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Corticosteroid therapy in TSP/HAM patients: The results from a 10 years open cohort

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Abstract

Background: The use of corticosteroids for treating tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM) has yielded controversial results. We report the use of corticosteroids for the treatment of TSP/HAM in an open cohort.
Methods: The clinical efficacy of long-term, high dose of corticosteroid therapy was studied in thirty-nine TSP/HAM patients. Disability and motor dysfunction was evaluated based on the Disability Status Scale (DSS), Osame's Motor Disability Scales (OMDS), and Incapacity Status Scale (ISS), before and after treatment. Treatment included use of methyl-prednisolone, 1 g/day for three days, every 3–4 months. The primary end-point was a change in the scores of the neurological scales from baseline until the fifth visit after therapy.
Results: After a mean follow-up of 2.2 years and an average of four pulses per patient, we noted a significant neurological improvement, reaching 24.5% according to the ISS score. No statistically significant differences in scores according to the OMDS and DSS scales were noted.
Conclusion: We observed neurological improvement with the use of corticosteroids, with physical therapy and antispastic-drugs as adjunctive treatment. However, randomized clinical trials should be done to assess the use of corticosteroids and other potentially useful immune-based therapies for TSP/HAM treatment.

Keywords: HTLV-1; TSP/HAM; Treatment; Brazil; Corticosteroid

1. Introduction

Tropical spastic paraparesis/HTLV-1 associated myelopathy (TSP/HAM), caused by human T lymphotropic virus type 1 (HTLV-1), has an incidence of 1 case per 100 HTLV-1 infected carriers in highly endemic populations [1]. The major histopathological characteristic of TSP/HAM is a chronic inflammation of the white and gray matter of the spinal cord followed by a degenerative process that preferentially affects the white matter in the lower spinal cord [2,3]. TSP/HAM is characterized by a chronic slowly progressive spastic paraparesis with bladder disturbances, absent or mild sensory loss and low back pain, with seropositivity for HTLV-1 antibodies, in the absence of spinal cord compression [4,5]. Despite the more usual presentation characterized by a slow progression, 21.5% of the patients may experience a rapid progression, with severe disability two years after the onset of symptoms [6]. This phenomenon is related to older

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age of onset, parenteral HTLV-1 transmission route, high viral loads, and high antibody titers [7–9].

There is no established therapy for TSP/HAM. Most treatments have been directed at reducing inflammation in the affected tissues. Others such as interferon-α [10–13] have both antiviral and immunomodulatory capacity. Various alternative treatments such as oral prednisolone, intrathecal hydrocortisone [13–15], plasmapheresis [16], vitamin C [17]. and antiretroviral drugs [18–21] have been reported. There are also some reports about the transient benefits of immunotherapy, Pentoxyfiline, Danazol and more recently milk drinks containing *Lactobacillus casei* [22–25]. Even though corticosteroids are the most widely used therapy for TSP/HAM, few clinical trials with corticosteroids have been published recently.

In Brazil HTLV-1 infection is endemic in some areas [26]. We have been following an open HTLV cohort since 1997 to study some epidemiological, laboratory and clinical characteristics of this infection in the city of São Paulo [27,28]. Therefore, we tried to assess the clinical corticosteroid effects on TSP/HAM in a long-term follow-up. Herein, we describe the results of this treatment.

2. Material and methods

This observational study of TSP/HAM patients was conducted at Institute of Infectious Diseases "Emilio Ribas" from June 1997 through June 2006; the Institute is a 250 bed public hospital in São Paulo, Brazil.

The TSP/HAM diagnosis was done according to the WHO TSP/HAM classification [29]. Inclusion criteria for the current study were: patients who had received intravenous methyl-prednisolone 1 g/day for three days (pulse therapy), absence of HIV infection, and at least two neurological scales entered (before and after pulse therapy) in their clinical records. The exclusion criteria were simultaneous use of other specific TSP/HAM therapy or diagnosis of diabetes mellitus. All participants signed an informed consent that was approved by the local Ethical Board at the Institute of Infectious Diseases.

The HTLV unit is composed of a multidisciplinary team including infectious diseases specialists, neurologists, a physical therapist and dentists. All study participants were examined both before and at least 40 days after pulse therapy. All patients had a previous urine examination to rule out a current urinary tract infection, and a stool examination for *Strongyloides stercoralis*, but regardless of the result they received empirical treatment with ivermectin. In some cases the pulse intervals were not regular, since several patients came from outside the city of São Paulo, making a regular follow-up not always possible.

All patients were clinically evaluated before and after pulse therapy. The following neurological scales were applied by neurologists in each patient visit: Disability Status Scale (DSS) proposed by Kurtzke in 1955 and the Incapacity Status Scale [30], both for Multiple Sclerosis [31,32], and the Osame's Motor Disability Score (OMDS), specific for TSP/HAM. The Incapacity Status Scale was devised to grade also disability. It consists of 16 items, namely: stair climbing, ambulation, toilet/chair/bed transfer, bowel function, bladder function, bathing/dressing, grooming, feeding, vision, speech and hearing, medical problems, mood and thought disturbances, met-nation, fatigability and sexual function. Each item is graded on 0–4 scale with 0 being normal function and 4 being loss of function. Motor dysfunction was evaluated on the basis of the Osame's Motor Disability Score, in which motor dysfunction is graded on a scale from 0 (normal walking and running) to 13 (completely bedridden).

The primary end-point was a change in the scores of the neurological scales from baseline until the fifth visit after pulse therapy. Student's *t*-test (paired) was used to assess the differences in the neurological scale scores. Statistical analyses were performed using SAS 9.1 (Cary, NC, EUA).

3. Results

During the period from June 1997 to June 2006, 66 patients were enrolled in our cohort with TSP/HAM. A total of 27 patients were excluded, either because of the absence of neurological examinations in their records before pulse

Table 1
Characteristics of the TSP/HAM patients by gender

Variables	Female (%)	Male (%)	Total (%)
	n=26	*n*=13	*n*=39
Age (range)	46 (23–74)	48 (24–72)	47 (23–74)
Clinical symptoms at admission			
Bladder disturbance	21 (81%)	11 (85%)	32 (82%)
Weakness in lower limbs	22 (85%)	9 (69%)	31 (79%)
Spasticity in lower limbs	21 (81%)	9 (69%)	30 (77%)
Impotence	–	8 (62%)	8 (62%)
Low lumbar pain	13 (50%)	6 (46%)	19 (49%)
Constipation	10 (38%)	7 (54%)	17 (44%)
Use of others medications			
Yes	20 (77%)	11 (84%)	31 (79%)
No	6 (13%)	2 (16%)	8 (21%)
Baclofen	18 (75%)	8 (62%)	26 (83%)
Tricyclic antidepressants	6 (26%)	2 (16%)	8 (27%)
Vitamin B	2 (10%)	1 (2%)	3 (10%)
Oxibutinine	1 (5%)	2 (16%)	3 (10%)
Physical therapy			
Yes	13 (50%)	3 (23%)	16 (41%)
No	13 (50%)	11 (77%)	23 (52%)
Risk factors for HTLV-1 infection			
IDU	–	1 (8%)	1 (3%)
Blood transfusion before 1993	2 (8%)	1 (8%)	3 (8%)
Sexual partner HTLV-1 infected	3 (12%)	–	3 (8%)
Sexual partner IDU	3 (12%)	–	3 (8%)
Mother HTLV-1 infected	3 (12%)	1 (8%)	4 (10%)
Unknown*	8 (31%)	8 (60%)	25 (63%)

*Unknown: Patients from endemic areas, with possible but not proven maternal transmission.

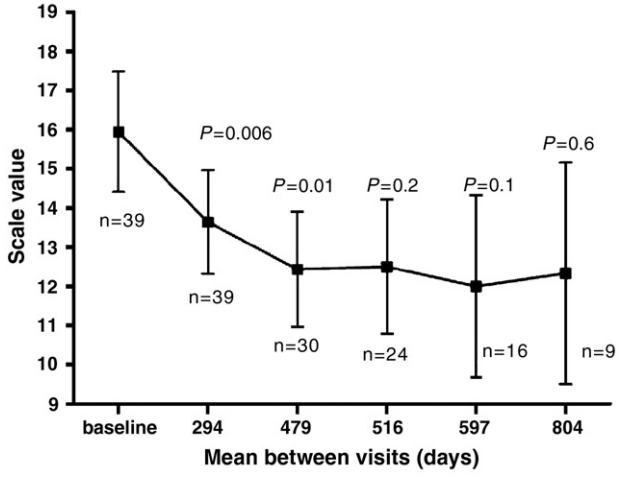

Fig. 1. Incapacity Status Scale-mean of values and standard deviation during the first five visits (mean of days between visits). Values at baseline and after pulse therapy with methyl-prednisolone.

therapy (9 patients), use of other specific therapy rather than corticosteroids (4 patients), or absence of a neurological evaluation (6 cases). In addition, 8 patients were excluded due to a contraindication of corticosteroid use (e.g. diabetes mellitus, tuberculosis, urinary tract infection).

Therefore, only 39 cases fulfilled the study inclusion criteria. The patients' characteristics are presented in Table 1. Twenty-six were female (67%). The mean age was 47 years at admission. Major symptoms at baseline were weakness of the lower limbs (79%), bladder disturbances (82%), bowel disturbance (44%), lower limbs spasticity (77%) and low lumbar pain (49%). The mean age at onset of symptoms was 39 years, ranging from 8 to 69 years. The mean duration of illness at first pulse therapy infusion was 8 years, ranging from 1.8 to 22 years; and the mean time from the onset of symptoms until the serological diagnosis was 6.1 years (range 0–21). The average number of pulses per patient was 3.4 (range 1–11).

The evaluation of the neurological scales revealed decreasing values of the scores in each reexamination after methyl-prednisolone treatment; however, only the Incapacity Status Scale showed a statistically significant improvement, of 24.5%, restricted to the first and second visits after baseline evaluation ($p=0.006$, $p=0.01$, respectively; Fig. 1). No statistically significant changes were seen on the DSS and OMDS scales over time (Table 2).

To identify groups for whom this treatment could be more beneficial we divided the patients by the severity of the disease at baseline visit (OMDS and DSS over or equal to score 5) and by the number of pulses of methyl-prednisolone (<4 or>4). It was observed that both groups had similar results. We also checked if physical therapy or other interventions, such as use of other medications (baclofen, tricyclic antidepressant or oxibutinine), could have had any potential influence in the patients' performances. Although not statistically significant, patients under physical therapy (16 patients) had a higher decrease in their scores' values on the DSS, ISS and OMDS (12.5%, 29% and 14% of maximum improvement, respectively). Only ISS score at visits one and two remained statistically significant.

We found that 23 patients (58%) were unable to walk unaided (OMDS >=5) at first visit. Eight patients experienced rapid progression, defined as a period of less than five years from the onset of symptoms until the inability to walk unaided. In this group, only one patient experienced the progression of the disease to severe disability in less than 2 years; mean age was 44 years (range: 23–60 years), and no patient had a previous history of blood transfusion or IDU.

4. Discussion

We studied 39 patients with HAM/TSP who received methyl-prednisolone treatment (1 g/day bolus for 3 days). They received an average of 3.4 pulses during follow-up. Some patients also received concomitant physical therapy, and symptomatic drugs such as baclofen, tricyclic antidepressants, B vitamin and oxibutinine. During this period we noticed a 24.5% improvement from baseline on the ISS scale, after a mean of 2.2 years of follow-up.

To date, data describing the real benefit of corticosteroids use for the treatment of TSP/HAM in the literature are limited. Partly, this is because few studies have had a longer follow-up time. Only ISS had statically significant improvement. One possible explanation is that changes in the scores of OMDS and DSS scales would only occur if substantial differences in neurological performance had occurred. This

Table 2
Effect of methyl-prednisolone in neurological scales values pre and post-treatment in 39 TSP/HAM patients

Neurological evaluations	DSS (*n**)	*P* value	ISS (*n**)	*P* value	OSAME (*n**)	*P* value	Interval days**
Baseline	3.6 (39)	–	15.9 (39)	–	4.8 (39)	–	–
1st visit	3.6 (39)	0.5	13.6 (39)	0.006	4.8 (37)	1	294
2nd visit	3.5 (30)	0.7	12.2 (30)	0.01	4.5 (28)	0.7	479
3rd visit	3.5 (24)	0.8	12.5 (24)	0.2	4.5 (21)	0.8	516
4th visit	3.8 (16)	0.4	12 (16)	0.1	4.2 (14)	0.8	597
5th visit	3.3 (9)	0.3	12.3 (9)	0.6	4.3 (7)	0.5	804
% of max. improvement***	9.3%	–	24.5%	–	12.5%	–	–

Notes: **n* = number of patients who were evaluated by scale.**Interval between the first evaluation (baseline) and subsequent visits. ***% of improvement between the baseline score (neurological scales) and the lowest value during the follow-up.
Disability Status Scale (DSS), Osame's Motor Disability Scales (OMDS) and Incapacity Status Scale (ISS) [30].

might be due to a lower sensitivity of those scales as compared with ISS, which can detect minor improvements, such as walking ability. To assess subtle improvement of TSP/HAM patients' symptoms, we believe IPEC (Evandro Chagas Clinical Research Institute) is likely to be the best scale. However, only six patients in this study had IPEC scores at baseline because this scale was available only after 2004 [33].

It is possible that corticosteroids produced only a limited improvement, as suggested by a better performance in the scores only up to visit two. However, TSP/HAM is a chronic and progressive illness. One recent study showed that the median times from onset of the disability until to assignment of scores 6, 6.5, and 8 were on DSS scale were 6, 13, and 21 years, respectively [34]. We believe that slowing the disability progression in the long run may itself represent a clinical benefit.

Our results should be interpreted cautiously, since we performed an open clinical trial, unblinded and not placebo controlled, and therefore with potential for several sorts of bias. However, our results were similar to those from a study which evaluated 200 TSP/HAM patients, and in ten patients had 30% motor improvement after the use of methyl-prednisolone, and a 69% improvement among patients who used oral prednisolone, and intrathecal hydrocortisone injection [13]. In contrast, in Brazil, of 23 patients in Rio de Janeiro, improvement was seen only in one patient who had short disease progression [14]. Thus, clinical trials for TSP/HAM are somewhat hard to conduct, since differences in age, gender, duration of symptoms, age of onset, disability scores, and time of progression may affect their outcomes. In addition, there is no consensus regarding the best parameters to measure the outcomes, such as neurological scales or measures of quality of life. Until now, our trial has the largest sample size using only methyl-prednisolone.

A reason for the apparent efficacy of corticosteroids could be that TSP/HAM is considered an immune mediated disease, mainly driven by IFN-γ overproduction [35]. Thus, the antiinflammatory properties of corticosteroids may have some impact on the myelin membrane inflammation process, improving some symptoms, mainly in those patients with only a few years from onset, when inflammation is more prominent [36]. In addition, corticosteroids decrease the number of mononuclear cells and α-2 microglobulin in the CSF, and probably decrease the HTLV-1 DNA proviral load [37,38].

Corticosteroids may improve the neurological symptoms and therefore, the quality of life of those patients. More importantly, they can prevent the TSP/HAM disease progression that could occur if no therapeutic measure is taken. Another major advantage of using this therapy is its feasibility, especially for the developing countries. The low cost, the relatively easy administration, and the reversible side effects indicate that this therapy is a promising strategy and allow a certain number of patients to avoid the more severity disabilities. Finally, only a double-blinded clinical trial, and placebo controlled study could ultimately determine the potential role of corticosteroids in TSP/HAM, a disease for which very few clinical trials were published. Furthermore, new approaches such as immune therapy as those used for multiple sclerosis, rather than antiretroviral therapy, could be used for treating this condition.

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