

# A RANDOMIZED CLINICAL TRIAL OF ORAL STEROIDS FOR ULNAR NEUROPATHY IN TYPE 1 AND TYPE 2 LEPROSY REACTIONS

José Antonio Garbino<sup>1</sup>, Marcos da Cunha Lopes Virmond<sup>2</sup>,  
Somei Ura<sup>1</sup>, Manoel Henrique Salgado<sup>2</sup>, Bernard Naafs<sup>3</sup>

**Abstract – Background:** Steroids regimens in leprosy neuropathies are still controversial in both types of reactions. **Method:** For this trial, 21 patients with ulnar neuropathy were selected from 163 leprosy patients, 12 with type 1 reaction (T1R) and nine with type 2 (T2R). One experimental group started with prednisone 2 mg/kg/day and the control group with 1 mg/kg/day. A clinical score based on tests for spontaneous pain, nerve palpation, sensory and muscle function was used. Neurophysiological evaluation consisted on the motor nerve conduction of the ulnar nerve in three segments. Student “t” test for statistical analysis was applied on the results: before treatment, first week, first month and sixth month, between each regimen and types of reaction. **Conclusion:** In both reactions during the first month higher doses of steroids produced better results but, earlier treatment with lower dose was as effective. Short periods of steroid, 1 mg/Kg/day at the beginning and tapering to 0,5 mg/Kg/day or less in one month turned out to be efficient in T2R.

**KEY WORDS:** leprosy, ulnar neuropathy, steroids, neurophysiology.

## Ensaio clínico sobre o tratamento com esteróides via oral da neuropatia ulnar em reação tipo 1 e tipo 2 da hanseníase

**Resumo – Introdução:** O tratamento da neuropatia da hanseníase com esteróides é ainda controverso nos dois tipos de reações. **Método:** Neste ensaio, de 163 pacientes foram selecionados 21 com neuropatia ulnar, 12 com reação tipo 1 e 9 com tipo 2. Um grupo experimental iniciou com 2 mg/kg/dia e o grupo controle com 1 mg/kg/dia. Foi composto um escore clínico pela avaliação da sensação dolorosa espontânea, palpação de nervos e funções sensitiva e motora. Realizou-se a condução nervosa motora do nervo ulnar em três segmentos. Aplicaram-se os estudos estatísticos com o teste t de Student nos resultados: antes do tratamento, primeira semana, primeiro mês e sexto mês. **Conclusão:** Em ambas as reações dosagens mais elevadas iniciais produziram melhores resultados, mas a dose menor quando administrada precocemente foi igualmente efetiva. Períodos curtos com doses efetivas, 1 mg/Kg/dia no início e reduzindo-se para 0,5 mg/Kg/dia ou menos em um mês foram eficientes na reação tipo 2.

**PALAVRAS-CHAVE:** hanseníase, neuropatia ulnar, esteróides, neurofisiologia.

Immune response to *Mycobacterium leprae* may lead to disability due to nerve damage, which occurs mostly during the acute inflammatory episodes named reactions. According to the immunity, leprosy patients can develop distinct clinical groups<sup>1</sup>: polar tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL) and polar lepromatous (LL). Mainly two types of reactions are known, the type 1 leprosy reactions (T1R) or reversal response, which happens in groups that have cell-mediated immune reaction,

TT, BT, BB even in BL patients and, the type 2 leprosy reaction (T2R) or *erythema nodosum leprosum*, which is predominantly immune-complex mediated and occurs only in BL and LL. Treatment of these reactions in nerves usually requires immunosuppressive or immunomodulating drugs. Therefore it is relevant to study different regimens in the treatment of these episodes in order to define the most appropriate ones. Oral prednisone or prednisolone are the most often used drugs. Dosages vary from 30–40 mg/day<sup>2-4</sup> to 60–80 mg/day in severe cases<sup>5-8</sup>. Based on

<sup>1</sup>Instituto Lauro de Souza Lima, Bauru SP, Brasil; <sup>2</sup>Departamento de Produção da Faculdade de Engenharia de Bauru, Universidade do Estado de São Paulo, Bauru SP, Brasil; <sup>3</sup>Departamento de Dermatologia do Centro Médico da Universidade de Leiden, Holanda.

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Dr. José Antônio Garbino – Instituto Lauro de Lima - Caixa Postal: 3021 - 17034-971 Bauru SP - Brasil. E-mail: garbino.blv@terra.com.br

a few studies the standard starting dose of prednisone/prednisolone for field use was established to be approximately 40 mg/day<sup>9,10</sup>. However, there are no references available relating body weight to steroid doses.

The follow-up of motor nerve function using Voluntary Muscle Testing (VMT) gives insight into behavior of nerves during reactions and treatment<sup>11</sup>. Magora<sup>12</sup> suggested using motor nerve conduction (MNC) for nerve monitoring in leprosy neuropathy. Naafs and Dagne<sup>13</sup> and later Naafs and Van Droogenbroeck<sup>14</sup> compared MNC with VMT and graded sensory testing (GST). The last two authors gathered all the parameters to compose a nerve severity index.

In this study, measurement of the MNC along the ulnar nerve was selected to investigate differences in nerve responses in the two types of leprosy reactions, type 1 and type 2, under two different steroid regimens advised by the Brazilian guidelines for leprosy control<sup>15</sup>, initial doses of 1 mg/kg/day to 2 mg/kg/day.

## METHOD

Patients presenting leprosy reaction and with active ulnar nerve involvement were selected at the outpatient department of the Instituto Lauro de Souza Lima in Bauru, Brazil. All patients provided informed written consent and the study was approved by the institutional Ethical Committee. Patients at risk of a neuropathy other than leprosy neuropathy were excluded, i.e. diabetes, alcoholism, HIV infection, also with family history of hereditary neuropathy and over 60 years of age. Patients with inactive neuropathy and/or chronic neuropathic pain, with nerve abscess and with nerves that had been submitted to neurolysis, as well as patients with a contraindication for steroids were also excluded.

Reactions were defined as:

Type 1 reaction (T1R) in the TT, BT, BB and BL patients: an increased inflammation of existing lesions with or without non-tender new lesions and/or acro-edema. Nerves may be enlarged, tender and show loss of function.

Type 2 reaction (T2R) in the LL patients: a sudden appearance of inflamed papules, nodules and plaques that are tender on palpation. The patient may be ill and run a mild fever. There may be signs of involvement of other organs, e.g., eyes, testes, joints, lymph glands and periosteum. Nerves may be enlarged, tender and show loss of function.

Out of 163 leprosy patients examined during the period of September 2003 to August 2005, 21 patients were eligible, and included in the study: 17 men and 4 women (ages 21–60, mean: 41.5). Twelve patients had T1R (3 BT and 9 BB) and nine T2R, all were LL.

Patients of both reaction types were assigned to treatment groups: experimental or control. The patients were assessed immediately prior to the beginning of treatment (1<sup>st</sup>), after one week (2<sup>nd</sup>), after one month (3<sup>rd</sup>) and thereafter monthly, the last follow-up occurred after six-months (8<sup>th</sup> assessment). All patients were submitted to clinical and dermatological exami-

nation in order to classify the leprosy groups, a general clinical evaluation and laboratory tests were performed to assess blood cells, blood sugar levels, liver and kidney functions.

## Clinical evaluation

1. Assessment of spontaneous pain – this utilizes a visual analog scale (VAS), in which zero represents no pain and 10 represents unbearable, incapacitating pain<sup>16</sup>. 2. Nerve palpation (NP) – this is done at the elbow. Size and tenderness were evaluated and graded: 0 (normal palpation) –5 (maximum nerve enlargement)<sup>17</sup>. 3. Graded sensory testing (GST) – nylon monofilaments (SORRI – Bauru/ Brazil Kit<sup>18</sup>, 0.5, 1, 2, 4, 10, 100 g), were used in two areas innervated by the ulnar nerve, one in the hypothenar region and one in the little finger. The results were computed to a maximum of 12 points, when no filament was felt in a completely damaged nerve, and zero when all filaments were felt for a normal nerve. 4. Voluntary muscle testing (VMT) – The tested muscles were the *abductor digiti minimi* muscle and the first *dorsal interosseus*. A normal score would be 10 points (2 × 5) and when paralyzed, 0 points. In this study it was employed a reverse scale in order to align the results and build the score. These results were comparable with the other tests, in which the greater values relate to diminishing function. A final *clinical score* (CS) was calculated by the somatory of the results of VAS, NP, GST and VMT. The VAS and NP were applied only by one examiner and the GST and VMT were applied by the institution staff of therapists.

## Neurophysiologic evaluation

Motor nerve conduction (MNC) studies were carried out over three segments of the ulnar nerve. Recording of the compound motor action potential (CMAP) was done with the active recording electrode on the *abductor digiti minimi* muscle belly and the reference electrode on a tendon or a bony surface<sup>19</sup>. The CMAP amplitude by supramaximal stimulation, measured from the base line to the negative spike, is a function of the number of functioning motor axons<sup>19</sup>.

1. The distal latency was measured over an 8 cm long segment from the active recording electrode to the wrist; the recording electrode was attached on the muscle belly. 2. The nerve was also stimulated just below the elbow and 11 cm proximal. The conduction velocity over the forearm segment and across the elbow was computed. 3. The CMAP temporal dispersion (TD), i.e., the duration of CMAP<sup>19</sup>, was measured below and above the elbow. Its values, in percentage, were summated. 4. The minimum value of the F wave latency, related to demyelination in all segments of the nerve from stimulating electrode to spine and back to the recording electrode, was measured over a series of 20 stimuli.

The period between the start of symptoms and the beginning of treatment was recorded as less than three months (<3 m) or more than three months but less than six (>3 <6 m).

Patients with T1R and T2R were randomly selected and two random sequences were built, by throwing a coin, for either ex-

Day	Experimental groups				Control groups																			
	EG1 (mg/day)		EG 2 (mg/day)		CG 1 (mg/day)		CG 2 (mg/day)																	
1°	120		120		60		60																	
2°	120		120																					
3°	120		120																					
4°	110		110																					
5°	100		100																					
6°	90		90																					
7°	80		80																					
8°	60		60						50															
9°			60																					
10°			50																					
11°			50																					
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14°			35																					
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16°			30		20-30																			
17°			30																					
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	mg/day	Days	mg/day	Days			mg/day	Days	mg/day	Days														
	40	15-30	20-30		40	15-30	20-30																	
	30-40	60			30-40	60																		
	20-30	60			20-30	60																		
	10-20	30			10-20	30																		
<b>Total</b>	Trial duration six months		After the 1 <sup>st</sup> month treatment based on findings		Trial duration six months		After the 1 <sup>st</sup> month treatment based on findings																	

Fig 1. Treatment regimes of experimental groups in T1R and T2R and control groups (1 and 2) in T1R and T2R, considering a patient with a 60 kg bodyweight.

Table 1. Distribution of nerves with active neural involvement, as type of reaction, grade of severity and duration of symptoms.

Grade	T 1 R (time)		T2 R (time)		Total of nerves
	<3 m	>3 <6 m	<3 m	>3 <6 m	
Partial lesion	12	5	8	3	28
Complete paralysis	0	2	1	3*	6
Total of nerves	12	7	9	6	34

\*These nerves have presented the symptoms for more than six months.

perimental group (EG), one receiving prednisone 2 mg/kg (12 patients), or other control group (CG), which received 1 mg/kg (nine patients), as initial treatment. This resulted in four groups: EG T1R, CG T1R and EG T2R, CG T2R (Fig 1).

Results of the CS and the neurophysiologic parameters at the beginning of the study (1<sup>st</sup> assessment) were compared with the results obtained after the first week (2<sup>nd</sup> assessment), with the results after the first month (3<sup>rd</sup> assessment) and following the 6<sup>th</sup> month (8<sup>th</sup> assessment), of each reaction type in the ex-

perimental and control groups, using the Student “t” test for statistical analysis.

### RESULTS

Out of 21 patients, 15 (71.4%) had finished multidrug-therapy around 17.7 months before the symptoms started. Eleven patients were taking inappropriate prednisone doses (mean 0.17 mg/kg/day) prior to inclusion in the protocol. The responses of their nerves were compared

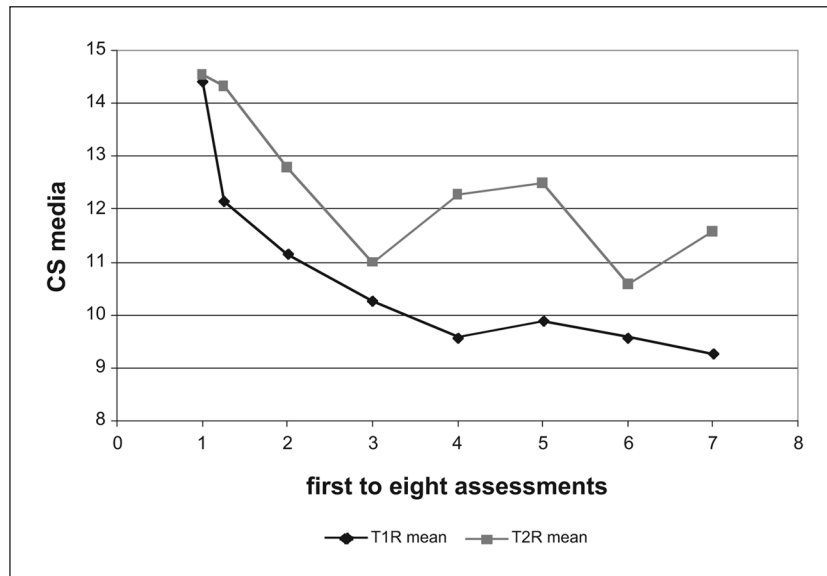


Fig 2. Mean of CS nerves results in patients with T1R and T2R (EG and CG together). The first CS mean was prior to the treatment, the second was after at the end of the first week, the third at the end of the first month and thereafter monthly until the last occurrence at the end of the sixth month.

Table 2. The neurophysiological results in patients of experimental group (EG) and control group (CG) (T1R and T2R) comparing the 1<sup>st</sup> evaluation with the 2<sup>nd</sup>, the 1<sup>st</sup> evaluation with the 3<sup>rd</sup> and 1<sup>st</sup> evaluation with the 8<sup>th</sup> (n=28). The highlighted data are the results with statistical significance and the underlined data are the borderline results.

Steroid regimens EG × CG	1 <sup>st</sup> × 2 <sup>nd</sup>	1 <sup>st</sup> × 3 <sup>rd</sup>	1 <sup>st</sup> × 8 <sup>th</sup>
Distal latency	0.057	0.082	0.095
CMAP wrist	0.968	0.380	0.663
CV in the forearm	0.023	0.057	0.787
CMAP at the elbow	0.981	0.279	0.310
CV across elbow	0.116	0.299	0.167
CMAP above elbow	0.322	0.680	0.267
TD (elbow + above)	0.095	0.032	0.703
F wave	0.054	0.157	0.121

with the results obtained in the patients without previous treatment. No significant differences were found. They were therefore included in the overall assessment.

Forty-two ulnar nerves from 21 patients were studied. Eight nerves did not show any active neural involvement during the study, six nerves were completely damaged, and 28 nerves were followed by CS and neurophysiology. The distribution of nerves according to type of reaction, and duration of symptoms are demonstrated in Table 1.

During the study, six out of the nine T2R patients needed additional drug treatment 2–3 months after initiation of treatment with prednisone. They received tha-

lidomide as an immunomodulator in doses of 100–200 mg/daily and a temporary slight increment of steroids. None of the T1R patients needed additional treatment. At the end of the time frame to develop this protocol all T1R patients were still on steroids, but tapering off, as well as six (out of 9) of the T2R group.

The values found for the CS within the four groups, when compared within each pair (before treatment, after one week, after 1 and 6 months), showed no significant differences, either for the EG compared with the CG (including both T1R and T2R) or for the T1R group compared with the T2R group (including both EG and CG). However, when the results before treatment (1<sup>st</sup> evaluation) and after 6 months (8<sup>th</sup> evaluation), were compared for each group, all groups showed significant improvement during the trial period (Student t test, p=0.000 for T1R and p=0.046 for T2R).

The graphic representation of the mean CS values (Fig 2) shows an obvious visual difference favouring T1R cases and a clear tendency to deterioration within the T2R group during dose reduction.

#### Neurophysiologic data

The most frequent abnormal findings observed were in the CV across the elbow (83.33%), F wave latency (69.44%) and in the TD at the elbow and above (across the elbow) (52.77%), followed by the CV along the forearm (38.89%) and the distal latency (30.56%).

The statistical differences between the parameters obtained in the EG and the CG are compared in Table 2, including all patients, independent on the type of reaction.

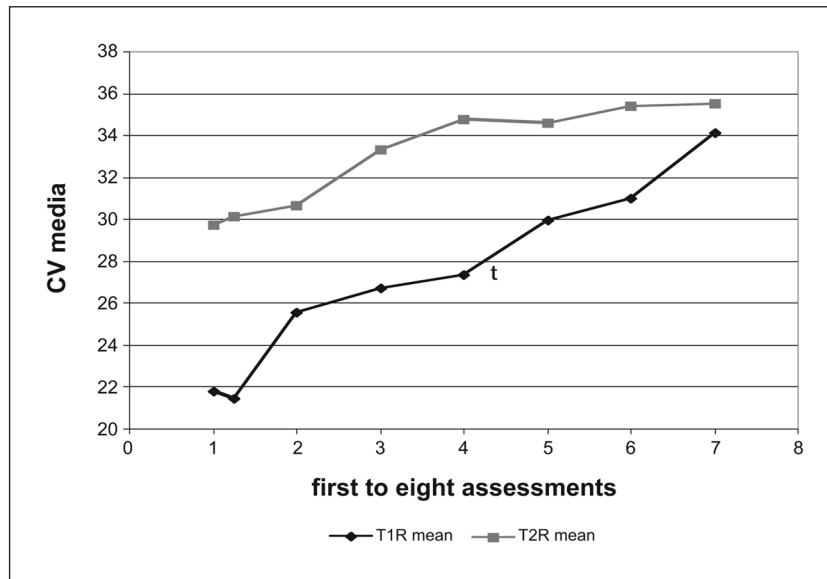


Fig 3. Mean of CV across the elbow during a cohort in nerves of patients of groups T1 R and T2 R (n=28). The first CV mean was prior to the treatment and the second was after at the end of the first week, the third at the end of the first month and thereafter monthly until the last occurrence at the end of the sixth month

Table 3. The neurophysiological results in nerves with at two different treatment delay periods: less than three months (<3 m) or more than three months but less than six (>3 <6 m), in patients of EG and CG (T1R and T2R) comparing the 1<sup>st</sup> evaluation with the 2<sup>nd</sup>, the 1<sup>st</sup> evaluation with the 3<sup>rd</sup> and 1<sup>st</sup> evaluation with the 8<sup>th</sup> (n=28). The highlighted data are the results with statistical significance and the underlined data are the borderline results.

Treatment delay period (<3 m) × (>3 <6 m)	1 <sup>st</sup> × 2 <sup>nd</sup>	1 <sup>st</sup> × 3 <sup>rd</sup>	1 <sup>st</sup> × 8 <sup>th</sup>
Distal latency	0.144	0.669	0.297
CAMP wrist	0.621	0.766	0.558
CV in the forearm	0.427	0.902	0.236
CAMP at the elbow	0.834	0.042	0.156
CV across elbow	0.114	0.014	0.043
CAMP above elbow	0.191	0.041	0.256
TD (elbow + above)	0.097	0.069	0.225
F wave	0.157	0.037	0.014

Table 4. The neurophysiological results in all nerves with symptoms for less than three months (<3 m) in patients of EG compared with CG (T1R and T2R) comparing the 1<sup>st</sup> evaluation with the 2<sup>nd</sup>, the 1<sup>st</sup> evaluation with the 3<sup>rd</sup> and 1<sup>st</sup> evaluation with the 8<sup>th</sup> (n=20). The highlighted data are the results with statistical significance.

Treatment delay period (<3 m) EG × (<3 m) CG	1 <sup>st</sup> × 2 <sup>nd</sup>	1 <sup>st</sup> × 3 <sup>rd</sup>	1 <sup>st</sup> × 8 <sup>th</sup>
Distal latency	0.046 (T1R)	0.176	0.229
CAMP wrist	0.295	0.390	0.251
CV in the forearm	0.046 (T1R)	0.142	0.129
CAMP at the elbow	0.028 (T2R)	0.481	0.006 (T2R)
CV across elbow	0.196	0.081 (T1R)	0.319
CAMP above elbow	0.041 (T2R)	0.168	0.005 (T2R)
TD (elbow + above)	0.480	0.155	0.374
F wave	0.107	0.038 (T1R)	0.053 (T1R)

The results showed a significant improvement of EG in the variables CV over the forearm and CMAP TD across the elbow during the first week and during the first month. The F wave latency also showed greater improvement at the end of the first week. In the first week the distal latency showed a slight impairment in the EG group. Improvement was found at the end of first month (p=0.082). The significant differences disappeared after 6 months.

Statistical differences between the 2 types of reaction were seen only in the improvement of the CV (p=0.015)

and the TD across the elbow (p=0.033) in nerves of patients suffering from T1R compared with patients with T2R after 6 months, i.e., at the end of the study. The graphic representation (Fig 3) of the CV in nerves in T1R compared with T2R, before treatment, shows CV markedly lower in T1R than in nerves in T2R.

Patients with symptoms lasting less than three months showed significantly greater improvement during the first month in several of the parameters: CMAP at the elbow, CV across the elbow, CMAP above the elbow, TD across



the elbow and F wave latency, at the end of first month (3<sup>rd</sup> assessment), when compared with patients whose treatment was delayed (Table 3).

Twenty out of the 28 nerves fell into the category of less than three months treatment delay (<3m). When only those 20 nerves were analysed, comparing the EG with the CG, minimal differences were observed. The same parameters improved in EG (CV in the forearm at the first week and F wave latency in the first week and in the last evaluation) and in the CG (CMAP amplitude at the elbow and CMAP amplitude above) in the first week and in the last evaluation. Other parameters, such as wrist CMAP amplitude, VC and TD across elbow did not show statistical differences.

The results show that there is a statistically a greater improvement in patients of the EG than CG, at the beginning of treatment, in the first week, and at the 6th month of evaluation (Table 4).

Two of the patients developed adverse effects of major severity during the trial period, both of them in the EG: one patient developed osteoporosis with collapse of the 10<sup>th</sup> dorsal vertebra and another developed hyperglycemia and cataracts. Patients of all groups had gained weight at the end of the study.

## DISCUSSION

Several studies have discussed the duration of steroids treatment for reactions and there is evidence that the treatment period for T1R should be longer than the three months recommended by World Health Organization, preferably six or, in some cases, even longer<sup>20</sup>. The duration of treatment for a single episode of T2R is not clear, but there are indications that a reaction usually lasts one month or less<sup>21</sup>. The therapy with higher doses of steroids should be confined to this period in T2R.

Initial steroid dose has infrequently been discussed, although different standard regimens employ different doses. In fact, the initial dose for both reactions and the duration of treatment specifically in neural T2R, has not been fully studied<sup>22-24</sup>.

When the results for the CS were compared, no significant differences were found, either for T1R and T2R (without considering the steroid regimen) or for EG and CG (with T1R and T2R grouped together). Similar results were seen in the literature<sup>25</sup> when different steroid regimens were compared. Meanwhile, all groups showed significant improvement over time ( $p=0.000$  for T1R and  $0.046$  for T2R), indicating the effectiveness of the chosen treatments (Fig 2). However, Figure 2 shows some differences between the T1R and T2R groups: nerves of T1R patients improve more and continuously while there is a tendency

to recur and to abate in T2R patients. In fact, when developing a new reaction, either clinically or in the follow-up parameters, 6 out of the 9 patients in the T2R group needed adjustment of treatment as allowed by the protocol. This usually occurred after one to two months of treatment, when the steroids had reached the doses of 20–30 mg/day. When increasing the steroid doses and introducing thalidomide improvement was again observed (Fig 2).

In T1R group, relapses of reactions did not occur, contrary to Manandhar's et al.<sup>9</sup> and Sundar Rao et al.<sup>26</sup> reports, as the treatment period of T1R patients was adjusted to the true duration of 4 to 18 months<sup>20</sup>.

In the comparison of neurophysiologic parameters of the EG and CG, regardless of the type of reaction, statistical differences were found at all three moments evaluated: after the first week (2<sup>nd</sup>), after the first month (3<sup>rd</sup>) and after six months (8<sup>th</sup> assessment) (Table 4). After the first week and at the end of the first month the CV along the forearm and the TD across elbow were significantly better for the EG. These results reflect remyelination. However, the improvement in the first week is most likely a result of reduction of intraneural edema.

These results favor the EG during the first month; this is probably due to the more anti-inflammatory, anti-edema effect of the higher steroid doses. After the first month, when the same dose was given to both groups, statistical differences disappeared. However, the improvement of the parameters in the different groups continued. These results indicate a *dose-response* effect of steroid in the treatment of leprosy neuropathy during reactions, especially at the initial period, when inflammation with edema formation is a major component. The changes in CV at the elbow demonstrate graphically a remarkable reduction after the second month of the T1R compared to the T2R, showing more pronounced and continuous remyelination in T1R than in T2R (Fig 3). The repetitive character of the T2R with neural involvement could be a major factor influencing the poor results of long-term treatment of a T2R neuropathy. When the two steroid regimens in T1R were compared, only the TD had significantly greater improvement after 1 month of treatment in nerves of the EG (Table 2). This indicates that an early release of edema may lead to an earlier start of remyelination. In both reactions higher doses show better responses, but in T2R shorter treatment courses may be effective. The use of a higher dose for even an initial short period, as in pulse therapy, should be considered in severe nerve involvement<sup>27,28</sup>.

When only the nerves ( $n=20$ ) with a delay of less than three months to begin treatment were compared in the EG and CG, the results were similar. These findings corroborate the results from literature<sup>2,5</sup>. Although there were

slightly better overall EG results in this trial, it is clear that early treatment is more important than the higher dose of steroids.

The frequency of major adverse side-effects of steroids treatment<sup>29</sup> in the patients of EG was relevant and it must always be taken into consideration.

In conclusion, the responses to steroid showed significance favoring the EG in both T1R and T2R nerves. The effect on nerve showed, at least initially, to be dose-dependent for both the T1R and T2R nerves. Short periods of high doses were effective in T2R, but additional doses and immunomodulating therapy are required between the reactional episodes. In nerves in which the treatment started early, i.e., less than three months after symptoms began, 1.0 mg/kg/day (CG) would be as effective as initial doses of 2 mg/kg/day (EG) for both reactions. Neurophysiologic parameters showed to be more consistent than clinical tests for the outcome assessment in clinical trials.

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