OUTCOME OF TREATMENT IN LEPROSY REACTIONS

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Thematic paper
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ABSTRACT

This retrospective study was conducted to describe the nature of leprosy reactions and their treatments, to determine the incidence rates of leprosy reactions, to determine responses to treatment for leprosy reactions, and to describe the disability grading pre- and post-treatment for these reactions. The medical records of patients treated in the Leprosy Clinic of Raj-Pracha Samasai Institute, from October 1998 to September 2005, were reviewed. Of 420 patients, 222 (52.9%) treated with multidrug therapy (MDT) had reactions; of the latter, only 158 were eligible for this study.

The incidence rate for leprosy reactions was 52.9%. 83.5% of patients with reactions had multibacillary leprosy (MB). The incidence rates for reversal reactions (RRs) and erythema nodosum leprosum (ENL) were 57.0 and 24.1%, respectively. 61.3% of patients with reactions had neuritis.

Prednisolone was used for all patients with reactions, with a mean prednisolone treatment duration of 8.2 ± 8.6 months. The majority of patients treated with prednisolone improved, but a few cases died or worsened. In those cases, tuberculosis and malignancy were included. Thalidomide was used for three patients refractory to prednisolone treatment, and efficacy was confirmed for every thalidomide case.

The incidence of side-effects (mostly attributable to prednisolone) was only 8.9%, but since significant side-effects did occur, so that close attention is required.

The pre- and post-MDT disability gradings for patients with reaction were the same, but examination of grading changes for these cases showed greater deterioration among patients with reactions than among patients without.

These findings showed that most patients with reactions improved with prednisolone treatment and the side-effects were few. Earlier detection of leprosy, and reactions, are needed because of worsened disability among patients with leprosy reactions.

KEY WORDS: LEPROSY REACTIONS / PREDNISOLONE / NEURITIS / DISABILITY GRADING

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LIST OF ABBREVIATIONS

Abbreviation	Term
AFB	Acid fast bacillus
ALP	Alkaline phosphatase
BB	Mid-Borderline Leprosy
BI	Bacteriological index
BL	Borderline Lepromatous Leprosy
BT	Borderline Tuberculoid Leprosy
BUN	Blood urea nitrogen
CDC	Center for Disease Control and Prevention
EHF	Eyes, hands and feet score
ENL	Erythema nodosum leprosum
GOT	Glutamate oxaloacetate transaminase
GPT	Glutamate pyruvate transaminase
Hb	Hemoglobin
Hct	Hematocrit
HIV	Human immunodeficiency virus
I	Indeterminate Leprosy
ILEP	The international federation of anti-leprosy association
INF	Impaired nerve function
J - P	Ridley-Jopling classification
LFT	Liver function test
LL	Lepromatous Leprosy
MB	Multibacillary leprosy
MDT	Multidrug Therapy
No.	Number
PB	Paucibacillary Leprosy
RR	Reversal Reaction
SD	Standard deviation
TB	Tuberculosis

LIST OF ABBREVIATIONS (Continued)

Abbreviation	Term
TT	Tuberculoid Leprosy
WBC	White blood cell
WHO	World Health Organization

CHAPTER I
BACKGROUND

Leprosy affects skin, peripheral nerves, and organs such as eye, nose, ear and testis. Those disorders may progress to disfigurements of body surface, motor and sensory nerve disturbances and many kinds of disabilities. Those were main causes of discrimination for leprosy patients from societies since ancient times. Although the specific treatments for leprosy have recently established and World Health Organization (WHO) has advocated that leprosy would be eliminated in the near future, still new infections occur steadily and patients remain with disabilities. Therefore, early detection and adequate treatments of leprosy patients and long standing care for prevention of disabilities were very important.

WHO has been working on the strategy to eliminate leprosy since 1991. Elimination is defined as a reduction in the prevalence of leprosy patients who are registered as receiving multidrug therapy (MDT) to less than 1 per 10,000 populations (WHO, 1991). Since it declared that leprosy would be eliminated from the world by 2000, this target had been attained at global level. There were 597,232 cases registered for treatment globally, with 719,330 cases detected during the 2000, resulting in a global prevalence of just below 1 per 10,000. But in annual case detection the number was not so different from 1994 to 2000 around 500,000 to 800,000 (WHO, 2002). It means that leprosy infection still continues nowadays too. In the beginning of 2005 registered cases were 286,063 and new cases detected during 2004 were 407, 791. In the beginning of 2005, 12 countries still was yet to reach the elimination goal. Of those countries India and Nepal were Asian countries (WHO, 2005).

In Thailand the registered cases of the beginning of 2005 were 1,440 (0.2/10,000) and new cases detected during 2004 were 652 (WHO, 2005). Thailand reached to the

elimination goal (prevalence rate less than 1 per 10,000) in 1994. Both prevalence and new cases detected have decreased steadily in Thailand.

On the course of leprosy at times the patients may be disturbed by the sudden onset of new signs and symptoms. These are considered as leprosy reactions (Sehgal, 2004). The reactions were divided into two categories: reversal reactions (Type1 reactions) occur in usually borderline (borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB) or borderline lepromatous leprosy (BL)) patients and erythema nodosum leprosum (ENL or type2 reactions) occur in borderline lepromatous(BL) and lepromatous(LL) patients. Type1 reactions are caused by delayed hypersensitivity (type4 cell mediated hypersensitivity of Gell and Coombs) (Virendra N Sehgal, 2004). ENL is thought to be immune-complex disorder (type3 hypersensitivity (allergic) reaction of Gell and Coombs). Both types of reactions are more common during treatment with MDT but may also occur before or after completion of MDT. If the reactions are not treated promptly, they cause motor and sensory loss that leaves the stigmata such as disfigurements on face or extremities.

The key of successful management of leprosy reactions is early diagnosis and initiation of anti-inflammatory treatments. The possible precipitating factor of the reactions should be removed and MDT should not be discontinued. First lined drug for treatment of leprosy reactions is corticosteroids (prednisolone). WHO recommended dose of prednisolone for adult as follows: 40mg for 2 weeks, then 30, 20, 15, 10, 5mg each 2weeks, total of 12weeks in fields (WHO, 1998). According to severity of the reactions dose of prednisolone should be raised to maximum 1mg per Kg body weight and the duration may be up to 6 months (ILEP, 1997). In severe cases or refractory cases, other medicines are needed such as high dose of clofazimine, thalidomide, pentoxifylline and other immune-suppressive agents (Moreira, et al., 1998). With prolonged use of prednisolone untoward effects should be aware. With steroid therapy for the reactions (type1 and 2) adverse effects such as moon face, steroid acne, gastritis, peptic ulcer (including perforated ulcer), fungus infection of the skin, cataract, diabetes, tuberculosis and osteoporosis were reported (Sugumaran, et al., 1998; Richardus, et al., 2003).

Impairment in sensory and motor nerves, skin and eye cause nerve function loss, visual loss, skin ulcers etc. If these impairments develop, the patients may have permanent deformities such as claw hands, foot drops, disfigurements or loss of hands and feet, blindness, and nose and ear destruction. These impairments and deformities lead to disabilities in leprosy.

When leprosy reactions occur in the course of leprosy, the development of those disabilities may be facilitated. Because the prevention of the occurrence of the reactions is very difficult, detecting the reactions early and treating properly for the prevention of the disabilities are very important.

Because Raj-Pracha Samasai Institute is tertiary referral center for leprosy in Thailand, many symptomatic leprosy with or without reactions are referred to the institute. Therefore the institute is most suitable for analyzing leprosy reactions in Thailand. The analyzing of leprosy reactions has not been updated more than several years since Shreuder PA's study, 1998 in northeastern Thailand.

CHAPTER II
OBJECTIVES

PRIMARY OBJECTIVE

The primary objective of this study is to describe the nature of leprosy reactions and their treatments in Raj-Pracha Samasai Institute.

SECONDARY OBJECTIVES

1. To determine incidence rate of leprosy reactions.
2. To determine the response of the treatments for leprosy reactions.
3. To describe the disability grading before and after treatment of the reactions.

CHAPTER III
REVIEW OF THE LITERATURE

Classification of leprosy

Mycobacterium leprae primarily attacks the skin, mucous membranes of the nose, and peripheral nerves. There is a continuous spectrum of disease between the two polar forms, tuberculoid and lepromatous leprosy, which depends on the ability of the body to mount an immune response to the invading bacilli. It is important to accurately classify cases by both clinical and histological assessment, as their position on this spectrum determines infectivity, prognosis, disease complications and treatment regimens (Northern Territory Government of Australia, 2002).

1. The Ridley-Jopling system

In the Ridley and Jopling system, there is a progression from the mildest to the more disseminated form of disease (Ridley and Jopling, 1962).

TT has been the commonest type in the past, making up more than a third of the cases. These cases have a well developed cell mediated immunity and a very low bacillary load (paucibacillary or PB). There are single or few skin lesions, which are hypopigmented patches, with a well defined, but irregular, and often slightly raised border. The lesions are non-sweating, have decreased hair, and decreased sensation. Peripheral nerve damage usually only occurs in one or two nerves and is asymmetrical, but the damage is severe, with accompanying swelling. Diagnosis depends on clinical examination and biopsy, as smears are usually negative.

LL is less common, but is a more serious and disabling disease. There is loss of leprosy specific cell mediated immunity, with no check on multiplication and spread of bacilli. There is therefore wide dissemination and a very high bacillary load (multibacillary MB). The skin lesions are extensive, presenting as erythematous nodules or maculae, which may resemble urticaria. There is little depigmentation, and usually no sensory loss in the lesions. In some cases the skin can be diffusely smooth

and shiny (infiltration), with no discrete lesions. The forehead and earlobes become thickened, and the eyebrows become thin, particularly laterally, and are eventually lost (madarosis). There is infiltration of the mucous membranes of the nose and mouth. The nasal septum can also be destroyed. Other organs such as the liver, spleen, eyes and testes can be involved. Some patients have gynaecomastia. Reactional episodes are also common. There is involvement of numerous peripheral nerves which is usually symmetrical, but often not as severe as in tuberculoid leprosy.

BB, BT, and BL lie in the middle of the spectrum between TT and LL. When there are few skin and peripheral nerve lesions the classification is borderline-tuberculoid (BT) leprosy. When there are many skin and peripheral nerve lesions it is classified as borderline-lepromatous leprosy (BL).

2. WHO classification

Leprosy can be classified on the basis of clinical manifestations and skin smear results. In the classification based on skin smears, patients showing negative smears at all sites are grouped as paucibacillary leprosy (PB), while those showing positive smears at any site are grouped as having multibacillary leprosy (MB). However, in practice, most programs use clinical criteria for classifying and deciding the appropriate treatment regimen for individual patients, particularly in view of the non-availability or non-dependability of the skin-smear services. The clinical system of classification for the purpose of treatment includes the use of number of skin lesions and nerves involved as the basis for grouping leprosy patients into multibacillary (MB) and paucibacillary (PB) leprosy.

WHO classification of leprosy (WHO expert committee, 1997)

Type of leprosy	**Single lesion PB**	**PB**	**MB**
Number of skin lesions	1	2 to 5	6 or more
	AND	AND	OR
Skin smears	Negative at all sites	Negative at all sites	Positive at any site
Ridley-Jopling Correlation	I. TT. some BT	TT. most BT	Some BT. BB.BL.LL

Diagnostic criteria

WHO defined the diagnosis criteria of leprosy as follows (WHO, 1998).

A case of leprosy is a person having one or more of the following features, and who has yet to complete a full course of treatment:

(1) Hypopigmented or reddish skin lesion(s) with definite loss of sensation.

(2) Involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation.

(3) Skin smear positive for acid-fast bacilli.

The case definition includes retrieved defaulters having signs of active disease as well as relapsed cases that have previously completed a full course of treatment, but does not include cured persons with late reactions or residual disabilities.

Treatment of leprosy

Multi-drug therapy (MDT) in diagnosed cases is the key to achieving cure in the individual and breaking the cycle of transmission. Recommended regimens for treatment have been based on those of the WHO Study Group on the Chemotherapy of Leprosy in 1994. If a patient has a positive skin smear, regardless of clinical classification, or if the classification is in doubt, treatment should be MDT for multibacillary disease (WHO, 1994).

Multibacillary leprosy

For adults the standard regimen is:

Rifampicin: 600 mg once a month

Dapsone: 100 mg daily

Clofazimine: 300 mg once a month and 50 mg daily

Duration= 24 months

Paucibacillary leprosy

For adults the standard regimen is:

Rifampicin: 600 mg once a month

Dapsone: 100 mg daily

Duration= six months

Although in 1994 recommendation the treatment duration of MB was 24 months, The 7th Expert Committee noted that the recommendation of 24 months of therapy for

MB remains valid but indicated that 12 months might be sufficient without increasing the risk of rifampicin resistance (WHO, 1997).

Leprosy reactions

Reactions may occur in 25% or more of all borderline and lepromatous patients at some time during the disease, most commonly when the patient is on therapy (Jacobson RR et al., 1999). Kumar B et al., 2004 reported that 30.9% of leprosy patients who have reactions presented with reactions at the time of first visit. The cumulative incidence of RR and ENL are 33% and 22.5% respectively. A majority of RR occurred during first 6 months after starting MDT whereas, ENL occurred in the second or third year after starting MDT. Patients with RR and ENL had 29.4% and 64.4% of recurrence rate (Kumar B et al., 2004). In the study from Thailand 53% of the BL and 42% of LL who had severe reactions had or developed one or another serious complication in need of steroid treatment (Shreuder PA, 1998).

Diagnosis criteria of reactions

Although there are no definite criteria of leprosy reactions, the case definition as followings is generally used as suggested by Nery JA et al., 1998.

Reversal reactions (RR)

RR is diagnosed if the patients have some of the following criteria. : the sudden and abrupt appearance of erythema and the swelling and tenderness of previously existing skin lesions; the appearance of new erythematous skin lesions; the occasional occurrence of edema on the face, hands or feet; pain and/or functional impairment of nerves; and disseminate cutaneous hyperesthesia.

Erythema nodosum leprosum (ENL)

ENL is diagnosed according to the following criteria: presence of painful isolated or disseminated dermal erythematous nodules, with or without systemic involvement, as, for example: fever and malaise, swollen nerves and pain, myalgia, lymphadenitis, epididymoorchitis and/or edema.

Definition of severity in reactions (RR, ENL)

Tamplin M et al. defined the severity of reactions as follows (Tamplin M et al., 2002). In case of severe reactions, cautious attention should be paid on the patient's conditions.

Mild

Occurs in skin only (as long as it dose not occur over a major nerve or in the face); there maybe mild fever and slight swelling (edema) of the limbs.

Severe

Pain or tenderness in the nerves.

New loss of feeling.

New muscle weakness.

Reaction in a skin lesion lying over a major nerve.

Reaction in a skin lesion on the face.

Signs of inflammation in the eye.

Severe edema of the limbs.

Involvement of other organs, such as testes, lymph nodes or joints.

Ulceration of skin lesions.

Definition of Neuritis

Neuritis is inflammation of a nerve presenting with any of the following: spontaneous nerve pain, paresthesia, tenderness, sensory, motor, or autonomic impairment of resent onset (Smith C et al., 2002). Neuritis is considered as a part of reactions and needs the treatments with corticosteroids.

Silent neuropathy

Silent neuropathy is a neuropathy with motor and/or sensory impairment, but without complains of nerve pain, paresthesia or nerve tenderness on palpation. It dose not refer to the chronic insidious destructive neuropathy of LL, but rather to the episodes of neuropathy that cause clinical nerve damage within a relatively short period (weeks to months) (Snathanam A, 2003).

With the difficulty to classify the silent neuropathy as either RR or ENL, in some studies to research for reactions, the cases of silent neuropathy are excluded. (Nery JA et al., 1998).

Relapse in leprosy

Because leprosy reactions may occur even after MDT, it is important to differentiate reactions from relapse. Even after appropriate MDT some cases keep positive in skin smear test; but they are not called as relapse, at times the differentiation is very difficult. Clinical features of relapse are resembled to RR.

Criteria for diagnosis of relapse; Increase in the extent of lesions, infiltration and erythema, fresh skin and nerve lesions, positive skin smears for AFB in previously negative cases; and in bacteriological positive cases during surveillance, an increase in BI by two logs at any site over the previous in two successive examinations (Richardus JH et al., 1996).

Disability in leprosy

The leprosy patients have already disabilities due to damage to peripheral nerves at the time of diagnosis and the disability status may change through the course of the leprosy. The rate of disability varies among the reports. In a study in Bangladesh, 9.8% of PB, 37.6% of MB had disabilities at the time of registration (Richardus JH et al., 1996). In an urban leprosy clinic in India, 35% of all evaluated patients had disabilities (Singhi MK et al., 2004). In an Amazon region of Brazil at the start of treatment, 20% of the PB and 37% of the MB patients had disabilities (De Oliveira CR, et al., 2003).

The WHO disability grading system is frequently used as method to evaluate impairment grade in leprosy patients. Since 1960, WHO has advocated the use of grading system in leprosy and has revised the grading system. The grading system used at presented was updated in 1998.

WHO disability grading system 1998

Hands and Feet
Grade 0: No anesthesia, no visible deformity or damage
Grade 1: Anesthesia present, but no visible deformity or damage
Grade 2: Visible deformity or damage present
Eyes
Grade0: No eye problem due to leprosy; no evidence of visual loss
Grade1: Eye problem due to leprosy present, but vision not severely affected as a result of these (vision 6/60 or better; can count fingers at six meters).
Grade 2: Severe visual impairment (vision: worse than 6/60; inability to count fingers at six meters), also includes lagophthalmos, iridocyclitis, and corneal opacities.

The maximum grade of any of these sites is used as an indicator of the leprosy patient's impairment status.

Treatment of reactions

Reversal reactions (type 1 reactions) manifest clinically with erythema and edema of skin lesions and tender peripheral nerves. Loss of nerve function can be dramatic (Britton WJ et al., 2004). The treatment of reactions is aimed at controlling acute inflammation, easing pain, reversing nerve and eye damage. MDT should be continued. Neuritis (nerve tenderness, new anesthesia, and/or motor loss) or moderately inflamed skin lesions should be treated with corticosteroids. The expected recovery rate for nerve function is 60–70%. Recovery is less in patients with pre-existing impairment of nerve function or with chronic or recurrent reactions (Britton WJ et al., 2004). Other immunosuppressant drugs might have a role in treating reactions. In a study in Nepal, patients had equivalent outcomes whether treated with an azathioprine/prednisolone combination or prednisolone alone (Marlowe SNS et al., 2004).

ENL can start during the first or second year of antimicrobial therapy and can relapse intermittently over several years. It is difficult to treat, necessitating repeated courses of corticosteroids. High dose of clofazimine has a useful anti-inflammatory effect in ENL and can be used at 300 mg daily for several months (Burte NP, et al., 1983). Thalidomide (300-400 mg daily) is better than steroids in controlling ENL and

is the drug of choice for young men with severe ENL (Jakeman P et al., 1994). Because of its well known effects of teratogenesity, thalidomide should not be used to women who are possible age of pregnancy. Pentoxifylline, which inhibits TNF alpha production, has been used to treat ENL but was inferior to both thalidomide and steroids (Moreira AL et al., 1998).

Prednisolone treatments in leprosy reactions

There is no clear consensus about optimum regimen of corticosteroids for treatments of leprosy reactions and no randomized controlled trials have been reported comparing regimens of differing dose and duration (CDC Northern territory, 2002).

Prednisolone is first line drug for treatment of leprosy reactions (RR and ENL). The initial dose is 40mg tapered to stop in duration of 12 weeks in field base and up to maximum 1mg/kg/day in hospital base (WHO, 1998). But there is concern that the dose may be insufficient and the relatively short duration could allow recurrence of NFI (CDC Northern territory, 2002). There are some studies in which longer duration of prednisolone treatments was advised for suppression of recurrences or prevention of INF. Naafs B, 2003 mentioned that type leprosy reaction should be treated with prednisolone for a longer period than the 12 weeks, advised by the WHO. In the study of northeastern Thailand (Schreuder PA, 1998), average duration of prednisolone treatment for RR was 5 to 6 months. In the study after standard regimen of WHO, 15 to 20 mg of prednisolone was continued for an additional month or more. In the study by Poche, Paul W, 1998, the average duration of prednisolone treatment was 15.8 weeks and the result was effective for improvement of nerve damage and it was advised that extended prednisolone treatment should be on the basis of the extent of involvement of nerves. In the study by Sugumaran DS, 1997, the duration of prednisolone treatment in paralytic deformities in leprosy was 4-9 months in BT, 6-12 months in BB and 6-24 months in BL.

With long duration of prednisolone treatments in leprosy reactions, side effects or complications could be encountered. In the study by Sugumaran DS, 1997, the complications were moon face, steroid acne, cutaneous fungal infection, cataract and gastritis. Most severe and important complications were perforated peptic ulcer,

steroid induced diabetes and tuberculosis. Smith WC et al., 2004, has shown similar results of complications in prednisolone treatments for four months.

CHAPTER IV
MATERIALS AND METHODS

1. Study design

This study was a hospital-based retrospective study.

2. Study site

This study was conducted at Raj-Pracha Samasai Institute of Samutprakan province in Thailand from 14 NOV 2005 to 6 JAN 2006.

3. Study population

Patients with leprosy reactions who were treated at Raj-Pracha Samasai Institute from 1999 to 2005.

4. Inclusion criteria

1) The patients who were diagnosed as leprosy reactions or neuritis with clear signs and symptoms.

2) The patients who are taking MDT properly as scheduled or had completed MDT.

3) The patients who were followed up at least 6 months after starting of first reaction.

5. Exclusion criteria

1) Patients who dropped from MDT or could not take MDT for the designated period.

2) Patients who had relapsed after completing of MDT or dapsone monotherapy..

3) Patients who were lost to follow up.

4) Patients whose medical records were not taken or preserved adequately (referred to or from other institutions or part of records are not available)

6. Definition of neuritis

1) When "neuritis" was put as valuable along with RR, ENL in this study, the "neuritis" meant a type of the leprosy reactions with pain or tenderness on the nerves, or localized neurological signs, symptoms without skin lesions of leprosy reactions.

2) When "neuritis" was referred as to signs and symptoms of leprosy reactions in this study, the "neuritis" meant one of the complications of the leprosy reactions with or without skin lesions of reactions.

7. Definition of new episode of leprosy reactions

New episode meant new reaction that occurred after one month of stopping the treatment of previous reaction.

8. Sample size estimation

When the sample size is calculated by prevalence rate of reactions, it is 322. (Prevalence 30%, the information from Ministry of Public Health of Thailand).

$$N = \frac{(1.96)^2 \times p \times (1-p)}{(0.05)^2} = 322$$

(p = prevalence of leprosy reactions)

9. Methods

1) Medical records of patients visiting leprosy clinic from 1999 to 2005 were reviewed.

2) Records of patients on MDT were identified.

3) Records of patients with reactions were selected.

4) Only patients who met the eligible criteria were selected.

10. Data analysis

The data with qualitative variables was summarized and expressed as frequency and percentage and statistical analysis was performed using Chi-square test.

The quantitative variables were expressed as mean and standard deviation (SD) and the quantitative variables with non-normally distributed were expressed as median, minimum and maximum. Statistical analysis for quantitative data was performed using student's t test or one way ANOVA. A p value of less than 0.05 was considered statistically significance.

CHAPTER V
RESULTS

Medical records of patients who were treated in leprosy clinic of Raj-Pracha Samasai Institute from October 1998 to September 2005 (In the system of government, fiscal year starts from October, therefore, in this study 1998 was referred to as 1999.) were reviewed. Number of total medical records was 1295 from which patients who were treated with MDT were selected (referred as active case or active patient in this study). Number of total active patients was 420 (shown in Figure 1). Patients were divided in three groups which were patients with leprosy reactions (222), patients without leprosy reactions (146) and unknown group (52). In unknown group the presence of reactions was not confirmed due to uncompleted records (but at least there is no evidence of reactions). From the number of 222 patients with reactions, incidence rate of reactions was calculated and for further analysis of treatments in leprosy reactions, 64 patients were excluded according to exclusion criteria in this study. Remaining patients (158) was analyzed in detail for treatments of leprosy reactions.

Demographic and baseline characteristics

Sex and age

In total active patients of 420, males were 267 (63.6%), females were 153 (36.4%). In patients with reactions males and females were 144 (64.9%) and 78 (35.1%) respectively. Mean age was 42.8 years in total active patients and 41.4 years in patients with reactions. There was no significant difference in sex and age among patients groups (patients with, without reaction and unknown group) (shown in Table 1).

Classification of leprosy

In total of 420 patients, PB and MB patients were 151 (36.0%) and 266 (63.3%). In patients with reactions, PB and MB were 33 (14.9%) and 187 (84.2%). In patients

without reactions, PB and MB were 97 (66.4%) and 49 (33.6%). Incidence of reactions was much higher in patients with MB than PB.

In Ridley-Jopling classification, the incidence of reactions was higher in patients with BB, BL and LL than in TT, BT.(shown in Table 1).

Bacterial index (BI)

Mean BI of total 420 patients was 1.10 ± 1.56. Those of patients with and without reactions were 1.66 ± 1.67 and 0.42 ± 1.07 respectively (shown in Table 1).

Place of birth

In total of 420 patients, 53% of patients were from the central region, 28% from northeast, 9% from the north, 6% from the east, 3% from the south and 1% from foreign countries (shown in Table1 and Figure 2).

Incidence rate of reactions

Incidence rate of leprosy reactions was 52.9% (222) of total active patients (420) who were treated in Raj-Pracha Samasai Institute from 1999 to 2005. The incidence of the reactions in PB was21.9% whereas that of MB 70.3 %.(shown in Table 1 and Figure 1, 2, 3).

Status of patients with reactions

Majority of status in patients with reactions was “new”, 184 (82.9%). “New” meant patients who had taken MDT for first time. There were few other statuses. “Reinstate” meant patients who had taken MDT with poor compliance; therefore the MDT was started again from the beginning. “Discharged from MDT” meant patients who had completed a course of MDT, leprosy reactions occurred after completing it. “Relapse” meant patients who had completed MDT or dapsone monotherapy but leprosy recurred (shown in Table 2).

Exclusion from evaluation for leprosy reactions

The reasons for exclusion from further evaluation of leprosy reactions and the number of patients who were excluded are shown in Table 3. Sixty-four patients were excluded from this study. The main reasons for exclusion referred from other

institutions (23.4%), not adequate or absent records (21.9%) and lost to follow up (20.3%).

Demographic and baseline characteristics of patients included and excluded

Sex and Age

In included and excluded cases, males and females were 102 (64.6%), 56 (35.4%) and 42 (65.6%), 22 (34.4%) respectively. Mean age was 41.0 ± 16.8 and 42.3 ± 15.3 in both groups respectively (shown in Table 4). In sex and age, there was no significant difference between included and excluded cases.

Type of leprosy

There was no significant difference between included and excluded cases when patients were classified by either WHO or Ridley-Jopling classification (shown in Table 4).

BI

BI was 1.56 ± 1.65 and 1.93 ± 1.71 in included and excluded cases. There was no difference between both groups (shown in Table 4).

Type of leprosy and reactions

WHO classification

In PB, incidence of RR and ENL was 73.1% and 0.0% respectively. In MB, incidence of RR and ENL was 53.8% and 28.8% respectively. There were smaller numbers of neuritis and RR + ENL (shown in Table 5). “RR + ENL” mean patients who had both types of reactions in their course of reactions.

Ridley-Jopling classification

TT, BT and BB had no ENL, whereas BL, LL had both types of reactions (shown in Table 6).

Onset of the first reaction

Majority of PB (84.6%) and MB (53.8%) had first reaction at the time of registration (It meant that they had reactions before starting of MDT). The first reaction during MDT occurred in MB than PB (shown in Table 7).

RR (64.4%) and ENL (57.9%) had first reaction at the time of registration. In any time of onset, there was no difference between RR and ENL (shown in Table 8).

Number of episodes of leprosy reactions

The majority of patients had single (53.8%) or two episodes (29.1%) of reactions. This trend was same in RR and ENL patients (shown in Table 9).

Drugs of leprosy reactions

Prednisolone was given to 158 patients. Thalidomide was given to 3 patients. Trental (Pentoxifylline) was given to 5 patients. (Two of them were combined with thalidomide). High dose of clofazimine was given to 38 patients /158 (24.1%). (RR13, ENL18, Neuritis2, RR + ENL5).

Prednisolone treatment

Prednisolone doses

Table 10 shows median doses of initial prednisolone from first to fifth episode. Majority patients had taken prednisolone 20 to 40 mg/day. Maximum prednisolone doses were 30 to 40mg (shown Table 11). “Initial prednisolone” means a dose which was given as first medication in each course of treatment. “Maximum prednisolone” means dose which was given as maximum dose during the course of the treatment. One hundred and fifty eight patients had 267 episodes of reactions. The mean initial and maximum doses of prednisolone in the 267 episodes were 25.9 ± 13.0 and 29.9 ± 14.1 months respectively (shown in Table 13).

The comparison of doses of prednisolone (initial and maximum) in first episodes by year of medical records was shown in Table 16. The prednisolone was given at high dose in the years 2002 to 2005 than 1999 to 2001.

Duration of prednisolone treatment

Table 12 shows mean durations of prednisolone treatments from first to fifth reaction. The durations were 4.2 to 10.3 months. Only in first episode, there was a significant difference in duration of treatment among the different type of reactions.

The duration of neuritis was the shortest (6.7 ± 4.1) and that of ENL was the longest (13.9 ± 12.9). Mean duration of 267 episodes was 8.2 ± 8.6 months (shown in Table 13). "Total duration" means the sum of durations of all episodes in one patient. The mean total duration was 13.7 ± 11.1 months (shown in Table 14). There was significant difference among the different type of reactions and the total duration of treatment (shown in Table 14). There was positive correlation between mean maximum doses of prednisolone and duration in 267 episodes. It meant the higher the maximum doses of prednisolone , the longer the duration of prednisolone treatment in each episode .There was negative correlation between mean maximum doses of prednisolone in first episodes and number of episodes in 158 patients. The higher the maximum doses of prednisolone in the first episodes, the fewer the number of episodes of reactions (shown in Table 15).

When compare the total duration of prednisolone treatments between patients with and without high dose of clofazimine in MB, the mean total duration of treatment with high dose of clofazimine (No. of patients, 36) was 18.4 ± 14.5 months and the one without high dose clofazimine (No. of patients, 96) was 14.1 ± 9.7 months. (P value 0.053, Student's t-test).

Outcome of treatment

Majority of reactions improved (248/267 episodes) (shown in Table 17 and 18). The improved rate of leprosy reactions after treatment was not significantly different among any types of reaction nor any types of leprosy. There were four cases of death and two cases of "worsened" (shown in Table 19 and 20).

Disability grading

Number of patients with reactions whose disability grading were recorded before and after MDT was 107 patients, whereas in patients without reactions, the number was 71 patients.

Disability grading before and after MDT

The rate of patients with disability (grade 1 or 2) in the reaction group at the time of registration (before MDT) was 46.7% (grade1: 22.4%, grade2: 24.3%). There was

no difference in disability grading between patients with and without reactions (shown in Table 21).

The rate of patients with disability (grade 1 or 2) in reaction group after MDT was 48.6% (grade1: 26.2%, grade 2: 22.4%). There was no difference in disability grading between patients with and without reactions (shown in Table 22).

Changing of disability grading before and after MDT

In patients with reactions, the disability grading of 13 patients (12.1%) were deteriorated after MDT, whereas in patients without reactions, the disability grading was the same before and after MDT (shown in Table 23).

Definition of EHF score: Disability grading of eyes, hands and feet was summed up to form total score (minimum 0, maximum 12). The EHF score was also deteriorated after MDT in 22 patients (20.6%) with reactions, whereas in patients without reactions, the EHF score was deteriorated in 5 patients (7.0%) (shown in Table 24).

Neuritis

Neuritis was present in 92 of 150 patients (61.3%) of patients with leprosy reactions. In different types of reactions and different types of leprosy, there was no difference in the occurrence of neuritis (shown in Table 25 and 26).

The most affected nerves were ulnar nerve (60 nerves), peronial nerve (30) and post tibial nerve (26) (shown in Figure 6).

Signs, symptoms

Table 27 shows the signs and symptoms of the leprosy reactions, apart from specific signs such as erythema nodosum leprosum (ENL) or edematous erythema of RR were present in 58 of 158 patients (36.7%). Frequent signs, symptoms were edema, eye involvement, fever, foot or hand ulcer, body pain and foot drop.

Complications

Thirty four of 158 patients (21.5%) had complications (shown in Table 28). Neuritis was not included in the table. Frequent complications were upper respiratory infection and anemia.

Side effects of treatments in leprosy reactions

Fourteen of 158 patients (8.9%) had side effects (shown in Table 29). Frequent side effects were steroid dependent and steroid acne.

Precipitating factors for leprosy reactions

Eleven of 158 patients (7.0%) had precipitating factors (shown in Table 30). Frequent precipitating factor was dental carries.

Underlying diseases

Twenty-two of 158 patients (13.9%) had underlying diseases (shown in Table 31). Frequent underlying diseases were diabetes mellitus, hypertension and liver disease.

Laboratory examination

There were no significant abnormalities except for mild anemia (shown in Table 32).

Table 1: Demographic characteristics and classification of leprosy

		With reaction	Without reaction	Unknown		Total
No. (%)		222(52.9)	146(34.8)	52(12.4)		420(100)
Sex					$p^{*} = 0.821$	
	Male	144(64.9)	90(61.6)	33(63.5)		267(63.6)
	Female	78(35.1)	56(38.4)	19(36.5)		153(36.4)
Age (yrs.)						
(mean ± SD)		41.4 ± 16.3	44.3 ± 18.9	44.6 ± 16.4	$p^{**} = 0.197$	42.8 ± 17.3
	≤15	6(2.7)	10(6.8)	1(1.9)		17(4.0)
	16-30	62(27.9)	30(20.5)	11(21.2)		103(24.5)
	31-45	70(31.5)	37(25.3)	15(28.8)		122(29.0)
	46-60	46(20.7)	36(24.7)	15(28.8)		97(23.1)
	61-70	37(16.7)	29(19.9)	9(17.3)		75(17.9)
	≥71	1(0.5)	4(2.7)	1(1.9)		6(1.4)
Place of						
birth	Central	105(47.3)	80(54.3)	31(59.6)		216(51.4)
	Northeast	64(28.8)	37(25.3)	11(21.2)		112(26.7)
	North	22(9.9)	12(8.2)	4(7.7)		38(9.0)
	East	11(5.0)	12(8.2)	0(0.0)		23(5.5)
	South	7(3.2)	2(1.4)	2(3.8)		11(2.6)
	Foreign	3(1.4)	2(1.4)	1(1.9)		6(1.4)
	Not recorded	10(4.5)	1(0.7)	3(5.8)		14(3.3)
WHO					$p^{*} = 0.000$	
Classification	PB	33(14.9)	97(66.4)	21(40.4)		151(36.0)
	MB	187(84.2)	49(33.6)	30(57.7)		266(63.3)
	Not recorded†	2(0.9)	0(0.0)	1(1.9)		3(0.7)
R - J						
Classification	TT	5(2.3)	39(26.7)	6(11.5)		50(11.9)
	BT	59(26.6)	74(50.7)	24(46.2)		157(37.4)
	BB	19(8.6)	1(0.7)	3(5.8)		23(5.5)
	BL	55(24.8)	11(7.5)	5(9.6)		71(16.9)
	LL	81(36.5)	18(12.3)	11(21.2)		110(26.2)
	Indeterminate	0(0.0)	3(2.1)	2(3.8)		5(1.2)
	Neural	3(1.4)	0(0.0)	1(1.9)		4(1.0)
BI		1.66 ± 1.67	0.42 ± 1.07	0.65 ± 1.29	$p^{**} = 0.000$	1.10 ± 1.56

∗ Chi square, ∗∗ One way ANOVA
† excluded from statistical analysis.

Table 2: Status of leprosy patients with reactions

Status	No. of patients	Percent
New	184	82.9
Relapse after DDS	9	4.1
Relapse after MDT	7	3.2
Reinstate	6	2.7
Discharged from MDT	2	0.9
Not recorded	14	6.3
Total	222	100.0

Table 3: Reasons of exclusion from evaluation for leprosy reactions

Reasons of exclusion	No. of patients	%
Referred from other institutions	15	23.4
Not recorded adequately or absence of records	14	21.9
Lost to follow up	13	20.3
Relapse after DDS mono therapy	9	14.1
Relapse after MDT	7	10.9
Referred to other institutions	5	7.8
Just start of MDT (not yet passed 6 months)	1	1.6
Total	64	100.0

Table 4: Demographic characteristics and classification of leprosy in included and excluded cases

		Included	Excluded	p value
No. (%)		158(71.2)	64(28.8)	
Sex				0.880*
	Male	102(64.6)	42(65.6)	
	Female	56(35.4)	22(34.4)	
Age (yrs.)				0.604**
		41.0 ± 16.8	42.3(15.3)	
	≤15	5(3.2)	1(1.6)	
	16-30	47(29.7)	15(23.4)	
	31-45	48(30.4)	22(34.4)	
	46-60	33(20.9)	13(20.3)	
	61-70	24(15.2)	13(20.3)	
	≥71	1(0.6)	0(0.0)	
Place of birth				
	Central	74(46.8)	31(48.4)	
	Northeast	46(29.1)	18(28.1)	
	North	18(11.4)	4(6.3)	
	East	5(3.2)	6(9.4)	
	South	4(2.5)	3(4.7)	
	Foreign	3(1.9)	0(0.0)	
	Not recorded	8(1.9)	2(3.1)	
WHO Classification				0.052*
	PB	26(16.5)	7(10.9)	
	MB	132(83.5)	55(85.9)	
	Not recorded***	0(0.0)	2(3.1)	
R - J Classification				
	TT	2(1.3)	3(4.7)	
	BT	51(32.3)	8(12.5)	
	BB	12(7.6)	7(10.9)	
	BL	37(23.4)	18(28.1)	
	LL	54(34.2)	27(42.2)	
	Neural	2(1.3)	1(1.6)	
BI		1.56 ± 1.65	1.93 ± 1.71	0.146**

* Chi square
** Student's t-test
*** Excluded from statistical analysis

Table 5: Type of leprosy (WHO classification) and reactions

Type of leprosy \ Type of reactions	RR	ENL	Neuritis	RR+ENL	Total
PB	19(73.1)	0(0.0)	7(26.9)	0(0.0)	26(100)
MB	71(53.8)	38(28.8)	12(9.1)	11(8.3)	132(100)
Total	90(57.0)	38(24.1)	19(12.0)	11(7.0)	158(100)

Table 6: Type of leprosy (Ridley-Jopling) and reactions

Type of leprosy \ Type of reactions	RR	ENL	Neuritis	RR+ENL	Total
TT	1(50.0)	0(0.0)	1(50.0)	0(0.0)	2(100)
BT	41(80.4)	0(0.0)	10(19.6)	0(0.0)	51(100)
BB	12(100.0)	0(0.0)	0(0.0)	0(0.0)	12(100)
BL	22(59.5)	5(13.5)	4(10.8)	6(16.2)	37(100)
LL	14(25.9)	33(61.1)	2(3.7)	5(9.3)	54(100)
Indeterminate	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(100)
Neural type	0(0.0)	0(0.0)	2(100.0)	0(0.0)	2(100)
Total	90(57.0)	38(24.1)	19(12.0)	11(6.9)	158(100)

Table 7: The onset of the first reaction in type of leprosy

Type of leprosy \ Time of onset	On registration	During MDT	After completing MDT	Total
PB N (%)	22(84.6)	3(11.5)	1(3.8)	26(100)
MB N (%)	71(53.8)	57(43.2)	4(3.0)	132(100)
Total N (%)	93(58.9)	60(38.0)	5(3.2)	158(100)

Table 8: The onset of the first reaction in type of reaction

Reaction \ Time of onset	On registration	During MDT	After completing MDT*	Total
RR N (%)	58(64.4)	30(33.3)	2(2.2)	90(100)
ENL N (%)	22(57.9)	14(36.8)	2(5.3)	38(100)
Neuritis N (%)	9(47.4)	9(47.4)	1(5.3)	19(100)
RR+ENL N (%)	4(36.4)	7(63.6)	0(0.0)	11(100)
Total N (%)	93(58.9)	60(38.0)	5(3.2)	158(100)

Table 9: The number of episodes of leprosy reactions in type of reaction

Episode / Reaction	1	2	3	4	5	≥6	Total
RR N (%)	49(54.4)	24(26.7)	12(13.3)	2(2.2)	2(2.2)	1(1.1)	90(100)
ENL N (%)	19(50.0)	12(31.6)	5(13.2)	2(5.3)	0(0.0)	0(0.0)	38(100)
Neuriti N (%)	14(73.7)	5(26.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	19(100)
RR+ENL N (%)	4(36.4)	5(45.5)	1(9.1)	0(0.0)	1(9.1)	0(0.0)	11(100)
Total N (%)	86(54.4)	46(29.1)	18(11.4)	4(2.5)	3(1.9)	1(0.6)	158(100)

Table 10: Initial prednisolone (mg)

	Median (mg) (minimum (mg) – maximum (mg)) No. of patients				
	RR	ENL	Neuritis	RR + ENL	Total
1st	20.0 (5.0 – 60.0) 90	30.0 (5.0 – 50.0) 38	40.0 (10.0 – 60.0) 19	30.0 (10.0 – 40.0) 11	30.0 (5.0 –60.0) 158
2nd	20.0 (5.0 – 40.0) 40	30.0 (5.0 – 40.0) 19	40.0 (15.0 – 40.0) 5	20.0 (10.0 – 40.0) 7	30.0 (5.0 – 40.0) 71
3rd	15.0 (10.0 – 40.0) 17	12.5 (5.0 – 40.0) 6		27.5 (15.0 – 40.0) 2	15.0 (5.0 – 40.0) 25
4th	20.0 (10.0 – 60.0) 5	20.0 (10.0 –30.0) 2		40.0 (40.0 – 40.0) 1	20.0 (10.0 – 60.0) 8
5th	40.0 (15.0 – 40.0) 3			40.0 (40.0 – 40.0) 1	40.0 (15.0 – 40.0) 4

Table 11: Maximum prednisolone (mg)

	Median (mg) (minimum (mg) – maximum (mg)) No. of patients				
	RR	ENL	Neuritis	RR + ENL	Total
1st	30.0 (5.0 – 60.0) 90	35.0 (10.0 – 60.0) 38	40.0 (10.0 – 60.0) 19	40.0 (30.0 – 60.0) 11	40.0 (5.0 – 60.0) 158
2nd	20.0 (5.0 –60.0) 40	40.0 (5.0 – 40.0) 19	40.0 (15.0 – 40.0) 5	20.0 (10.0 – 60.0) 7	30.0 (5.0 – 60.0) 71
3rd	20.0 (10.0 –40.0) 17	30.0 (5.0 – 40.0) 6		27.5 (15.0 – 40.0) 2	20.0 (5.0 – 40.0) 25
4th	20.0 (10.0 –60.0) 5	20.0 (10.0 – 30.0) 2		40.0 (40.0 – 60.0) 1	20.0 (10.0 – 60.0) 8
5th	40.0 (15.0– 40.0) 3			40.0 (40.0 – 40.0) 1	40.0 (15.0 – 40.0) 4

Table 12: Mean duration of s (months)

	Mean ± SD (No. of patients)					
	RR	ENL	Neuritis	RR + ENL	p value	Total
1st	9.1 ± 8.7 (90)	13.9 ± 12.9 (38)	6.7 ± 4.1 (19)	13.8 ± 12.9 (11)	0.018*	10.3 ± 10.1 (158)
2nd	4.7 ± 4.6 (40)	5.9 ± 4.4 (19)	4.2 ± 2.0 (5)	5.3 ± 3.57 (7)	0.724*	5.0 ± 4.3 (71)
3rd	3.5 ± 1.8 (17)	6.0 ± 3.9 (6)		4.0 ± 4.2 (2)	0.128*	4.2 ± 2.6 (25)
4th	4.4 ± 2.7 (5)	5.0 ± 4.2 (2)		4.0 ± 0.0 (1)	0.959*	4.5 ± 2.6 (8)
5th	7.3 ± 6.7 (3)			24.0 ± 0.0 (1)	0.162**	11.5 ± 9.9 (4)

* One way ANOVA
** Student's t-test

Table 13: Mean of initial and maximum dose of prednisolone and mean duration of all 267 episodes.

	Initial prednisolone (mg)	Maximum prednisolone (mg)	Duration (mo.)
Mean ± SD	25.9 ± 13.0	29.9 ± 14.1	8.2 ± 8.6

Table 14: Type of reactions and total duration of prednisolone treatment

	RR[a*]	ENL[b*]	Neuritis[ac*]	RR + ENL[ab*]	P value**	Total
Duration (months) mean ± SD	12.4 ± 9.8 (N = 90)	18.1 ± 12.2 (N = 38)	7.8 ± 5.0 (N = 19)	20.5 ± 16.4 (N = 11)	0.001	13.7 ± 11.1 (N = 158)

* abc, Difference in letter shows statistically significant difference at p value < 0.05.
** One way ANOVA

Table 15: Correlation between dose of prednisolone and duration of treatment, No. of episodes of reactions.

Independent factor	Dependent factor	r	p value
Maximum prednisolone doses (in 267 episodes)	Duration of each episode (in 267 episodes)	0.377	0.000
Maximum prednisolone doses of first episode (in 158 patients)	No. of episodes (in 158 patients)	- 0.205	0.010

Table 16: Comparison of doses of prednisolone in first episode by years of medical records

	No. of patients	1999-2001	2002-2005	P value*
Initial prednisolone mean ± SD (mg)	70	20.9 ± 12.0	32.2 ± 11.2	0.000
Maximum prednisolone mean ± SD (mg)	88	27.1 ± 14.7	37.0 ± 10.9	0.000

* Student's t-test

Table 17: Outcome of the treatment in type of reactions

Outcome	Type of reactions (No.)				
	RR	ENL	Neuritis	RR+ENL	Total
Improved	149	56	23	20	248
Not changed	4	6	1	2	13
Worsened	1	1	0	0	2
Died	2	2	0	0	4
Total	156	65	24	22	267

Table 18: Outcome of the treatment in type of leprosy

Outcome	Type of leprosy (No.)		
	PB	MB	Total
Improved	31	217	248
Not changed	1	12	13
Worsened	0	2	2
Died	1	3	4
Total	33	254	267

Table 19: Causes of death (8 patients)

No.	Age	Sex	WHO	R-J	BI	Reaction	Duration (mo.)	Causes of death
1	43	M	MB	LL	4.00	ENL	18	DM, TB
2	67	M	PB	BT	0.00	RR	4	Renal failure
3	40	M	MB	LL	2.22	RR	18	Meningitis(suspected)
4	17	M	MB	LL	3.66	ENL	19	Unknown
5	60	M	MB	LL	3.25	ENL	≥10	Convulsion (meningitis suspected)
6	49	M	MB	BL	1.25	RR+ ENL	10	Laryngeal cancer
7	45	F	MB	LL	3.75	ENL		Melanoma, metastasis to lung, liver?
8	49	M						TB?

Patients of No. 1 – 5 are "included cases" for analysis of 158 patients. The time of the death of Patients of No. 1 – 4 is during treatments of leprosy reactions. The time of the death of Patients of No. 5 is after successful treatment of the leprosy reactions.
Patients of No. 6 – 8 are excluded from analysis of treatments of leprosy reactions due to inadequate medical records.

Table 20: Cases of "worsened" (2 patients)

No.	Age	Sex	WHO	R-J	BI	Reaction	Duration of prednisolone (mo.)	Factors
1	23	F	MB	BL	2.76	ENL	41	Poor compliance
2	75	M	MB	BT	0	RR	29	Cutaneous T cell lymphoma

Table 21: Disability grading before MDT

Grading / Reactions	0	1	2	P value*	Total
With reactions	57(53.3)	24(22.4)	26(24.3)	0.228	107(100)
Without reactions	45(63.4)	9(12.7)	17(23.9)		71(100)
Total	102(57.3)	33(18.5)	43(24.2)		178(100)

* Chi square

Table 22: Disability grading after MDT

Grading / Reactions	0	1	2	P value*	Total
With reactions	55(51.4)	28(26.2)	24(22.4)	0.067	107(100)
Without reactions	47(66.2)	9(12.7)	15(21.1)		71(100)
Total	102(57.3)	37(20.8)	39(21.9)		178(100)

* Chi square

Table 23: Changing of disability grading before and after MDT

Difference of grading / Reactions	Same	Improved	Deteriorated	Total
With reactions	81(75.7)	13(12.1)	13(12.1)	107(100)
Without reactions	67(94.4)	4(5.6)	0(0.0)	71(100)
Total	148(83.1)	17(9.6)	13(7.3)	178(100)

Table 24: Changing of EHF score before and after MDT

Difference of EHF score / Reactions	Same	Improved	Deteriorated	Total
With reactions	63(58.9)	22(20.6)	22(20.6)	107(100)
Without reactions	59(83.1)	7(9.9)	5(7.0)	71(100)
Total	122(68.5)	29(16.3)	27(15.2)	178(100)

Table 25: Association between type of reactions (RR and ENL) and neuritis

Neuritis \ Type of reactions	RR	ENL	p value*	Total No. (%)
Present	46	22	0.238	68 (56.2)
Not present	41	12		53
Total	87	34		121** (100.0)

* Chi square
** From 158 patients types of neuritis and RR + ENL were excluded and in 8 patients records were not taken.

Table 26: Association between type of leprosy and neuritis

Neuritis \ Type of leprosy	PB	MB	p value*	Total No. (%)
Present	17	75	0.453	92(61.3)
Not present	8	50		58(38.7)
Total	25	125		150** (100.0)

* Chi square
** Not recorded in 8 cases.

Table 27: Signs, symptoms

Signs, symptoms	No. of cases
Edema on hands, legs, face	21
Eye involvement	14
Fever	13
Foot or hand ulcer, wound	12
Body pain except for ENL, RR lesions	9
Foot drop	7
Arthralgia	3
Diarrhea	2
Malaise	2
Hair loss	2
Abdominal pain	2
Lymphadenitis	2
Itching	2
Claw hand	1
Gynecomastia	1
Appetite loss	1
Insomnia	1

(58 patients of tatal 158 had signs, symptoms. 36.7%)

Table 28: Complications

Complications	No. of cases
Upper respiratory infection	14
Anemia	10
Skin cellulites	2
Tuberculosis	2
Orchitis	2
Scabies	2
Dapson syndrome	2
lower respiratory infection	1
appendicitis	1
subcutaneous abscess	1
herpes simplex labialis	1
panniculitis	1
allergic dermatitis	1
renal failure	1
urinary tract infection	1
eczema	1
hook worm infection	1
balanitis (infection)	1
Eosinophilia	1

(34 patients of total 158 had complications. 21.5%)

Table 29: Side effects of treatments in leprosy reactions

Side effects	No. of cases
Steroid dependent	5
Steroid acne	4
Moon face	3
Osteoporosis	2
Steroid induced hypertension	2
Abdominal striae	1
Cushing syndrome	1
Cataract	1
Thrombosis of vein (thalidomide)	1
Erythema multiforme (thalidomide)	1

(14 patients of total 158 had side effects. 8.9%)

Table 30: Precipitating factors for leprosy reactions

Precipitating factors	No. of cases
Dental carries	10
Stress	2
Pregnancy	1

(11 patients of total 158 had precipitating factors. 7.0%)

Table 31: Underlying diseases

Underlying disease	No. of cases
Diabetes mellitus	7
Hypertension	6
Liver disease or abnormal LFT	6
Psychiatric state	3
HIV infection	2
Laryngeal cancer	1
Cutaneous T cell lymphoma	1

(22 patients of total 158 had underlying diseases. 13.9%)

Table 32: Laboratory examination (CBC and biochemistry)

	Normal range	No. of patients	Mean
WBC	4500-11000/mm^3	51	10283.1
Hb	M13.5-17.5, F12-16g/dl	50	12.5
Hct	M41-53, F36-46%	50	36.9
Neutrophil	66-75%	50	71.4
Lymphocyte	25-33%	50	24.8
Platelet	150-400×10^3/ mm^3	28	303×10^3
BUN	7-18mg/dl	39	13.8
Creatinine	0.6-1.2mg/dl	42	1.1
GOT	0-40U/L	32	33.6
GPT	0-40U/L	42	24.7
ALP	26-117U/L	38	49.5
Albumin	3.5-5.0 g/dl	18	3.6
Globulin	2.4-3.5 g/dl	17	3.0

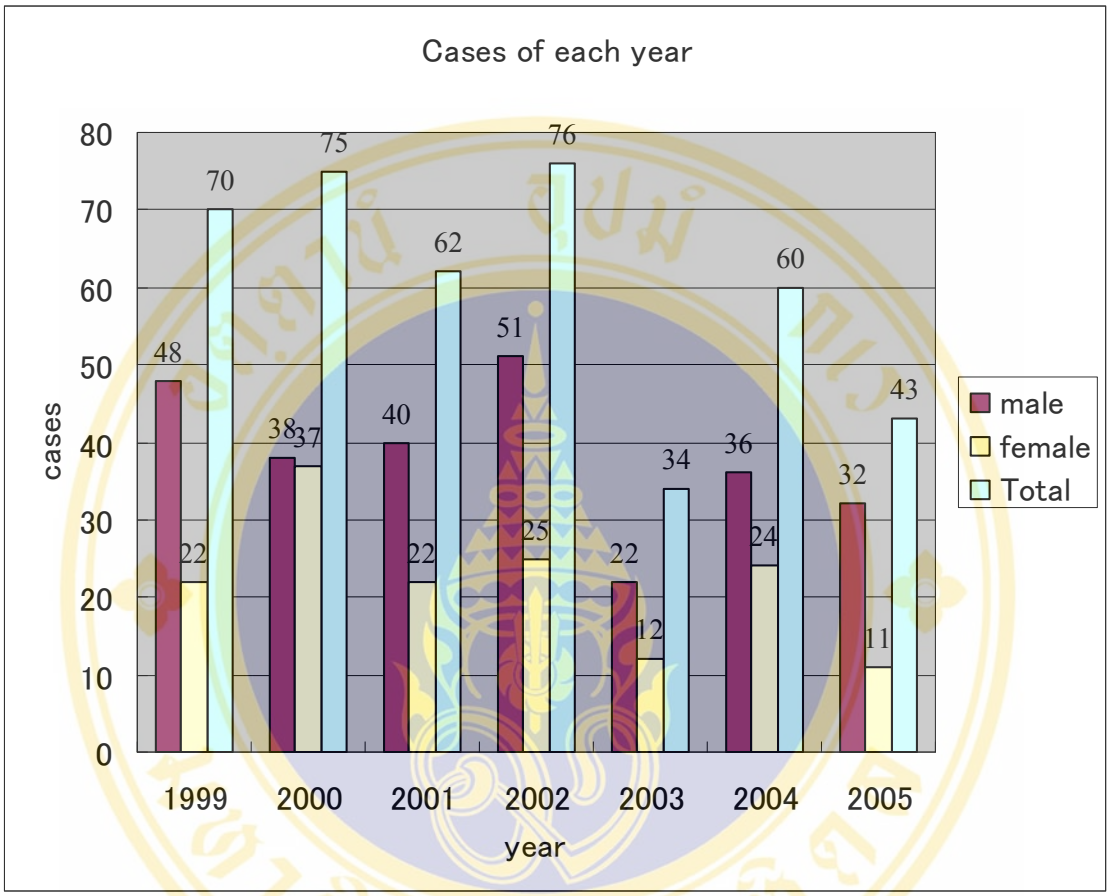

Figure 1: Number of all active leprosy patients from 1999 to 2005. (N = 420)

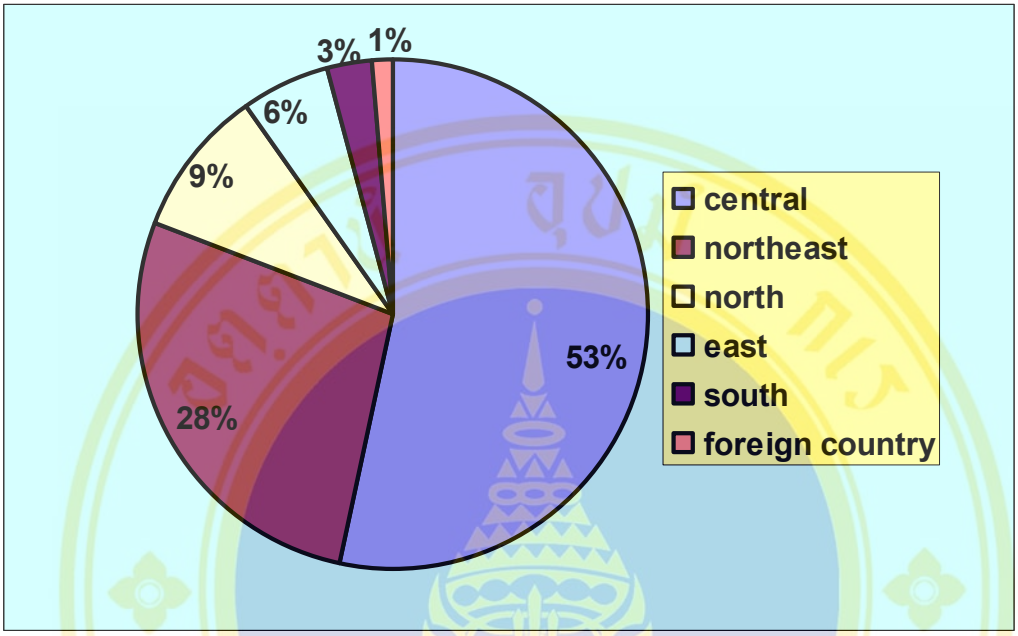

Figure 2: Place of birth in all patients who took MDT. (N = 420)

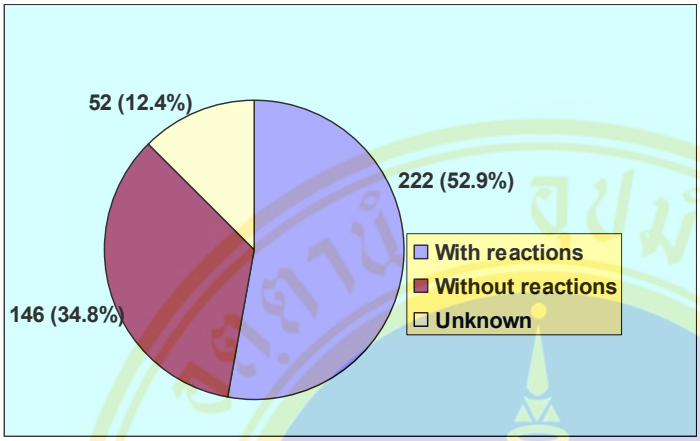

Figure 3: Incidence of reactions in all patients who took MDT. (N = 420)

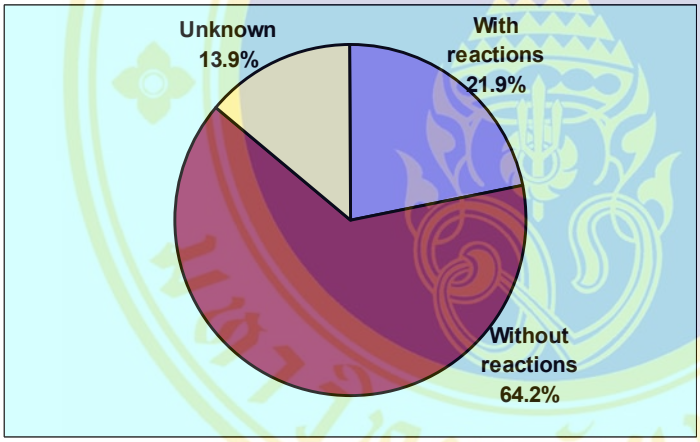

Figure 4: Reactions in PB (N = 151)

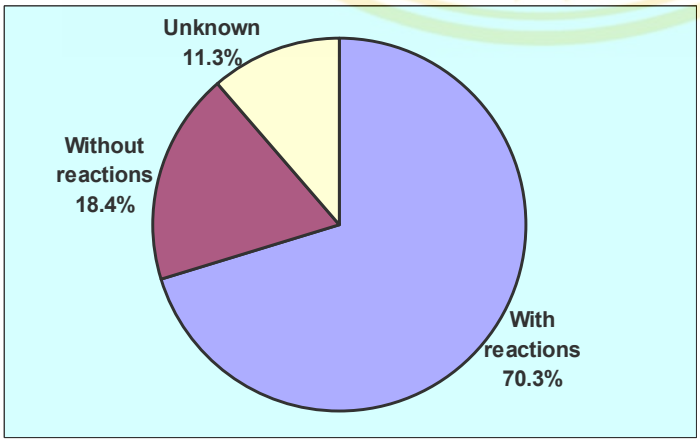

Figure 5: Reactions in MB (N = 266)

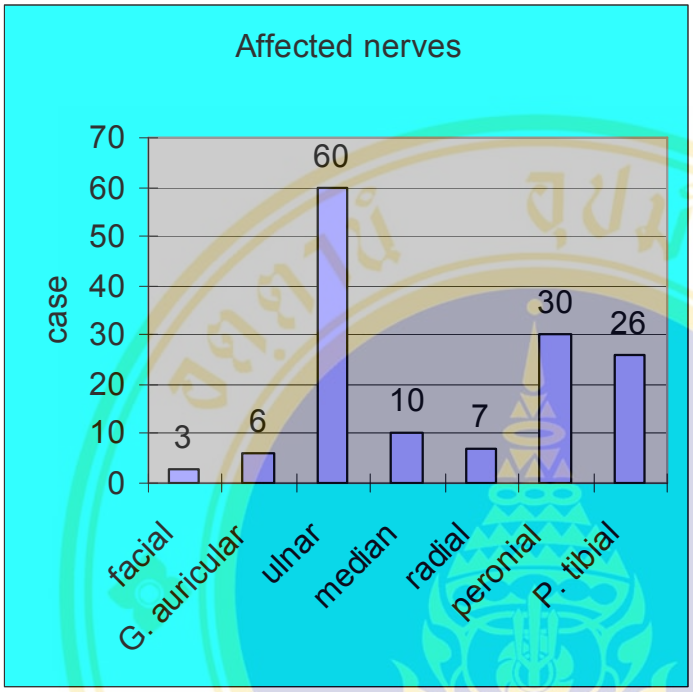

Figure 6: Affected nerves
(No. of patients with neuritis = 90*, total affected nerves = 143)
* Affected nerves were not recorded in 2 patients with neuritis.

CHAPTER VI
DISCUSSION

The incidence rate of leprosy reactions was 52.9% (222) of total active patients (420) who were treated in Raj-Pracha Samasai Institute from 1999 to 2005. In PB patients 22% of reactions occurred, while in MB patients 71% of reactions occurred. These incidents were higher than the previous studies of leprosy reactions which reported as 42 % (Scollard DM et al., 1994), 16 % (Santarma V et al., 2004) in total incidence and 2.5% in PB, 34% in MB (Richardus JH et al., 2004). In this study higher incidence in MB is very prominent. This may be due to the fact that Raj-Pracha Samasai Institute is the referral center for leprosy in Thailand and almost patients who have visited the institute already had symptomatic reactions.

When compare some variables such as sex and age between patients with reactions and patients without reactions, there is no significant difference. In patients with reactions, the highest incidence rate of age group was 31- 45 years. This was older than previous study of 21 – 30 years group as highest shown by Van Brakel WH et al., 2005. The reason is unclear.

The rate of RR and ENL were 57.0% and 24.1% in 158 patients with reactions respectively. The rates of these were similar to the study by Santaram V et al., 2004 in which RR and ENL were diagnosed in 68.7 and 31.3% respectively. Distribution of leprosy reactions according to the different type of leprosy is shown that RR predominates in BB (100%), whereas ENL predominates in LL (61.1%). These results are similar with the study by Nery JA et al., 1998.

Majority of PB (84.6%) already had the first episode of reaction at the time of registration, whereas in MB, 57.7 % of the first reaction occurred at the time of registration and 43.2 % of the first reaction occurred during MDT. These results were similar to the study by Shreuder PA in Thailand 1998. Majority of RR had the first reaction at the time of registration (64.4%) and during MDT 24 of 30 patients (80.0%) occurred within 6 months of start of MDT, whereas in ENL during MDT 12 of 14

patients (85.7%) occurred within 6 months of start of MDT as RR. These results were different from the study by Britton WJ et al., 2004 in which they showed that majority ENL occurred after 6 months of starting the MDT. The earlier occurrence of reactions in ENL in this study was unclear.

The majority of patients had single (53.8%) or two episodes (29.1%) of reactions. Nery JA et al., 1998 showed that the recurrence rate (multiple episodes) of ENL was higher than that of RR, but in this study there was no difference in number of episodes between RR and ENL (up to 4^{th} episodes. $p = 0.783$). The reason why the number of episodes of ENL was fewer may be that high doses of clofazimine were given to 18 of 38 patients with ENL (47.4%).

Main drugs of treatments for reactions were prednisolone, thalidomide, pentoxifylline and high dose of clofazimine. Prednisolone was prescribed for all 158 patients with reactions. Thalidomide was given to only 3 patients. Pentoxifylline was given to 5 patients. The efficacy of pentoxifylline was unclear in this study. The cases of thalidomide are shown in appendix. The three patients who were treated with thalidomide had common clinical features. (1) Younger age. (2) Longer duration of prednisolone treatment, 2.6 to 3.5 years. (3) No discontinuation of prednisolone. (4) Side effects of prednisolone. (4) Although ENL subsided during thalidomide treatment, prednisolone was started or the dose of prednisolone increased after stopping thalidomide. There were studies which showed the efficacy of thalidomide for ENL (shown by E Frankes MEet al., 2004).

The high dose of clofazimine (300mg/day for 2-3 months) was a treatment for ENL, but in this study the high dose of clofazimine was used not only for ENL, but also for RR and neuritis. The number of patients, whom the high dose of clofazimine was used, was 38 patients (24.1 % of 158 patients with reactions). In RR, ENL, neuritis and RR + ENL, the number of patients was 13/90, 18/38, 2/19 and 5/11 respectively.

Initial doses of prednisolone were around 20-40mg/day (minimum 5mg/day, maximum 60 mg/day) and maximum doses were slightly higher than initial doses. The doses were almost the same in any type of reactions. There were 267 episodes of reactions in 158 patients with reactions. The mean doses of initial and maximum

prednisolone were 25.9 ± 13.0 and 29.9 ± 14.1mg/day respectively. These doses were lower than 40mg of the recommended dose in field by WHO, 1998 (Initial dose is 40mg/day and is tapered to stop gradually for 12 weeks) and even ILEP, 1997 advised up to 1mg/kg/day. The reason why low doses of prednisolone was given in this study might be that prednisolone treatments were conducted for many mild reactions cases. And in analyzing of doses of prednisolone yearly, higher doses were given for recent four years (2002 to 2005) compared with that of old three years (1999 to 2001).

Median durations of 1st to 5th episodes were 4.2-10.3 months. Only 1st episode had different durations among different type of reactions. Neuritis was 6.7 ± 4.1 months, RR was 9.1 ± 8.7 months and ENL was 13.9 ± 12.9 months in first reaction (table 12). Although the mean duration of prednisolone treatments in all 267 episodes (8.2 ± 8.6 months, table 13) was longer than 12 weeks of the recommendation by WHO, 1998, these durations were almost the same as the recommendation of up to 6 months of treatments shown by ILEP, 1997. These durations also are comparable with the study that Roshe PW et al., 1998 treated the patients with reactions for average 15.8 weeks (4 to 74 weeks). Sugumaran DS, 1997 has shown that prednisolone should have be given to TT for 3-6 months, to BB for 6-9 months, to BL for 18-24 months for patients with reactions and the longer duration of prednisolone treatments improved the nerve function impairment. The longer duration of prednisolone treatments might block the occurrence of the nerve function impairment (Smith WC, 2004). Therefore, the longer durations in this study may be reasonable. Mean total duration of prednisolone (sum up durations of each episode in each patient) was 13.7 ± 11.1 months. Although the duration seems to be much longer considering side effects of corticosteroids for long administration, the duration may also be practical in clinical situation.

There is positive correlation between maximum dose of prednisolone and duration of each episode (267 episodes). This may reflect severity of the reactions. There is negative correlation between maximum dose of prednisolone in first episode and number of episodes (158 patients). This may show that the administration of high dose prednisolone in first episode of reactions may decrease the number of episodes with caution for the side effects.

Although there is a possibility that high dose of clofazimine may decrease the duration of prednisolone treatments, there was no significant difference in the duration of treatment between the patients with and without high dose of clofazimine in this study.

Although ultimate objective of the treatments of leprosy reactions is to prevent nerve function impairment and disability, it is very difficult to decide the outcome of the treatments in each episode of reaction. In this study the outcomes in each episode were gotten from improvements of skin lesions, general signs and symptoms such as fever, malaise and pain. Majority of patients in either any type of reactions or any type of leprosy had improved. There were few cases of “worsened” or “died”. Among the patients with outcome of “worsened” or “died” there were 3 patients with malignancy and 2 patients with tuberculosis. It was shown by Sethuraman G et al., 2001 that the leprosy was associated with various visceral and lymphoreticular malignancies. They reported the peripheral cutaneous lymphoma in a LL patient. Two patients with tuberculosis died (TB occurred in one patient during prednisolone treatment and died during the prednisolone. In another patient, clinical course of TB and cause of death was unclear due to uncomplete recordes.). Although it was unclear wheather their causes of death were related to the side effects of prednisolone treatments or not, and as Sugumaran D et al., 1997 has shown that three patients developed pulmonary tuberculosis within 6 months of prednisolone therapy, clinicians should look for ttuberculosis in patients with leprosy reactions under prednisolone treatments for leprosy reactions.

Analysing outcome of treatment by evaluating the disability in each episode of reactions is very difficult. Therefore, in this study the disability grading system recommended by WHO 1998 was analysed before and after MDT. The rate of patients with disability (grade 1 or 2) at the time of registration (before MDT) was 42.7% (grade1: 18.5%. grade2: 24.2%). This was slightly higher than previous studies of 37.6 % of MB by Richardus JH, et al., 1996 and 37% of MB by Oliveira CR, et al., 2003. In this study the patients of PB were included. There was no difference in disability grading between patients with and without reactions. A similar result was

shown by Jose A.C. et al., 1998. The disability in grading after MDT was also at the same level as that before MDT and no difference in the grading between patients with and without reactions was shown. In this study, the changing of disability grading before and after MDT was calculated (Subtraction of the grading after MDT from that before MDT. Zero meant no change in disability grading "same", negative value meant "deteriorated" and positive value meant "improved". With comparison of both group (with and without reactions), patients with reactions was more deteriorated than patients without reactions. (Significantly different in both grading and EHF score). Roche PW et al., 1998 has shown similar result but not significantly different.

Neuritis was found in 92 patients of 150 patients (61.3%) and the incidence was not different among types of reactions nor types of leprosy. The study by Pimentel MI et al., 2004, showed that the lower incidence of neuritis (45%). Most common affected nerves were ulnar, peronial and posterior tibial in the order. But according to the study by Pimentel MI et al., 2004, most affected nerves were ulnar, fibular and posterior tibial in the order. The higher incidence of peronial neuritis in this study was not shown by the study of Pimentel et al. The reasons of high incidence of neuritis in this study were that Raj-Pracha Samasai Institute was a referral center and many patients with symptomatic neuritis might visit the institution.

There is difficulty to differentiate complications from underlying disease. According to the frequency, upper respiratory infection, anemia, diabetes mellitus, hypertension and liver diseases were prominent. The occurrence of TB and malignancy was mentioned already. As the association between HIV and leprosy has been unknown (Machado P, et al., 1998), there were no specific clinical features in 2-HIV patients with leprosy reactions (shown in appendix).

In this study the side effects were recorded in 14 patients of 158 patients with reactions (8.9%). Majority of the side effects were due to prednisolone. Although the result is lower than 21 % by S Smith WC et al., 2004, the difference may be due to the selection of variables. In this study such variables as TB, DM and some of infections were not included as side effects. The important side effects were steroid induced

hypertension, Cushing syndrome, cataract and osteoporosis. Therefore, vigilant attention is needed while treatment of leprosy reactions with prednisolone.

In this study, there was a case in which thrombosis of leg vein occurred as side effect by thalidomide. The first case of deep vein thrombosis was reported by Sharma NL et al., 2004.

CHAPTER VII
CONCLUSION

1. Incidence of leprosy reactions is higher than other reports, in particularly among MB patients.
2. All patients with reactions were treated with prednisolone. High dose of clofazimine was also prescribed in many patients. Few patients were treated with thalidomide or pentoxifylline.
3. Majority of patients with reactions who were treated with prednisolone improved.
4. There were few cases of death and worsened cases. Whether these causes (in particularly malignancy and TB) were related to the reactions or to the side effects of prednisolone were unclear. However, it is needed to pay vigilant attentions to the patients with reactions under prednisolone treatment.
5. The doses of prednisolone used for the treatment of reactions in years of 1999 to 2001 were lower than recommended standard dose in field by WHO.
6. The durations of treatment with prednisolone were much longer than recommended duration of 12 weeks by WHO.
7. There was correlation between the maximum dose of prednisolone in first episode and the number of episodes of reactions in each patient. Therefore, there is possibility that high dose of prednisolone in first reactions can decrease the following episodes of reactions.
8. The treatments with thalidomide were effective. The prednisolone could be stopped or the dose could be decreased.
9. The disability grading in the patients with and without reactions before and after MDT was not different. But in the changing of grading points and EHF score before and after MDT in each patient, the patients with reactions had more deteriorated than the patients without reactions. Therefore, prompt and effective treatments in leprosy reactions are needed.

10. The neuritis occurred with the reactions were mostly ulnar nerve and peronial nerve. And the incidence of neuritis in the patients with reactions was also higher than previous reports.
11. The studies for more effective treatments of leprosy reactions with less side effects will be needed.

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APPENDIX

Treatments with thalidomide 3 cases

1. 21years, Male, LL, MB, BI 3.16, ENL on registration, start of MDT 2001, use of thalidomide 2005
   Prednisolone Initial 40, Maximum 60, Total duration 3.5 years
   No interval of steroid
   Side effects of prednisolone
   Steroid dependent
   Moon face
   Osteoporosis
   Abdominal striae
   Cushing syndrome
   Steroid induced hypertension

During thalidomide treatment ENL subsided and dose of prednisolone could be decreased and finally stopped. But after stopping of thalidomide, the ENL reappeared and prednisolone was started again.
Thalidomide was stopped because of the side effect of deep vein thrombosis at right calf.

2. 21 years, Male, LL, MB, BI 2.75, ENL on registration, start of MDT 2001, use of thalidomide 2005
   Prednisolone Initial 40, Maximum 60mg, total duration 36 months (3 years)
   No, interval of steroid
   Side effects of prednisolone
   Osteoporosis
   During thalidomide treatment ENL subsided but prednisolone could not be discontinued.

3. 15 years, Male, LL, MB, BI 4.0, ENL on registration, start of MDT 2001, use of thalidomide 2005
   Prednisolone Initial 40, Maximum 40mg, Total duration 31 months
   Side effects of prednisolone
   Steroid dependent
   Steroid induced hypertension
   During thalidomide treatment ENL subsided and prednisolone could be stopped. But prednisolone was started again later after stopping of thalidomide. Side effects of thalidomide was erythema multiforme.

Cases of HIV coinfection with leprosy with reactions.

1. 59 years, female, LL, MB, BI 0.0, ENL on registration, single reaction, maximum prednisolone 30mg, duration of treatment: 3 months, outcome of treatment of reaction: improved

2. 27 years, male, BT, PB, BI 0.0, RR on registration, single reaction, maximum prednisolone 40mg, duration of treatment: 7 months, outcome of treatment of reaction: improved.

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