treatment with a mean incubation time of 22 months.¹⁴

The studies attributed inadequate treatment for early onset relapse, and “persisting” or “drug-resistant mutants” for late onset relapse.^{11,14} Re-infection may be one of the factors that contribute to late relapse.¹⁴ A study in West Bengal showed that a history of contact with an active leprosy patient and irregular treatment led more PB cases to relapse

than control cases.¹⁵ The possibility of re-infection was negligible in the present relapse case because clinical deterioration took place within 1 year of cessation of MDT and no contact with active leprosy patients was reported. Thus, the early relapse case identified in the present study may be due to inadequate treatment and not to drug-resistant mutation or re-infection.

The primary risk factors for relapse included BL or LL patients with a high BI initially in MB, and a large number of skin lesions and involvement of nerves in PB.^{15,16} A study conducted by Gelber *et al.* also concluded that relapse was largely confined to BL or LL patients with a high initial BI, and occurred long after the discontinuation of therapy.¹⁶ The relapsed case in the present study was BL with a high BI both at diagnosis and at completion of 1 year of fixed MDT. Therefore, BL or LL with high initial BI should be considered as a high risk of relapse. Thus in Japan, instead of 1-year WHO-MDT, 2–3-year treatment by RFP, DDS and clofazimine (MDT for MB) was recommended for high bacterial load MB cases depending upon their clinical response.¹⁷ However, a comparative study in Brazil performed on the initial and final bacillary indices of 128 MB patients who received 12 doses (MDT-WHO) and 85 MB patients who took 24 doses of (MDT-WHO) showed that the reduction in bacillary levels and mean bacillary indices at 24 months were similar in the two groups.¹⁸

Generally, the higher the initial BI, the longer the time required to reach bacteriological negativity.¹⁹ Because the incubation period of relapse for MB is generally longer, a study in China suggested clinicians should conduct annual follow ups for at least 5 years for PB and 10 years for MB patients after being released from WHO-MDT.²⁰ However, the study in India showed that the relapse rate declines with time after release from treatment.¹² Because the patients included in the present study were in different intervals from the point of release from treatment to present assessment, further follow up may be required to identify the actual magnitude of the relapse problem. While the results so far may not be sufficient to evaluate the impact of the 1-year WHO regimen for MB patients, it does suggest that it is important to follow up patients for at least 3 years following completion of MDT in order to detect possible lepra reactions and relapses.

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