

Double-blind trial of the efficacy of pentoxifylline vs thalidomide for the treatment of type II reaction in leprosy

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Abstract

Type II reaction in leprosy, or erythema nodosum leprosum (ENL), is often characterized by severe clinical symptoms together with nerve function impairment leading to permanent disabilities. Thalidomide has been shown to be a highly effective drug for the treatment of ENL. It is, however, contraindicated for women of childbearing age due to its teratogenicity. On the other hand, pentoxifylline, used to treat hypercoagulable states, is not teratogenic and, like thalidomide, can inhibit the synthesis of tumor necrosis factor- α and other cytokines. In the present randomized double-blind clinical study we compared the effectiveness of orally administered pentoxifylline vs thalidomide in treating type II reaction in 44 patients. Daily doses of 300 mg thalidomide or 1.2 g pentoxifylline were administered for 30 days to multibacillary leprosy patients undergoing type II reaction. Randomly chosen patients were included in the study before, during, and after specific multidrug therapy. Clinical evaluations were performed on the 1st, 7th, 14th, 21st, and 30th days of treatment and laboratory tests were carried out on the 1st and 30th days. As expected, overall, thalidomide proved to be more effective in the treatment of type II leprosy reaction. Nevertheless, continuous treatment with pentoxifylline was effective in relieving the clinical signs of ENL, especially limb edema and systemic symptoms, in 62.5% of the patients.

Key words

- Leprosy
- Reactional episodes
- Therapy
- Pentoxifylline
- Thalidomide

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Introduction

Reactional states are acute inflammatory events that commonly occur in leprosy during the course of the disease. Reactions are classified as type I, or reversal reaction, and type II, or erythema nodosum leprosum (ENL) (1). Rarely severe enough to require hospitalization, both types have been found

to cause nerve inflammation (neuritis), representing the primary cause of irreversible deformities.

Known to occur in borderline-lepromatous and lepromatous-lepromatous patients, the frequency of ENL may vary. In a previous study, it was demonstrated that 57% of patients undergoing multibacillary multidrug therapy presented reaction, with 55% having

ENL (2). Type II reaction, characterized by the appearance of tender, erythematous, subcutaneous nodules located on apparently normal skin, is frequently accompanied by systemic symptoms such as fever, malaise, enlarged lymph nodes, anorexia, weight loss, arthralgia, and edema (3,4). Additional organs, including the testes, joints, eyes, and nerves, may also be affected. Furthermore, a patient may present significant leukocytosis that typically recedes after the reactional state has subsided (5). Some reports have confirmed the presence of high levels of proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), IL-6, and IL-1 in the sera of ENL patients, suggesting that these pleiotropic inflammatory cytokines may be at least partly responsible for the clinical manifestations of type II reaction (6,7).

The treatment of ENL has been a controversial topic for many years (8). While clearly very effective, thalidomide has a teratogenic effect, causing it to be banned in many countries. However, although prohibited for women of childbearing age, the drug has been officially recommended by the Brazilian Leprosy Program of the Ministry of Health to treat type II leprosy reaction (9). In contrast, corticosteroids are the drugs of choice for ENL leprosy patients suffering from neuritis. The WHO has recommended the anti-inflammatory clofazimine (10) for chronic and severe ENL that does not respond satisfactorily to corticosteroid treatment or in cases in which the risk of toxicity is high. Many studies performed during the last 10 years have shown that thalidomide not only is a potent modulator of the immune response but also has a substantial beneficial effect in blocking the effects of TNF- α , most probably a critical factor in the control of ENL (11,12). It is known that the recognized side effects of thalidomide do not represent a serious threat and that peripheral neuropathy only rarely occurs.

Pentoxifylline, a methylxanthine derivative with potent hemorheologic-like proper-

ties, was initially marketed to treat patients with intermittent claudication (13). Pentoxifylline, believed to have a potentially crucial effect on the control of ENL, blocks the synthesis of TNF- α messenger RNA by inhibiting gene transcription (14). In non-controlled studies, pentoxifylline has been found to be both well tolerated and effective in reducing local and systemic symptoms of ENL (15). Its key advantage is that it has been shown to have no teratogenic effects and, hence, can be taken by female patients of childbearing age without concern.

The present randomized, double-blind trial was carried out to determine the efficacy and safety profiles of pentoxifylline *vs* thalidomide in treating ENL.

Patients and Methods

A randomized, double-blind trial was carried out on two groups of patients to compare the results of treatment regimens consisting of 300 mg thalidomide *vs* 1.2 g pentoxifylline. The study was conducted at the Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, RJ, Brazil, from February 1998 to June 2001 and was approved by the Ethics Committee of FIOCRUZ. All subjects gave informed written consent to participate in the study.

The following inclusion criteria were applied: 1) a diagnosis of multibacillary leprosy, 2) males between 18-60 years of age and females over 49 (postmenopausal), 3) clinical and histopathological data demonstrating the occurrence of a type II reaction, defined as inflammatory cutaneous nodules or polymorphic cutaneous lesions (erythema multiforme), 4) nerve examinations performed by an experienced neurologist that excluded any sign of acute neuritis requiring corticosteroid therapy, and 5) patients giving informed written consent.

Females under 49 and all leprosy patients suffering from hepatic, renal, or mental diseases, diabetes and/or immune-defi-

ciencies related to HIV or not were excluded from the study.

Patients who showed no improvement after 15 days of treatment, or who presented any severe adverse effects related to ingestion of the medication, i.e., gastrointestinal disturbances (vomiting, diarrhea), headaches, and dizziness, or developed acute neuritis, were removed from the study. These patients were treated with regular regimen recommended by the Ministry of Health with thalidomide or corticosteroids. Furthermore, all patients were clinically evaluated on the 1st, 7th, 14th, 21st, and 30th days of treatment. Blood was collected for tests that included a complete blood cell count and assessment of C-reactive protein (CRP) levels at the beginning and at the end of the study.

Clinical evaluation was based on the following parameters: axillary temperature and the presence of reactional cutaneous lesions, enlarged peripheral lymph nodes, edema, and other symptoms (nausea, vomiting, adynamia, headaches, arthralgia, myalgia). Patients were considered to be reaction free when, at the end of 30 days of treatment, the following criteria were satisfactorily met: complete elimination of type II reactional skin lesion inflammation, normal body temperature and/or regression of systemic symptoms.

Analyses were based on intention to treat. The resulting data were analyzed statistically using the Epi-Info 6.04 software program (Centers for Disease Control and Prevention, Atlanta, GA). The significance of the difference between proportions was tested by the Yates-corrected chi-square test. A P value of less than 5% was used as the level of statistical significance.

An outside observer assigned to periodically evaluate the results interrupted the study when a significant difference was found between the effects of the drugs.

After rigorous screening, 44 leprosy patients were selected for the study. Two were included twice since two independent reac-

tional episodes were observed in these patients at separate 3-month intervals. Twenty group 1 patients received thalidomide and 24 group 2 patients were given pentoxifylline. In the thalidomide group, 19 of the 20 patients completed the full 30-day treatment while in the pentoxifylline group, only 17 of the 24 patients were able to complete treatment.

Patients excluded during the treatment

Of the 7 patients taking pentoxifylline, 1 had gastrointestinal intolerance to the drug in the form of nausea and intense vomiting; 2 had taken other medications (1 ingested pentoxifylline on his own and the other developed acute neuritis during the course of the protocol when corticosteroids were introduced); 3 presented fever and continuing lesion inflammation after 2 weeks of treatment; 1 pentoxifylline-treated patient did not return for weekly visits; 1 thalidomide-treated patient did not complete treatment. All of these patients were removed from follow-up and categorized as treatment non-responders.

Results

The characteristics of the two groups are shown in Table 1. Table 2 provides the status of clinical and laboratory features on days 1, 7, 14, 21, and 30. At the end of the study, 20% of thalidomide-treated and about 12% of pentoxifylline-treated patients continued to present enlarged lymph nodes. Pentoxifylline performed somewhat better than thalidomide in inducing regression of enlarged nodes and edema. In contrast, thalidomide was more successful in reducing inflammatory nodules typical of type II reaction. Among all patients analyzed during reaction, 91% presented cutaneous nodules. Notably, however, approximately 95% of thalidomide-treated and a much lower 59% of pentoxifylline-treated patients showed skin

Table 1. Characteristics of patients before treatment with thalidomide or pentoxifylline.

	Thalidomide (N = 20)	Pentoxifylline (N = 24)
Age 18-69 (average)	37.1 years	33.4 years
Gender		
Male	85% (17)	87.5% (21)
Female	15% (3)	12.5% (3)
Disability grade		
0	40% (8)	45.8% (11)
1	35% (7)	29.2% (7)
2	25% (5)	25% (6)
Clinical form		
BL	30% (6)	16.7% (4)
LL	70% (14)	83.3% (20)
Bacillary index (average)	2.39	2.42

Data are reported as percent with number of patients in parentheses. BL = borderline-lepromatous; LL = lepromatous-lepromatous. There were no statistical differences between groups (chi-square test, $\alpha = 0.05$).

Table 2. Clinical and laboratory features of type II reaction upon initial examination and their evolution during treatment.

Clinical and laboratory features	Day 1	Day 7	Day 14	Day 21	Day 30
Inflammatory skin nodules					
Thalidomide	70% (14)	5% (1)	5% (1)	5% (1)	10% (2)
Pentoxifylline	65% (11)	41% (7)	35% (6)	23% (4)	12% (2)
Temperature ≥ 37.6					
Thalidomide	14% (3)	5% (1)	11% (2)	0%	0%
Pentoxifylline	9% (2)	0%	11% (2)	6% (1)	7% (1)
Edema					
Thalidomide	55% (11)	50% (10)	50% (10)	45% (9)	40% (8)
Pentoxifylline	40% (7)	30% (5)	18% (3)	30% (5)	18% (3)
Enlarged lymph nodes					
Thalidomide	30% (6)	20% (4)	15% (3)	20% (4)	20% (4)
Pentoxifylline	41% (7)	23% (4)	6% (1)	6% (1)	12% (2)
Other symptoms					
Thalidomide	75% (15)	35% (7)	30% (6)	35% (7)	25% (5)
Pentoxifylline	59% (10)	53% (9)	35% (6)	44% (7)	29% (5)
White blood cells $\geq 11,000$					
Thalidomide	29% (6)	-	-	-	0%
Pentoxifylline	45% (10)	-	-	-	8% (1)
Positive C-reactive protein					
Thalidomide	72% (13)	-	-	-	33% (6)
Pentoxifylline	60% (9)	-	-	-	20% (3)

Data are reported as percent with number of patients in parentheses. Laboratory tests were carried out only at the beginning and the end of the study.

lesion regression after 7 days. The analysis of other symptoms occurring during the reaction revealed that 74% of all patients suffered from nausea, vomiting, headaches, adynamia, myalgia, and/or arthralgia. It was also found that among the 75% of thalidomide-treated patients presenting other symptoms at diagnosis (day 1), only 25% presented these same symptoms on day 30. Likewise, in pentoxifylline-treated patients, among the 59% presenting other symptoms at diagnosis, only 29% maintained the same symptomatology at the end of the study.

The results of white blood cell count and the positivity of CRP levels were found to vary more frequently. In about 45% of thalidomide-treated and 29% of pentoxifylline-treated patients, leukocytosis (more than 11,000 white blood cells/mm³) was observed at the initial examination even though regression occurred in both groups. CRP levels were found to be positive in 72% of group 1 and 60% of group 2 patients, whereas on day 30 the percentage of thalidomide-treated and pentoxifylline-treated patients presenting a positive test had sharply declined to 33 and 20%, respectively.

To evaluate the performance of each drug and compare the respective data, analyses were carried out to measure their effectiveness after 2 weeks and at the end of treatment. Table 3 summarizes and grades the results as follows: 1) partial improvement when 1 or more symptoms were manifested; 2) total improvement when 100% improvement occurred after a type II reactional episode; 3) general improvement considering both groups together (partial improvement + total improvement). As shown by an intention to treat analysis, at the end of 2 weeks patients taking thalidomide showed a general improvement rate of 95% while those taking pentoxifylline obtained a 75% rate. However, at the end of 4 weeks, whereas the general improvement rate of the thalidomide group remained at 95%, that of the pentoxifylline group dropped to 62.5%. When these

data were compared by the Yates-corrected chi-square method at 4 weeks, there was a statistically significant difference between the drugs ($P = 0.02$).

Most of the adverse reactions caused by each drug, especially those related to gastrointestinal complaints and nausea, occurred during the first week, tending to completely disappear over the remaining weeks of treatment. Only 1 pentoxifylline patient discontinued treatment due to the severity of these adverse effects. No significant difference in the occurrence of adverse reactions was detected between the two drugs (at the end of the first week and at the end of the third week; see Table 4).

Discussion

It is clear that the results of this double-blind controlled study strongly support the beneficial effects of pentoxifylline in treating ENL (15,16). However, at the end of 1 month of treatment, the clinical results showed that the overall response to thalidomide was significantly superior to the response to pentoxifylline. At the end of treatment, the improvement rate of patients taking pentoxifylline was a noteworthy 62.5% compared to 95% for those taking thalidomide. Furthermore, thalidomide acted more rapidly in reducing skin lesions. By day 7, only 5% of the patients presented skin lesions vs 41% of those taking pentoxifylline. In agreement with these results, in a clinical trial with thalidomide and acetylsalicylic acid, Iyer et al. (17) demonstrated that, by day 8, skin lesions had disappeared in 73% of the ENL reactional patients treated with thalidomide. In our study, pentoxifylline also contributed remarkably to the regression of edema and lymph node enlargement.

It is known that ENL patients often present severe leukocytosis capable of attaining a maximum of $30,000/\text{mm}^3$, characteristic of a leukemoid reaction (6). Oliveira et al. (18) have shown that, in ENL patients, poly-

morphonuclear neutrophils participated in the acute inflammatory response as an additional source of $\text{TNF-}\alpha$, correlating to the intense neutrophil infiltrate in these lesions. In the present study, the leukocyte count similarly regressed as a consequence of treatment with both drugs.

Foss et al. (19) have reported high CRP levels along with a positive correlation (95%) between elevated $\text{TNF-}\alpha$ and CRP levels in the serum of ENL patients. In the present study, on day 1, a high percentage of the ENL patients in both groups presented high serum levels of CRP (72% of group 1 and 60% of group 2) that regressed by day 30. Taken together, leukocytosis and CRP could be considered as laboratory parameters to be used to follow up the systemic inflammatory response and the decrease in serum $\text{TNF-}\alpha$ levels (18,19).

Table 3. Comparison of the effectiveness of treatment on the clinical signs and symptoms of leprosy type II reaction between thalidomide-treated and pentoxifylline-treated patients.

	15 days			30 days		
	PI	TI	GI (PI + TI)	PI	TI	GI (PI + TI)
Thalidomide	60%	35%	95%	50%	45%	95%*
Pentoxifylline	58.3%	16.7%	75%	29.2%	33.3%	62%

In this intention to treat analysis, the randomized schedule was followed rigorously. PI = partial improvement; TI = total improvement; GI = general improvement.

* $P = 0.02$, comparison of the two groups at 30 days (t -test).

Table 4. Adverse reactions to thalidomide and pentoxifylline at the end of weeks 1 and 3.

Adverse reactions	End of 1st week		End of 3rd week	
	Thalidomide (N = 20)	Pentoxifylline (N = 23)	Thalidomide (N = 19)	Pentoxifylline (N = 18)
Presence	5 (25%)	7 (30.4%)	3 (15.8%)	2 (11.1%)
Absence	15 (75%)	16 (69.6%)	16 (64.2%)	16 (88.9%)

Data are reported as number of patients with percent in parentheses. There were no statistical differences between drugs at the end of the 1st or 3rd week (chi-square test).

The present results obtained in the clinical evaluations carried out at the end of 30 days of treatment clearly indicated that the overall response to thalidomide was significantly better than the response to pentoxifylline. However, pentoxifylline could represent a good alternative treatment for ENL patients for whom thalidomide is contraindicated.

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