Article

Use of Oral Corticosteroids to Treat HTLV-1-Associated Myelopathy (HAM) in São Paulo, Brazil

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Simple Summary: Our findings provide observational evidence supporting oral corticosteroids therapy as maintenance therapy for HTLV-1-associated myelopathy (HAM). The daily use of oral, low-dose prednisone seems to be useful in some subsets of HAM patients and needs to be evaluated in randomized controlled trials.

Abstract: Background: During the development of human T-cell lymphotropic virus (HTLV-1)-associated myelopathy (HAM), the inflammatory phenomenon is very prominent and is a major factor in the outcome of the disease. The use of corticosteroids can modify their natural history, and in this study, we evaluated the effectiveness of using daily low-dose prednisone. Methods: This was a cross-sectional study using data collected by physicians monitoring patients with HAM at the Institute of Infectious Diseases "Emilio Ribas", the main referral center for patients with infectious diseases in São Paulo, Brazil. The objective was to determine if daily low-dose oral prednisone would be able to stabilize the progression of HAM. The outcome measure was a change in the Osame Motor Disability Score (OMDS). Results: Fifty-four patients used treatment with oral prednisone, 5 milligrams daily. Nine cases were excluded from the study because they did not have at least two rating scales within a minimum interval of one year, and six were excluded for being co-infected with HIV and/or HCV. Thirty-nine patients met this criterion and were included for analysis. The majority were women (71.8%), the mean age was 56.51 years old (SD ± 9.74), and the median time of use of prednisone was 16 months. Thirty-two patients (82.05%) maintained the same OMDS, 5/39 (12.82%) had clinical worsening, and 2/39 (5.13%) improved. Conclusions: There was a trend toward clinical stability with the use of oral corticosteroids. However, randomized controlled trials are necessary to evaluate the use in clinical practices in all stages of HAM.

Keywords: human T-lymphotropic virus 1; HTLV-1-associated myelopathy; prednisone; treatment; Brazil

1. Introduction

In the last few years, human T-cell lymphotropic virus 1 (HTLV-1) has become a central endemic in several parts of the world, with an estimated 5–10 million people living with

HTLV (PLHTLV), but only 1/3 has been mapped worldwide [1]. Furthermore, new regions have been disclosed as potential high-endemic areas, such as Iran and Australia [2]; Brazil accounts for almost 1 million cases of PLHTLV-1 [3]. HTLV-1 infection can cause adult T-cell leukemia/lymphoma (ATLL) and HTLV-1-associated myelopathy (HAM) in around 0.25% to 5% of infected people [4].

In addition to HAM, several clinical aspects have been reported, mainly recently, with early symptoms having been described by our research group [5]. It is important to highlight that the majority of these subjects may not progress to some relevant clinical outcome; however, there are some studies showing that 30% of PLHTLV-1 cases that are considered asymptomatic present minor neurological symptoms and some other systemic manifestations [5,6], but this does not complete the clinical criteria for HAM [7]. In the Brazilian HTLV cohort, it has been observed that PLHTLV-1 has a higher risk of developing HAM when compared with the Japanese cohort, for example [3,5,8–11].

A minor part of PLHTLV-1 will develop HAM during the chronic infection; the mechanism by which HTLV-1 induces HAM is not yet clear. The studies showed that HAM is an inflammatory disease of the central nervous system (CNS), potentially considered an immune-mediated disease, mainly due to the increase in cytokines and chemokines, in which it stands out due to the elevation of IFN-γ levels [12–15]. Thus, the accumulation of these elements in the blood–brain barrier induced damage to the myelin sheath, resulting in initially mild inflammation and, over the years, irreversible lesions [16].

Unfortunately, until now, there has been no curative treatment for HAM; however, when it happens, few pharmaceutical compounds have so far been used in the clinical setting, regardless of localization in developed or developing countries [17]. Thus, the first treatment addressed for HAM was the use of antiretrovirals and interferons, reproducing the HIV treatment experience [18]. In fact, in antiretroviral therapy (ART), drugs act directly and specifically on viral enzymes that are involved in viral replication. This class of drugs acts on RNA reverse transcription, DNA integration, and viral polyprotein cleavage, such as raltegravir [19]. Despite reduction in spontaneous lymphoproliferation, there is no significant inhibition of the HTLV-1 proviral load (PVL), and a subset analysis demonstrated differential inhibitions of the HTLV-1 PVL in some cases in either peripheral blood mononuclear cells (PBMC) or cerebrospinal fluid (CSF) [19].

Another important strategy that could decrease the hyperactivation of the immune system is the use of corticosteroids. This treatment for HAM has been proposed since the discovery of the disease and it is the most commonly used therapy today [17,20]. This strategy's approach may have some impact and would be cost-effective in developing countries, and it is easy to deliver, usually over 45 days as part of the intravenous administration of methylprednisolone or with low-dose corticosteroids daily orally. This recommendation was based on previous observational studies [20,21]. It is known that this drug reduces CSF cellularity and decreases the HTLV-1 PVL, and this justifies its use in HAM. There is also a reduction in α-2 microglobulin in the CSF, which acts as a marker of the inflammatory response [22].

In 2008, our group analyzed intravenous treatment with high-dose corticosteroid pulse therapy (HDCPT) with methylprednisolone, one gram per day for three consecutive days, and every three to four months apart. After a follow-up with a mean time of 2.2 years and four HDCPT per patient, a significant neurological improvement was noted, reaching 24.5% according to the Osame Motor Disability Score (OMDS) after two years of observation [20].

The last International Retrovirology Association guideline shows that corticosteroids seem to be the best efficacy therapy for HAM [17]. Despite this rationality of its use, few publications referring to this therapy have been assessed, with controversial results [17]. The classic use of corticosteroids, ART, immunomodulators, and others has been in a small- and short-time frame, achieving a disappointing efficacy in real-world scenarios [17].

Recently, a phase 2 study named HAMLET-P [21] was comprised of two trial arms: the prospective, randomized, open, and blinded endpoint trial, to assess the efficacy of intravenous HDCPT induction therapy for rapid progressors, and was compared to oral

prednisolone therapy for slow progressors. A proportion of patients receiving intravenous HDCPT achieved improvements in the OMDS, or 10 m walking time, at week 2 compared to those receiving non-HDCPT. All the patients experienced pulse therapy, but none of them without pulse therapy experienced an improvement in the OMDS ($p < 0.05$). The authors concluded that oral prednisolone alone is insufficient among rapid progressors, and intravenous methylprednisolone is more effective for the rapid improvement and maintenance of motor functions [21].

In recent years, monoclonal antibodies, anti-CxCR4, have been studied among PL-HTLV, but despite good results, the high cost may make their use difficult in developing countries [23]. Thus, clinical studies should be performed, especially in high-endemic areas using more affordable strategies, such as oral corticosteroid pulse therapy or intravenous HDCPT [20,21,24]. In this sense, the aim of this study was to determine if daily low-dose oral prednisone would be able to stabilize the progression of HAM.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional study using data collected by physicians monitoring patients with HAM at the Institute of Infectious Diseases "Emilio Ribas" (IIER), the main referral center for patients with infectious diseases in São Paulo, Brazil. The study was developed in March 2021, and the objective was to determine if daily low-dose oral prednisone would be able to stabilize the progression of HAM.

2.2. Cohort Characteristics

This study was carried out at the IIR, in São Paulo, Brazil. This cohort was set up in 1997, and it now has 667 HTLV-1-infected subjects in regular follow-up, making it one of the largest cohorts in Brazil. This is an open cohort, with new patients added at a rate of approximately 30–50 per year, and it also includes patients with HIV and/or HCV co-infections. The clinic is staffed with five neurologists, two infectious disease doctors, nurses, psychologists, physical therapists, nutritionists, and other health care professionals.

2.3. Case Definition

Participants were classified according to Castro-Costa et al.'s [7] criteria for the degree of neurological impairment, as determined by one or more neurologists. We recruited patients who were using oral prednisone with at least two rating scales at least one year apart. Patients who were co-infected with HIV and/or HCV infections were not enrolled as subjects in this study.

2.4. Definition of the Outcome

The clinical worsening was defined by the OMDS [25]. The score ranges from 0 to 13, where 0 indicates no motor disability and higher scores indicate increasingly severe motor disability, the criteria used to define the outcome a decreased by one point or more and stability was defined depending on whether this scale was stable or improved during oral prednisone therapy.

2.5. Neurological Evaluation

The HAM diagnostic criteria were based on recommendations from Castro-Costa et al. [7]. Briefly, definite HAM is a non-remitting progressive spastic paraparesis with sufficiently impaired gait to be perceived by the patient. Sensory symptoms or signs may or may not be present but, when present, they are subtle and without a clear-cut sensory level. Urinary and anal sphincter signs or symptoms may or may not be present. Besides clinical evaluation, the laboratory criteria include presence of HTLV-1 antibodies in CSF.

Regarding treatment, HDCPT begins with 1000 milligrams (mg) intravenous methyl-prednisolone in a single dose every 4 to 6 weeks. Reassessment to accompany this treatment is performed after three consecutive doses of the drug. If there are side effects

that make it impossible to use or when there is great difficulty in attending the hospital schedule for intravenous treatment, we propose pulse therapy with daily oral prednisone. Some patients have contraindications to the use of steroids and are treated only with symptomatic medications.

Patients with HAM using intravenous corticosteroids treatment are evaluated every six weeks; those with HAM who were not using it were evaluated every three months; and asymptomatic patients were evaluated every six to twelve months. Oral prednisone was used to replace HDCPT in IIER cohort, which was introduced in May 2017 (Figure 1), and this switch was exclusively made between March 2020 and March 2021 because of the coronavirus 2019 disease (COVID-19) pandemic.
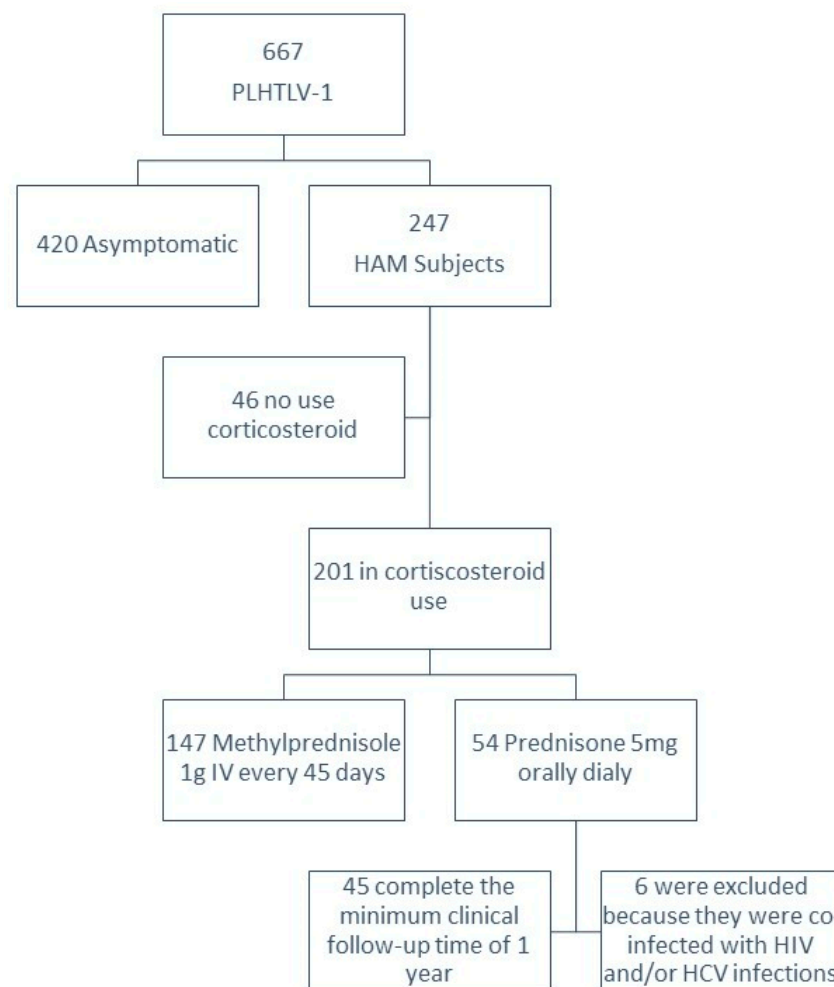

Figure 1. Algorithm used to assess the experience of the use of oral prednisone for HAM patients São Paulo.

A standardized questionnaire was used for detection of clinical and neurological signs. Clinical evaluation and a standardized screening neurological examination were performed, blinded for HTLV-1 clinical condition, for all subjects. Only symptoms/signals that were already associated with HTLV-1 infection in previous reports were considered, and they should have no other clinical explanation. Each patient had at least two neurological/clinical evaluations. A standardized questionnaire was used, with separate questions for clinical and neurological aspects. Neurological evaluation included tests of strength in upper and lower limbs, cranial nerve function, and patellar, biceps, and plantar reflexes, as well as an appraisal of the vibration sense. The presence of minimal changes in muscular strength or gait was explored: subjects were asked to walk on their heels, toes, tandem

gait, and rise from a chair without help from their arms. We analyzed the variation in the OMDS based on a cutoff equal to, below, or above 4 as it marks the difference between independent walking and the need for support to walk.

2.6. Data Curation

Our clinical and laboratory database was organized on an internet-based platform using REDCap® database, a software developed at Vanderbilt University by an informatics core supported by National Center for Research Resources NCRR and National Institutes of Health (NIH) grants. All clinical data, which have been updated on a regular basis over the last 24 years, were entered into a specific REDCap® database.

2.7. Ethical Issues

This study complies with resolution 196/96 of the Brazilian National Health Council on research with human beings according to the Declaration of Helsinki. The information was collected after the project was approved by the protocol (Number 86379218.6.1001.0061) by the Ethics and Research Committee of the Institute of Infectious Diseases (IIER). We obtained signed informed consent from all participants prior to study inclusion, and all participants were adults.

2.8. Statistical Analysis

Statistical analysis was conducted using Mann–Whitney test for non-parametric data, and Chi-square or Fisher exact test for proportions. Variables associated with the outcome at a significance level of $p < 0.05$; performed with the aid SPSS® 21 (Statistical Package for the Social Sciences-21. Statistical Software. IBM, New York, NY, USA). For data analysis, normality was verified for each variable. Age and gender data were treated using descriptive statistics through mean, minimum, and maximum values and absolute and relative frequencies (percentage). OMDS data were analyzed as means, medians, and standard deviations, and the ANOVA test was used to compare the progression of disease groups.

3. Results

From July 1997 to March 2021, a total of 667 adult individuals were diagnosed with the HTLV-1 infection and classified as asymptomatic (n = 420) or HAM (n = 247), following a complete neurological examination. Of the 247 patients with HAM, only 46 of them did not undergo any treatment with corticosteroids during the time they were followed up at our service. Of the 201 patients on corticosteroid treatment, 147 used only intravenous methylprednisolone, and, up to March 2021, 54 HAM patients underwent treatment with oral prednisone. Six patients were excluded from this study because they were co-infected with HIV and/or HCV infections, and nine other patients were also excluded because they did not complete the minimum clinical follow-up time of one year, despite being on regular follow-ups. A total of 39 patients were included in the study and 5 of them had not previously received intravenous corticosteroids or any other oral anti-inflammatory medications.

Table 1 shows that most of the patients evaluated in this study were female, considering the entire sample (71.8%) and the subgroups OMDS ≤ 4 (66.7%) and OMDS > 4 (72.7%). The mean age of all 39 patients was 58.03 years (SD ± 9.71) and the median was 58 years. Patients with OMDS ≤ 4 at the start of treatment have a mean age of 48.33 years (SD ± 14.04) and a median of 51.50 years. For patients with OMDS > 4, there was a mean age of 59.79 years (SD ± 7.77) and a median age of 60 years.

Table 1. Characteristics of HAM individuals who started pulse therapy with oral prednisone based on the neurological ODMS scale.

Variable	Category	OMDS ≤ 4 (n = 6)	OMDS > 4 (n = 33)	Total (n = 39)	*p* Value
Gender	Male	2 (33.3%)	9 (27.3%)	11 (28.2%)	0.762
	Female	4 (66.7%)	24 (72.7%)	28 (71.8%)	
Age (years)	Mean (±SD)	48.33 (±14.04)	59.79 (±7.77)	58.03 (±9.71)	0.035
	Median	51.50	60.00	58.00	
Time of myelopathy symptoms (years)	Mean (±SD)	10.33 (±7.39)	17.00 (±8.83)	15.97 (±8.88)	0.053
	Median	9.00	14.00	12.00	
Time in the cohort (years)	Mean(±SD)	5.33 (±2.16)	8.58 (±5.37)	8.08 (±5.13)	0.197
	Median	5.50	8.00	8.00	

OMDS: Osame Motor Disability Score; SD: standard deviation.

Regarding the duration of myelopathy symptoms until the beginning of treatment with oral prednisone, the results were a mean of 15.97 years (SD ± 8.88) and a median of 12 years. Patients with OMDS ≤ 4 had a mean of 10.33 years of active disease (SD ± 7.39) and a median of 9 years when they started using oral prednisone. For those with a more advanced disease and OMDS > 4, the results were a mean of 17 years of active disease (SD ± 8.83) and a median of 14 years. Patients with more advanced disease (OMDS > 4), as expected, are older compared to the general group, and they have a longer disease duration prior to the start of the intervention. Considering the total time of clinical follow-up at the HTLV outpatient clinic of the IIER, for the entire sample, the mean was 8.08 years (SD ± 5.13) and the median was 8 years. For patients with OMDS > 4, this time is longer: with a mean of 8.58 (SD ± 5.27), and a median that was also equal to 8. The mean and median lengths of clinical follow-ups for patients with OMDS ≤ 4 are shorter: 5.33 (SD ± 2.16) and 5.5, respectively.

Table 2 shows the comparison between patients who presented clinical worsening (n = 5) or stability (n = 34) with treatment with oral prednisone; we also considered stable patients who did not worsen. Patients with worsening OMDS with oral prednisone had a mean age of 57.20 years (SD ± 7.19) and a median of 61 years. For patients who remained stable, the mean age was 58.15 years (SD ± 10.11) and the median was 58 years. Patients with worsening OMDS with oral prednisone had a mean of 15.80 years of active disease (SD ± 8.88) with a median time of 13 years when they started using oral prednisone. For those who remained stable, there was a mean result of 15.99 years of active disease (SD ± 9.13) and a median of 12 years.

Patients who used HDCPT did so for a mean time of 6.41 years (SD ± 4.95), and a median of 5 years. Patients with worsening OMDS had a shorter mean time, 4.2 years (SD ± 6.06), and a median of 2 years. For those who remained stable, they had a mean time of 6.79 years (SD ± 4.75) and a median of 5 years.

All five patients with worsening OMDS used HDCPT with intravenous methylprednisolone before oral treatment. Only one of the patients who had clinical worsening after switching to oral prednisone had a longer duration of use of methylprednisolone (ten years). The other four patients used it for a shorter time (one or two years), and this may be a factor related to the clinical worsening after the change in treatment, but in our study, it did not show statistical significance. We also observed that patients with worsening OMDS had a shorter follow-up time in our cohort (Table 2), which was also without statistical significance.

Thirty-two patients maintained the same OMDS (82.05%), five patients (12.82%) had clinical worsening, and two/thirty-nine (5.13%) improved; one patient used bilateral support, and another who needed a wheelchair started walking with unilateral support.

Table 2. ODMS analysis before more than 12 months of continuous use of prednisone 5 mg daily.

Variable	Category	Worsening OMDS n = 5 (12.8%)	OMDS Stability n = 34 (87.2%)	Total n = 39	*p* Value
Gender	Male	2 (40.0%)	9 (26.5%)	11 (28.2%)	0.438
	Female	3 (60.0%)	25 (73.5%)	28 (71.8%)	
Age (years)	Mean (±SD)	57.20 (±7.19)	58.15 (±10.11)	58.03 (±9.71)	0.803
	Median	61.00	58.00	58.00	
Time of myelopathy symptoms (years)	Mean (±SD)	15.80 (±8.88)	15.99 (±9.13)	15.97 (±8.88)	0.823
	Median	13.00	12.00	12.00	
Time in the cohort (years)	Mean (±SD)	5.80 (±3.42)	8.41 (±5.29)	8.08 (±5.13)	0.184
	Median	5.00	8.00	8.00	
Intravenous HDCPT	No	——	5 (14.7%)	5 (12.8%)	0.483
	Yes	5 (100%)	29 (85.3%)	34 (87.2%)	
Time of venous HDCPT (years)	Mean (±SD)	4.20 (±6.06)	6.79 (±4.75)	6.41 (±4.95)	0.122
	Median	2.00	5.00	5.00	
Time of prednisone therapy (months)	Mean (±SD)	18.20 (±4.09)	18.00 (±7.56)	18.03 (±7.17)	0.581
	Median	17.00	16.00	16.00	

OMDS: Osame Motor Disability Score; HDCPT: high-dose corticosteroid pulse therapy; SD: standard deviation.

Thirty-four patients used venous HDCPT with methylprednisolone, twenty-seven maintained the same OMDS (79.41%), five worsened (14.71%), and two improved (5.88%). Regarding the worsening of the OMDS, four of the five patients had a worsening of only one point on the scale. The other patient had a worsening of two points, evolving from the unilateral support mark to using a wheelchair. All five patients who started treatment with oral prednisone maintained stability, according to the OMDS.

4. Discussion

We evaluated, during the first year of the COVID-19 pandemic in Brazil, 39 HAM patients (seronegative to SARS-CoV-2 antibodies), the majority of whom had previously undergone venous HDCPT with a methylprednisolone regimen, for the use of 5 mg of prednisone orally once daily. The oral dose was effective for 34 patients (87.2%), maintaining the same outcome or even improving in the evaluation using the OMDS. None of the patients had side effects with oral prednisone treatment and only five patients returned to HDCPT with intravenous methylprednisolone after one year because of the clinical worsening during the follow-up. Since there is still no established therapy for the treatment of HTLV-1 infection, most of the treatments proposed to date aim to reduce the effects of the inflammatory process on the central nervous system (CNS) [15,26–28]. The corticosteroid is a classic treatment for HAM, and the current evidence is favorable to the use of both venous HDCPT and low doses taken orally continuously [20,21,24]. In the present report, to perform the comparative analysis, the volunteers were divided into two groups: those who had previously undergone treatment with venous HDCPT with methylprednisolone, and individuals who started pulse therapy with oral prednisone.

The alternative of taking prednisone orally was required to maintain the continuity of the patients' treatment during the COVID-19 pandemic [29]. As the cases spread, most of the countries adopted some kind of restriction to avoid the collapse of health systems, and in Brazil, this was a reality [30]. The IIER in São Paulo is a national referral center that opened to conduct the infectious diseases outbreak. In this way, the HTLV out clinic was closed, and we proposed the oral use of prednisolone to patients; they did not need to go to the hospital regularly and stay for about 4 hours for the methylprednisolone infusion. It seems that best efficacy therapy for HAM is corticosteroids, which are our clinical options, either oral or intravenous, as referred to in the last International Retrovirology Association guideline [17].

In this direction, a Japanese study [24] evaluated the long-term response of the corticoid in relation to disease progression, as well as the comparison between groups with and without treatment. Of these, 57 were treated with low doses of oral corticosteroids and 29 did not receive any type of medication, which showed that treated patients improved more than untreated patients, considering the OMDS, and this change was seen despite the base OMDS. In addition, even patients with OMDS > 7 had a benefit, despite the longer follow-up period, disease progression, and the tendency for clinical worsening [24]. More recently, one randomized controlled trial [21] compared the use of corticosteroids in patients with rapid or slow progression of HAM, who have a variation of one point on the OMDS or an improvement of more than 30% in the time to cover the 10-meter distance [21], which endorses the use of HDCPT in the clinical setting.

One study conducted a clinical trial that involved 23 adult patients with HAM in Rio de Janeiro, Brazil, using intravenous methylprednisolone for five consecutive days, every four months apart, but this strategy showed no clinical improvement [31]. This was probably due to the late stage of disease, which may not have been inflammatory in the spinal cord. In fact, we have shown that cytokines are proinflammatory, such as interferon gamma production [13,15]. Thus, our study may contribute to encouraging other groups and some collaborative partnerships to involve more HAM patients worldwide to treat these patients as soon as possible.

In Japan, there was an observable improvement in the long-term and stability in the OMDS in a group of 200 patients with HAM; 69% of patients who used oral prednisolone improved [32]. A total of 40% of those underwent intrathecal injection of hydrocortisone (75 mg) and 30% of those underwent venous methylprednisolone (500 to 1000 mg per day for three consecutive days) [32]. Despite the existence of few datasets regarding the use of corticosteroids in recent decades, these findings support this strategy. Furthermore, decreasing neuroinflammation caused by either replication or bystander release of proinflammatory/inflammatory and chemokines may contribute to justifying use of the HDCPT [33].

A more recent study using mogamulizumab, a humanized, monoclonal anti-CXR4 antibody, showed a reduction in the number of cells infected by HTLV-1 and in the levels of inflammatory markers, with a reduction in spasticity and motor disabilities [23]. It was a study carried out with 21 patients within a short observation time [23]. However, the elevated cost and lack of evidence in studies lasting a long time have made the implementation of this strategy difficult, especially in the developing countries, which are the epicenters of this condition.

The present study recruited a limited number of participants that were evaluated for a short period of time. There is a longer clinical follow-up and even longer time of HDCPT with intravenous methylprednisolone in those patients with higher OMDS, which is expected considering the natural history of the disease. This can influence the comparative analysis in relation to patients with a lower degree of disease progression.

The present report showed that there was clinical stability in most patients, good tolerability of the medication, and no serious adverse effects that would require a discontinuation of treatment. These findings provide evidence to support oral corticosteroids as a maintenance therapy for HAM during a clinical follow-up, and assess the time to change the approach, from venous to oral pulse therapy. It could also be a viable and cost-effective approach for use in endemic areas, for example, in developing countries such as Brazil, and could help many patients around the world.

the editors consider relevant to the content of the manuscript have been disclosed. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Institute of Infectious Diseases Emilio Ribas (protocol n. 37/98, approved in August 1997).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patient confidentiality.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Gessain, A.; Cassar, O. Epidemiological Aspects and World Distribution of HTLV-1 Infection. *Front. Microbiol.* **2012**, *3*, 388. [CrossRef]
2. Einsiedel, L.J.; Pham, H.; Woodman, R.J.; Pepperill, C.; Taylor, K.A. The Prevalence and Clinical Associations of HTLV-1 Infection in a Remote Indigenous Community. *Med. J. Aust.* **2016**, *205*, 305–309. [CrossRef] [PubMed]
3. Coordenação-Geral de Vigilância das Infecções Sexualmente Transmissíveis (CGIST/DCCI/SVS); Rosadas, C.; Espinosa Miranda, A.; Utsch Gonçalves, D.; Caterino-de-Araujo, A.; Assone, T.; Ishak, R. Prevalência da infecção por HTLV-1/2 no Brasil-Boletim Epidemiológico. *SVS/MS* **2020**, *51*, 102274.
4. Yamano, Y.; Sato, T. Pathophysiology, treatment and biomarkers for HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Nihon Rinsho Jpn. J. Clin. Med.* **2013**, *71*, 870–875.
5. Haziot, M.E.; Gascon, M.R.; Assone, T.; Fonseca, L.A.M.; Luiz, O.C.; Smid, J.; Paiva, A.M.; Marcusso, R.M.N.; de Oliveira, A.C.P.; Casseb, J. Detection of Clinical and Neurological Signs in Apparently Asymptomatic HTLV-1 Infected Carriers: Association with High Proviral Load. *PLoS Negl. Trop. Dis.* **2019**, *13*, e0006967. [CrossRef]
6. Tanajura, D.; Castro, N.; Oliveira, P.; Neto, A.; Muniz, A.; Carvalho, N.B.; Orge, G.; Santos, S.; Glesby, M.J.; Carvalho, E.M. Neurological Manifestations in Human T-Cell Lymphotropic Virus Type 1 (HTLV-1)-Infected Individuals Without HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis: A Longitudinal Cohort Study. *Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am.* **2015**, *61*, 49–56. [CrossRef] [PubMed]
7. De Castro-Costa, C.M.; Araújo, A.Q.C.; Barreto, M.M.; Takayanagui, O.M.; Sohler, M.P.; da Silva, E.L.M.; de Paula, S.M.B.; Ishak, R.; Ribas, J.G.R.; Rovirosa, L.C.; et al. Proposal for Diagnostic Criteria of Tropical Spastic Paraparesis/HTLV-I-Associated Myelopathy (TSP/HAM). *AIDS Res. Hum. Retroviruses* **2006**, *22*, 931–935. [CrossRef] [PubMed]
8. Marcusso, R.M.N.; Van Weyenbergh, J.; de Moura, J.V.L.; Dahy, F.E.; de Moura Brasil Matos, A.; Haziot, M.E.J.; Vidal, J.E.; Fonseca, L.A.M.; Smid, J.; Assone, T.; et al. Dichotomy in Fatal Outcomes in a Large Cohort of People Living with HTLV-1 in São Paulo, Brazil. *Pathogens* **2019**, *9*, 25. [CrossRef] [PubMed]
9. Gessain, A.; Mahieux, R. Tropical Spastic Paraparesis and HTLV-1 Associated Myelopathy: Clinical, Epidemiological, Virological and Therapeutic Aspects. *Rev. Neurol.* **2012**, *168*, 257–269. [CrossRef]
10. Proietti, F.A.; Carneiro-Proietti, A.B.F.; Catalan-Soares, B.C.; Murphy, E.L. Global Epidemiology of HTLV-I Infection and Associated Diseases. *Oncogene* **2005**, *24*, 6058–6068. [CrossRef] [PubMed]
11. Iwanaga, M. Epidemiology of HTLV-1 Infection and ATL in Japan: An Update. *Front. Microbiol.* **2020**, *11*, 1124. [CrossRef]
12. Puccioni-Sohler, M.; Yamano, Y.; Rios, M.; Carvalho, S.M.F.; Vasconcelos, C.C.F.; Papais-Alvarenga, R.; Jacobson, S. Differentiation of HAM/TSP from Patients with Multiple Sclerosis Infected with HTLV-I. *Neurology* **2007**, *68*, 206–213. [CrossRef]
13. Prates, G.; Assone, T.; Corral, M.; Baldassin, M.P.M.; Mitiko, T.; Sales, F.C.S.; Haziot, M.E.; Smid, J.; Fonseca, L.A.M.; Toledo, F.; et al. Prognosis Markers for Monitoring HTLV-1 Neurologic Disease. *Neurol. Clin. Pract.* **2020**, *11*, 134–140. [CrossRef]
14. Assone, T.; Malta, F.M.; Bakkour, S.; Montalvo, L.; Paiva, A.M.; Smid, J.; de Oliveira, A.C.P.; de Toledo Gonçalves, F.; do Carmo Luiz, O.; Fonseca, L.A.M.; et al. Polymorphisms in HLA-C and KIR Alleles Are Not Associated with HAM/TSP Risk in HTLV-1-Infected Subjects. *Virus Res.* **2018**, *244*, 71–74. [CrossRef] [PubMed]
15. Espíndola, O.M.; Oliveira, L.C.; Ferreira, P.M.S.; Leite, A.C.C.B.; Lima, M.A.S.D.; Andrada-Serpa, M.J. High IFN-γ/IL-10 Expression Ratio and Increased Frequency of Persistent Human T-Cell Lymphotropic Virus Type 1-Infected Clones Are Associated with Human T-Cell Lymphotropic Virus Type 1-Associated Myelopathy/Tropical Spastic Paraparesis Development. *Intervirology* **2015**, *58*, 106–114. [CrossRef] [PubMed]

16. Yamauchi, J.; Sato, T.; Yagishita, N.; Araya, N.; Hasegawa, D.; Tsutsumi, S.; Nagasaka, M.; Coler-Reilly, A.; Inoue, E.; Takata, A.; et al. Use of Cerebrospinal Fluid CXCL10 and Neopterin as Biomarkers in HTLV-1-Associated Myelopathy/Tropical Spastic Paraparesis Treated with Steroids. *J. Neurol. Neurosurg. Psychiatry* **2020**, *91*, 321–323. [CrossRef] [PubMed]

17. Araujo, A.; Bangham, C.R.M.; Casseb, J.; Gotuzzo, E.; Jacobson, S.; Martin, F.; Penalva de Oliveira, A.; Puccioni-Sohler, M.; Taylor, G.P.; Yamano, Y. Management of HAM/TSP: Systematic Review and Consensus-Based Recommendations 2019. *Neurol. Clin. Pract.* **2021**, *11*, 49–56. [CrossRef]

18. Taylor, G.P.; Goon, P.; Furukawa, Y.; Green, H.; Barfield, A.; Mosley, A.; Nose, H.; Babiker, A.; Rudge, P.; Usuku, K.; et al. Zidovudine plus Lamivudine in Human T-Lymphotropic Virus Type-I-Associated Myelopathy: A Randomised Trial. *Retrovirology* **2006**, *3*, 63. [CrossRef] [PubMed]

19. Enose-Akahata, Y.; Billioux, B.J.; Azodi, S.; Dwyer, J.; Vellucci, A.; Ngouth, N.; Nozuma, S.; Massoud, R.; Cortese, I.; Ohayon, J.; et al. Clinical Trial of Raltegravir, an Integrase Inhibitor, in HAM/TSP. *Ann. Clin. Transl. Neurol.* **2021**, *8*, 1970–1985. [CrossRef]

20. Croda, M.G.; de Oliveira, A.C.P.; Vergara, M.P.P.; Bonasser, F.; Smid, J.; da Duarte, A.J.S.; Casseb, J. Corticosteroid Therapy in TSP/HAM Patients: The Results from a 10 Years Open Cohort. *J. Neurol. Sci.* **2008**, *269*, 133–137. [CrossRef]

21. Yamauchi, J.; Tanabe, K.; Sato, T.; Nakagawa, M.; Matsuura, E.; Tsuboi, Y.; Tamaki, K.; Sakima, H.; Ishihara, S.; Ohta, Y.; et al. Efficacy of Corticosteroid Therapy for HTLV-1-Associated Myelopathy: A Randomized Controlled Trial (HAMLET-P). *Viruses* **2022**, *14*, 136. [CrossRef]

22. Yamamoto, J.K.; Barré-Sinoussi, F.; Bolton, V.; Pedersen, N.C.; Gardner, M.B. Human Alpha- and Beta-Interferon but not Gamma-Suppress the in Vitro Replication of LAV, HTLV-III, and ARV-2. *J. Interferon Res.* **1986**, *6*, 143–152. [CrossRef]

23. Sato, T.; Coler-Reilly, A.L.G.; Yagishita, N.; Araya, N.; Inoue, E.; Furuta, R.; Watanabe, T.; Uchimaru, K.; Matsuoka, M.; Matsumoto, N.; et al. Mogamulizumab (Anti-CCR4) in HTLV-1-Associated Myelopathy. *N. Engl. J. Med.* **2018**, *378*, 529–538. [CrossRef]

24. Coler-Reilly, A.L.G.; Sato, T.; Matsuzaki, T.; Nakagawa, M.; Niino, M.; Nagai, M.; Nakamura, T.; Takenouchi, N.; Araya, N.; Yagishita, N.; et al. Effectiveness of Daily Prednisolone to Slow Progression of Human T-Lymphotropic Virus Type 1-Associated Myelopathy/Tropical Spastic Paraparesis: A Multicenter Retrospective Cohort Study. *Neurother. J. Am. Soc. Exp. Neurother.* **2017**, *14*, 1084–1094. [CrossRef]

25. Osame, M. Pathological Mechanisms of Human T-Cell Lymphotropic Virus Type I-Associated Myelopathy (HAM/TSP). *J. Neurovirol.* **2002**, *8*, 359–364. [CrossRef]

26. Montanheiro, P.; Vergara, M.P.P.; Smid, J.; da Silva Duarte, A.J.; de Oliveira, A.C.P.; Casseb, J. High Production of RANTES and MIP-1alpha in the Tropical Spastic Paraparesis/HTLV-1-Associated Myelopathy (TSP/HAM). *J. Neuroimmunol.* **2007**, *188*, 138–142. [CrossRef]

27. Ahuja, J.; Lepoutre, V.; Wigdahl, B.; Khan, Z.K.; Jain, P. Induction of Pro-Inflammatory Cytokines by Human T-Cell Leukemia Virus Type-1 Tax Protein as Determined by Multiplexed Cytokine Protein Array Analyses of Human Dendritic Cells. *Biomed. Pharmacother.* **2007**, *61*, 201–208. [CrossRef] [PubMed]

28. Best, I.; Adaui, V.; Verdonck, K.; González, E.; Tipismana, M.; Clark, D.; Gotuzzo, E.; Vanham, G. Proviral Load and Immune Markers Associated with Human T-Lymphotropic Virus Type 1 (HTLV-1)-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) in Peru. *Clin. Exp. Immunol.* **2006**, *146*, 226–233. [CrossRef] [PubMed]

29. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.-L. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* **2021**, *19*, 141–154. [CrossRef] [PubMed]

30. De Andrade, C.L.T.; de Pereira, C.C.A.; Martins, M.; Lima, S.M.L.; Portela, M.C. COVID-19 Hospitalizations in Brazil's Unified Health System (SUS). *PLoS ONE* **2020**, *15*, e0243126. [CrossRef]

31. Araújo, A.Q.; Afonso, C.R.; Leite, A.C.; Dultra, S.V. Intravenous Methylprednisolone in HTLV-I Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP). *Arq. Neuropsiquiatr.* **1993**, *51*, 325–328. [CrossRef] [PubMed]

32. Nakagawa, M.; Nakahara, K.; Maruyama, Y.; Kawabata, M.; Higuchi, I.; Kubota, H.; Izumo, S.; Arimura, K.; Osame, M. Therapeutic Trials in 200 Patients with HTLV-I-Associated Myelopathy/Tropical Spastic Paraparesis. *J. Neurovirol.* **1996**, *2*, 345–355. [CrossRef] [PubMed]

33. Puccioni-Sohler, M.; Poton, A.R.; Cabral-Castro, M.J.; Yamano, Y.; Taylor, G.; Casseb, J. Human T Lymphotropic Virus Type 1-Associated Myelopathy: Overview of HTLV-1/2 Tests and Potential Biomarkers. *AIDS Res. Hum. Retroviruses* **2022**, *38*, 924–932. [CrossRef] [PubMed]