Prevention of repeated episodes of type 2 reaction of leprosy with the use of thalidomide 100 mg/day*

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Abstract: BACKGROUND: Leprosy can have its course interrupted by type 1 and 2 reactional episodes, the last named of erythema nodosum leprosum (ENL). Thalidomide has been the medication of choice for the control of ENL episodes since 1965. OBJECTIVES: These episodes can repeat and cause damages to the patient. In order to prevent these episodes, an extra dose of 100 mg/day thalidomide was used during six months, followed by a follow-up period of six more months after thalidomide discontinuation. METHODS: We included 42 patients with multibacillary (MB) leprosy who had episodes of ENL. They were male and female patients aged between 18 and 84 years. RESULTS: Of the 42 patients, 39 (92.85%) had the lepromatous form and three (7.15%) had the borderline form. We found that 100% of patients had no reactional episode during the use of the drug. During the follow-up period after thalidomide discontinuation, 33 (78.57%) patients had no reactional episode and nine (21.43%), all of them with the lepromatous form, had mild episodes, which were controlled using non-steroidal anti-inflammatory. There were no thalidomide-related side effects. CONCLUSION: A maintenance dose of 100 mg/day of thalidomide showed to be effective to prevent repeated type 2 reactional episodes of ENL.
Keywords: Erythema nodosum; Leprosy; Medication therapy management; Thalidomide

INTRODUCTION

Leprosy is a chronic disease caused by Mycobacterium leprae (M. leprae), an obligate intracellular bacillus, discovered by Hansen in 1873.[1,2]

People are the only source of transmission of M. leprae, and the respiratory tract is the major route of release of bacilli.[3-6]

For operational purposes, leprosy is classified as paucibacillary (PB) and multibacillary (MB) according to the presence or absence of bacilli. PB leprosy includes the tuberculoid and indeterminate forms, whereas MB leprosy includes the borderline and lepromatous forms.

Leprosy may have its chronic course interrupted by acute phenomena called reactions. Such reactions may be type 1 or type 2 (erythema nodosum leprosum, ENL). ENL may occur in 50% to 70% of patients with the lepromatous form and, more rarely, in patients with the borderline form.[7-13]

ENL is characterized by the sudden appearance of skin papules, erythematous plaques, erythematous and painful hard lumps distributed throughout the whole body, and general symptoms such as fever, arthralgia, loss of appetite, and malaise. ENL may result in severe damage to nerve trunks, causing intensely painful and destructive neuritis, as well as iridocyclitis and orchiepididymitis, among others. These events usually persist until the beginning of the treatment.[11-16] ENL is more common in men than in women and in the age group between 20 and 40 years.[12]

Bacterial or viral infections, stress, childbirth, surgeries, and, especially, the massive bacillary death that occurs after the beginning of the treatment are

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considered triggers.[7,17] Because it is a systemic process, ENL may affect many different organs and all areas where there is bacterial infiltration.[11,18]

Although the reaction may occur before, during, or after the treatment, it most generally occurs during the treatment, between the 4th and 6th drug doses.[12,13,19] Reactions usually last for 15-20 days, and they may become continuous. According Naafs, the occurrence, intensity, and number of ENL reactional episodes depends on how long it takes to establish the diagnosis and begin the treatment.[19]

ENL is considered a classic example of immune complex disease, occurring due to the massive release of antigens, antibody formation, with consequent deposition of immune complexes in different organs.[8,20]

In the polar forms of leprosy, there is correlation between the local cellular immune response and the cytotoxic ability to control the growth of bacilli.[21-23] The effectiveness of macrophages in defending the body by stimulating local cellular immunity is provided by the cytokines produced by CD4, Th1, and Th2 lymphocytes. When the bacterial load is low, there is activation of Th1 lymphocytes and production of interferon gamma, suggesting macrophage activity.[22,23]

Conversely, in the lepromatous form, the bacterial load is high and the disease is disseminated. Therefore, there is activation of Th2 lymphocytes with production of cytokines, mainly IL-4 and IL-10, which are responsible for the humoral response and the failure to produce epithelioid cell granulomas. Intense production of anti-phenolic glycolipid-1 (PGL-1) antibodies against PGL-1 antigens (M. leprae specific antigens) has been observed in this clinical form.[22,23] The T cells mentioned above are anergic, thus they are not activated. This effect appears to be specific to these microorganisms because there is no change in the immune response against other antigens.[24]

However, the etiology of ENL is still unknown and its pathogenesis remains unclear.[25]

The pathogenesis of ENL is related to the humoral response, and some authors have demonstrated the influence of the cellular immune response.[26,27]

ENL severity has been associated with increased production and release of pro-inflammatory cytokines produced by Th1 lymphocytes, including TNF-alpha and INF-gamma, which are important components of the immunopathogenesis of ENL.[28] Several authors have confirmed the increased serum levels of TNF-alpha in patients with ENL.[29]

Thalidomide is the drug of choice for treating ENL. Prednisone is added to the treatment when the reactions are difficult to control, or when there are complications, especially neuritis.[12,13,14,21,28]

The dose of thalidomide recommended to control reactions ranges from 100 to 400 mg/day.[17,21,30]

This drug is derived from glutamic acid, and it has antiemetic, sedative, and hypnotic effect; furthermore, it is well tolerated and has low toxicity.[30-33]

The following side effects of thalidomide are known: teratogenicity, nausea, vomiting, constipation, sedation, swelling in the arms or legs, dizziness, mood changes, facial edema, increased appetite, dryness of the mouth, peripheral neuropathy, eosinophilia, and lymphopenia.[14,16,27,30]

Teratogenicity is the most important side effect. Its mechanisms have not been fully understood, and the greatest risk is between the 34th and 57th day after the last menstrual cycle. The use of thalidomide in women of childbearing age is restricted.[14,16,21,28,31,34]

Several authors have found significant clinical improvement within 24 to 48 hours, with normal levels of previously abnormal laboratory results.[8,13,14,30,35-38]

Thalidomide is a potent inhibitor of in vitro TNF production, enabling the control of the diseases caused by this cytokine.[21,38,39]

This drug is used to treat type 2 reaction until clinical improvement, with no clear prescription as to the period and length of use or even the maintenance dose. In many cases, after the drug is discontinued, there is relapse of reaction, which leads to resumption of treatment with thalidomide and/or its use in combination with systemic corticosteroids.[21]

It has been demonstrated that many cases of recurrent ENL were controlled with thalidomide, even those that persisted after the end of the specific treatment for leprosy.[12]

Objectives

General Objective

To investigate the occurrence of ENL in patients using 100 mg/day of thalidomide for six months.

Specific Objective

1) To observe the occurrence of ENL reaction.
2) In cases of possible occurrence of ENL reaction, to assess:
2.1 - the clinical manifestation of ENL;
2.2 - the occurrence of thalidomide side effects;
2.3 - the occurrence of ENL reaction after drug discontinuation.

PATIENTS AND METHODS

All female and male patients with MB leprosy and older than 18 years were evaluated.

Inclusion criteria

Leprosy patients with moderate to severe ENL at the time of the medical visit.

Exclusion criteria

- Female patients of childbearing age according to the guidelines of the Ministry of Health;[34]

- Patients who used systemic corticosteroids during the reactional episode;

- Patients who received an alternative medication scheme during treatment.

Patients

We included all ENL patients who met the inclusion criteria and were seen at the Outpatient Clinic of Dermatology of the Faculdade de Medicina de Botucatu (UNESP) from January 2006 to July 2010. Thus, all patients who agreed to sign the written consent form were included in our sample.

Initially, the sample had 152 patients with MB leprosy. Of these, 100 had ENL; however, 58 were excluded because they did not meet the inclusion criteria. Thus, 42 female and male patients older than 18 years participated in the study. They were followed up for six months in this prospective, nonrandomized clinical trial. The present study was approved by the Research Ethics Committee of the Faculdade de Medicina de Botucatu, UNESP.

Upon receiving a diagnosis of ENL, patients were treated with an initial dose of 300 mg/day of thalidomide. After the initial episode was controlled, they started to receive a dose of 100 mg/day, which was prescribed for a period of six consecutive months. Patients underwent monthly clinical evaluations performed by the same health professional throughout the whole study period.

Female patients were given thalidomide according to the technical criteria established by the Report of the Contribution of the Brazilian Society of Dermatology at the ministerial decree No. 1377 effective as of 2000, namely: women of childbearing age who have not had menses for the past 12 months and sterilized women.[34]

In patients presenting with reactional episodes, the clinical severity of the episodes were evaluated based on the classification by Waters (1967), which was adapted and suggested by Penna: - Mild: less than 10 nodules per body segment, little painful, and absent or mild systemic signs; - Moderate: 10-20 nodules per body segment, more than one painful nodule, fever lower than 38.4 °C, mild systemic symptoms, presence of local and/or regional lymph node; - Severe: more than 20 nodules per body segment, spontaneously painful nodules that may group together and ulcerate, fever higher than 38.5 °C, poor general condition, chills, anorexia, fatigue, arthralgia, and presence of local and regional lymph nodes.[21,40]

Statistics

The association between sex and clinical form, both for ENL patients and those receiving thalidomide, was established using Goodman's homogeneity test, involving comparisons between and within binomial populations. Significance level was set at 5%.[41,42]

We used descriptive measures expressed as percentages to describe some characteristics of the reactional episodes.

RESULTS

The table below describes the characteristics of the 100 patients with ENL.

We found that of all MB patients with ENL, 78 (78%) were male and 22 (22%) were female. In terms of clinical form, 90 (90%) had the lepromatous form and 10 (10%) had the borderline form.

Table 1 shows that there was a significant predominance ($p<0.01$) of the lepromatous form in both sexes, and the distributions did not show any significant difference ($p>0.05$).

There is a higher number of cases in the age group above 40 years (76.20%), with most cases affecting 50-year-old or older patients (50.00%).

Of the 100 patients with ENL, 42 (42%) were followed up. These patients received a dose of 100 mg/day of thalidomide (Table 2). Fifty-eight (58%) patients were excluded because of the need to add

Table 1: Distribution of the clinical forms of leprosy in ENL patients according to sex.

Sex	Clinical form				P-value (clinical form)	TOTAL
	Lepromatous		Borderline			
Male	72	(92.30%)	6	(7.70%)	($p<0.01$)	78
Female	18	(81.80%)	4	(18.20%)	($p<0.01$)	22
P-value (sex)	($p>0.05$)		($p>0.05$)			
Total	90	(90.00%)	10	(10.00%)		100

Source: Faculdade de Medicina de Botucatu/Period: January 2006 to July 2010

Table 2: Distribution of the clinical forms of leprosy in patients receiving 100 mg/day of thalidomide according to sex

Sex	Clinical form				P-value	TOTAL
	Lepromatous		Borderline		(clinical form)	
Male (78.57%)	32	(97.00%)	1	(3.00%)	(p<0.01)	33
Female	7	(77.80%)	2	(22.20%)	(p<0.01)	9 (21.43%)
P-value (sex)	(p>0.05)		(p>0.05)			
Total	39	(92.85%)	3	(7.15%)		42 (100%)

Source: Faculdade de Medicina de Botucatu/Period: January 2006 to July 2010

systemic corticosteroids to the treatment due to the occurrence of neuritis.

The result of Goodman's test showed a similar distribution between sexes in terms of clinical forms and a significant prevalence (p<0.05) of the lepromatous form among patients of the same sex.

None of the patients (100%) had type 2 reaction while using the drug.

Graph 1 shows the patients' behavior 6 months after discontinuing thalidomide.

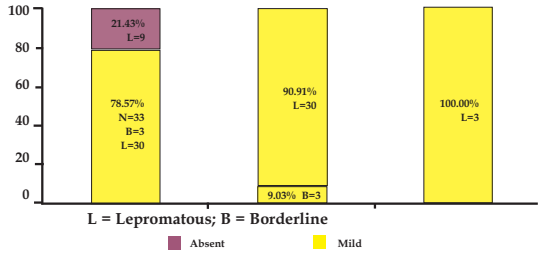
We found that there were no reactional episodes in the borderline form, whereas in 9 (21.43%) cases of the lepromatous form there were mild reactional episodes without any local or systemic effects.

The statistical analysis did not show any significant differences (p<0.001). Furthermore, the statistical analysis demonstrated that the absence of relapse was significant (p<0.001).

Our patients did not have any thalidomide-related side effects.

DISCUSSION

Initially, we evaluated 152 patients with MB leprosy. In terms of sex, 68.46% were male and 31.5% were female, which is in agreement with the ratio of males to females of 2:1 described in the literature.[8] Of these, 100 (65.78%) had clinically severe ENL. Such high rate of ENL is corroborated by data from the literature, suggesting a frequency of 50% and 70%.[8,12,13,21]



Source: Faculdade de Medicina de Botucatu/Period: January 2006 to July 2010

Graph 1: Percentage of severity of ENL episodes after discontinuation of thalidomide according to clinical

As to the clinical forms, 90% of our sample had the lepromatous form and 10% had the borderline form. Such finding is higher than the rate provided in the literature, which was 2.7% for the borderline form.[43] In terms of age, ENL was predominant in patients older than 40 years (76.2%). This age group is very important because it is related a period of life when people are professionally active.[8,12,13,19]

Both ENL and its complications lead patients to leave their professional activities for a period of time or permanently, thus causing socioeconomic problems. Undoubtedly, repeated episodes, with or without associated neuritis, result in longer periods of withdrawal from the labor market, causing significant losses to both the employee and the employer.

It is noteworthy that patients aged over 40 years were also those who had the highest bacillary indexes at the beginning of the treatment (higher than or equal to 3). Occurrence of ENL under these conditions of high bacillary indexes is in agreement with the literature.[8,12,13,19] It is clear that this is a consequence of the involvement of other problems related to leprosy, such as late diagnosis and treatment.[43,44]

Of the 100 patients with ENL in our sample, 58 (58%) were excluded mainly because of neuritis and the need to use corticosteroids. Our data demonstrate the importance of the occurrence of neuritis during the reactional episode. The percentage we found was higher than that reported in the literature.[13]

ENL may have repeated episodes, even after the end of the treatment, with a variable number of episodes.[12,17,18,19]

Considering the relapse of reactional episodes, 51% of our sample had more than one episode, and some of these patients had up to eight reactional episodes. Other studies have reported a mean rate of

three episodes per borderline patient and four episodes per lepromatous patient.[12]

Single episodes of ENL may cause significant damage to the patient. In cases of repeated episodes, such damage can be more severe, thus increasingly aggravating the damage to nerve trunks. It is worth mentioning that such episodes may continue to occur even after the end of the treatment, which may interfere with the confidence in the treatment and cure of the disease.

In many cases, new episodes may occur after discontinuation of thalidomide, ranging from mild to severe episodes. In a previous study, the authors found that most of these episodes were controlled with resumption of the treatment with a dose of 100 mg/day of thalidomide.[13] This finding led us to conduct the present study, administering the same maintenance dose after controlling the ENL episode.

Our sample consisted of 42 patients, 39 (92.98%) with the lepromatous form and three (28.6%) with the borderline form. These patients used 100 mg/day of thalidomide for six months and were followed up by means of monthly clinical evaluation. There is a high frequency of severe ENL, which requires the use of systemic corticosteroids. Therefore, cases of severe ENL without neuritis and treated only with thalidomide without corticosteroids are rare.[21] Hence, our sample of 42 patients can be considered quite reasonable for this type of study.

According to the main objective of our study, we found that the ENL episodes were controlled in 100% of cases during the use of thalidomide, i.e., for a period of six months, including those cases of repeated episodes.

In the beginning of the treatment, no possible cause related to the occurrence of the reactional episode was detected. During treatment with this dose of thalidomide, patients also did not report any related events that could change the evolution of the reactional episode.

Regardless of the possible causes of ENL during the use of thalidomide, the condition was completely controlled and there was no relapse. Thus, we believe that thalidomide controlled and prevented the occurrence of new episodes.

Our findings are much impressive when compared to those previously presented.[12] It is possible to raise the hypothesis that at least some of our patients (58%) who had neuritis could have been benefited by the absence of another episode if thalidomide had been used according this regimen. These patients could have been protected from the harmful effects of neuritis.

After the treatment period, thalidomide was discontinued, but the patients continued to be followed up for another six months on a monthly basis. We found that 33 (78.56%) did not have ENL relapses; 30 (71.42%) of them had the lepromatous form and 3 (28.58%) had the borderline form.

According to our findings, there was not relapse of ENL in 100% of cases while the patients received 100 mg/day of thalidomide. During the 6-month follow-up period after thalidomide discontinuation, there was only one new episode in nine patients (21.43%), and all of them had the lepromatous form. This result was statistically significant. However, it was a single mild reactional episode and there were not any local or systemic complications. In this clinical form, the reactional episode was completely controlled with or without the use of non-steroidal anti-inflammatory; thus, it was not necessary to resume treatment with thalidomide.

Nevertheless, the statistical test shows that the absence of relapses was significant when compared to a purely casual occurrence, i.e., 78.57% is a significant percentage compared to a result of biological chance.

It is also worth mentioning that, at the initial evaluation of all patients, the clinical manifestation of ENL was considered moderate to severe, and some patients required hospitalization.

In the present study, ENL episodes were less frequent in those patients with the borderline form (only 10% of cases), which is in agreement with the literature. There was also a low frequency of repeated episodes.[8,12]

Twenty-two patients were female and nine of them participated in the study, following the guidelines of the Ministerial Decree. The remaining female patients were excluded either because they did not meet the criteria of the decree or because of the presence of neuritis and use of corticosteroids.[34] The present study was initiated in January 2006. Therefore, the 2010 Ministerial Decree, which allows the use of thalidomide in women of childbearing age, was not in force. We believe that some of our excluded female patients could have been benefited if our study had been started in 2010.[45]

During the 6-month use of thalidomide, none of the side effects related to this drug were observed in our patients.

According to some authors, one of the side effects of thalidomide is peripheral neuropathy, mainly sensory symptoms, sometimes combined with muscle weakness, with evidence of pyramidal tract damage. Such side effects resolve after thalidomide discontinuation.[46,47]

Other studies have shown that peripheral neuropathy is not related to the dose or duration of treatment, suggesting that there is a genetic predisposition to this side effect.[48,49]

In leprosy patients, it may be very difficult to differentiate a neuropathy caused by thalidomide

from a neuropathy caused by the disease itself. However, we did not face this difficulty in our study because the patients who had neuritis were properly treated and excluded from the study. Therefore, in those patients who did have this complication, we were able to observe any manifestations of neuropathy if they occurred.

Another possible side effect is sleepiness. Patients did not report this side effect because they took the medication at night before going to bed.

Other authors, who used higher doses of thalidomide (300 to 400 mg/day), have reported that it was well tolerated and there were no side effects.[50]

In short, considering the results of our study, it is possible to raise the hypothesis that if this dose of thalidomide is administered to MB patients since the beginning of the treatment, even the first reactional episode could be prevented.

We believe that further studies should be conducted to investigate this hypothesis.

CONCLUSIONS

Based on the findings of our study, we conclude that the use of 100 mg/day of thalidomide for six months resulted in:

1 - Absence of ENL episodes in the study period;
2 - No side effects;
3 - Low frequency and mild episode of ENL after thalidomide discontinuation. ❑

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