Therapeutic responses to interferon-alpha in HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP): Differing clinical responses to leukocyte-derived human interferon-alpha versus recombinant interferon-alpha

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ABSTRACT

Introduction: HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a progressive spinal cord syndrome seen in patients infected by human T-lymphotropic virus type 1 (HTLV-1). Initial infection by the virus is usually asymptomatic. As the disease progresses, a series of neurological symptoms can appear gradually in years or, in some cases, rapidly within months. Interferon-alpha (IFN-α) is still considered one possible disease modifying treatment option for this disease due to the immunological pathogenesis of HAM/TSP. Case Series: We followed 3 HTLV-1 infected HAM/TSP patients who presented with rapidly progressive neurological impairment. Each patient underwent serial neurological examinations that were recorded according to the Expanded Disability Status Scale (EDSS). Then treatment with preparations of human leukocyte-derived natural interferon-α (IFN-αn3) was started and continued for varying intervals of time according to the availability of IFN-αn3. With this treatment, the HAM/TSP symptoms were controlled and even alleviated, with decreased EDSS scores. However, interferon-α was switched to the recombinant product IFN-α2b when the supply of IFN-αn3 was unavailable. Surprisingly, all patients experienced a significant worsening of their neurological symptoms and EDSS scores after they switched to IFN-α2b. Conclusion: Since IFN-α is still used to treat HAM/TSP patients globally, this differential response to IFN-αn3 and IFN-α2b treatment is important to be monitored and warrants further reporting.

Keywords: Human T-lymphotropic virus type 1, Interferon-alpha, Myelopathy, Tropical spastic paraparesis

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INTRODUCTION

Human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy and tropical spastic paraparesis (HAM/TSP) is a progressive neurological disorder clinically resembling primary progressive multiple sclerosis (PPMS) [1–4]. It is estimated that at least 20 million people are infected with HTLV-1 globally, with the highest prevalence in Southwestern Japan, the Caribbean islands, sub-Saharan Africa, and some regions of South America [5]. HTLV-1 infection represents a 1.3-fold increased risk for all cause of death in the Japanese population compared to Caribbean population, excluding patients with adult T-cell leukemia/lymphoma (ATLL) [6].

While primary infection with HTLV-1 is asymptomatic, affected persons typically present with a spastic paraparesis of slow onset, worsening over years and decades that may also be associated with bowel and bladder dysfunction and erectile dysfunction. Although back pain may be prominent early in the course of illness, other sensory manifestations occur but are less striking. HAM/TSP is not a monolithic illness. In certain populations, particularly those posttransfusion of cellular blood products, the disease may have a rapidly progressive course requiring cane, walker, or wheelchair within three years of disease onset [7, 8]. By contrast, endemic infection in Caribbean populations, such as in Jamaica, is typically slowly progressive; patients may still be walking with a cane 2–3 decades after disease onset. Both higher proviral loads and older age at onset are independently associated with a poorer prognosis for HAM/TSP [9]. Currently, there is no single, specific management strategy for HAM/TSP, though HAM/TSP remains a global cause of disabling progressive neurological disease. The optimal goal of treatment for HAM/TSP is to definitively halt or reverse the progression of neurological disability, but the available therapeutic options are most effective at alleviating the most frequent symptoms, such as spasticity, urinary symptoms, and constipation [4].

We followed 3 patients with rapidly progressive HAM/TSP serially in our Multiple Sclerosis (MS) clinic. The 3 patients lived in two different Caribbean nations. None had received blood transfusions, which is known to be a special risk factor for rapidly progressive HAM/TSP [7]. All 3 of our patients had proof of HTLV-1 viral infection by Western blot and polymerase chain reaction (PCR) assays, and negative tests for other disorders resembling HAM/TSP, that is, HTLV-2, HIV, syphilis, other infections, vitamin B12 deficiency, and other nutritional deficiencies. The initial treatment decision was based on documentation of rapid neurological deterioration of these patients and reports of apparently successful management of HAM/TSP in Japan using human (lymphoblastoid) multispecies interferon-α1 (IFN-α1; Alferon N®; Hemispherix). They were followed in our MS clinic over intervals from 12 to 30 months. When IFN-α1 became unavailable, we instituted treatment with equivalent doses of recombinant interferon-α2b (IFN-α2b, Intron; Schering-Plough). The patients were monitored specifically for evidence of adverse effects (AEs), symptomatic response to both treatments, and changes in disability based on recorded neurological examinations and calculated EDSS scores.

CASE SERIES

Patient 1

A 53-year-old man developed increasingly severe low back pain and sought a neurological consultation two years after onset of the symptom. The neurological examination and magnetic resonance imaging (MRI) of the brain and spinal cord were normal. Urinary frequency and sexual dysfunction developed within another year, and serum HTLV-1 antibody was detected. One year after development of the urogenital symptoms, weak hip flexors, hyperreflexia, bilateral Babinski reflexes, and a spastic gait was found at a follow-up visit; EDSS was 3.5. IFN-α2b at a dose of 5.0 million international units (MIU) subcutaneously (SQ) four times a day was initiated. After 11 months of treatment there was a significant improvement of back or limb pain, as well as strength, and decrease in spasticity. This was reflected in improvement of EDSS from 3.5 to 2.5 (Figure 1A). Treatment was changed to an equivalent dose of recombinant IFN-α2b when IFN-α1 was commercially unavailable. After six months of IFN-α2b treatment, the patient had lost 25 pounds and experienced generalized weakness. He was diagnosed with hyperthyroidism, and IFN-α2b was stopped. Three months later and after normalization of his thyroid function, IFN-α2b was reintroduced without AE and without impact on thyroid function. One year after reintroduction of IFN-α2b treatment, thyroid function was normal, and he was stable neurologically with EDSS of 2.5. Then IFN-α3 again became unavailable. Withdrawal of IFN-α3 was followed by a rapid worsening of weakness and spasticity (EDSS 4.5) so IFN-α2b was then reintstituted. Hyperthyroidism did not recur, but spasticity and gait progressively worsened. After one year of IFN-α2b treatment, the patient refused worsening leg stiffness and limited gait; EDSS was reported as 5.0. Despite the recommendation that he should discontinue the treatment, he continued IFN-α2b, and within three years, he had severe proprioceptive loss in his lower extremities. He was able to ambulate with a walker but could not walk more than 20 feet (EDSS 7.0). IFN-α2b was then withdrawn, but he did not have any clinical improvement (Figure 1A).
Patient 2

A 57-year-old woman was diagnosed with HTLV-1 infection after viral exposure. Approximately 15 months later, she developed worsening of back pain, followed by increasing spastic weakness of her lower extremities with sensory involvement (EDSS 3.5). IFN-α3 was initiated at a dose of 5.0 MIU SQ on alternate days, and within six months, her pain and sensory symptoms disappeared (Figure 1B). After one year of treatment with IFN-α3, the patient was reporting subjective improvement with residual paresthesia of her feet. Despite improved strength and gait, urinary frequency continued unabated. Examination revealed normal tone and strength. Hyperreflexia persisted with bilateral Babinski reflexes. An independent examination by the referring neurologist confirmed the improvement. Expanded Disability Status Scale had decreased to 2.5. Studies done at another institution revealed that no proviral DNA was detectable after one year. After 18 months of IFN-α3 treatment, EDSS remained stable at 2.5. Her EDSS score gradually decreased to 1.0 over the 33 months since the start of IFN-α3 treatment. By this time, the patient felt well with only mild urinary frequency and constipation. Examination revealed slight difficulty with tandem gait, brisk reflexes in upper and lower extremities, more on the right. Strength was normal and sensation was normal. Though the patient was doing well, an equivalent dose of recombinant IFN-α2b had to be substituted for her interferon treatment because IFN-α3 was no longer available. IFN-α2b was tolerated initially, but rapid neurological deterioration ensued, with marked increase in disability and EDSS score. She required the use of bilateral assistance to walk (EDSS of 6.5) just eight months later. Human leukocyte-derived interferon-alpha (Multiferon®, Swedish Orphan) became available again, and it was re instituted two months after IFN-α2b withdrawal. The patient experienced a rapid return of a sense of well-being with slow but constant neurological improvement. After 12 months on Multiferon® treatment, she was able to walk over 100 meters without a cane (EDSS 5.5), and after 24 months, she was able to walk 200 meters (EDSS 5.0) (Figure 1B).

Patient 3

A 37-year-old woman developed urinary dysfunction leading to incontinence, then severe back pain and progressive gait impairment over a 3 to 4-year interval. Walking was associated with severe burning pain in her legs, and gait deteriorated to where she was unable to work and required a cane to walk short distances. HTLV-1 infection was then established, and the patient received physical therapy. Ten months later, increasingly severe pain in her back and legs prompted neurological reassessment, which revealed lower extremity spasticity, mild distal weakness, a T4 sensory level, and severe postural hypotension. Initially, she was wheelchair confined, EDSS 7.0. She was treated with intravenous (IV) corticotropin, fludrocortisone, and physical rehabilitation. She was subsequently started on IFN-α3 dosed at 5.0 MIU SQ on alternate days. Within three months, there was resolution of the orthostatic hypotension, but the neurological exam showed mild bilateral weakness of distal upper extremities, moderate hip flexor weakness, mild hamstring weakness, and hyperreflexia. Vibration was impaired distally in all four extremities, but she was ambulating with a walker (EDSS 6.5) (Figure 1C). After another three months on treatment, she was able to walk with a cane despite mild (4/5) weakness of both hip and knee flexors, lower extremity spasticity, and continued diminished lower extremity sensation (EDSS 6.0). After 13 months of treatment of IFN-α3, EDSS decreased to 5.0 as the patient was walking without a cane. Subsequently, when IFN-α3 had been unavailable for two months, she experienced worsening fatigue and increasing foot numbness. Examination revealed increased tone with mild left hip flexor weakness. Recombinant IFN-α2b was started at 5.0 MIU SQ on alternate days. Within a month, gait worsened, and severe (2/5) hip flexor weakness ensued, with anesthesia below mid-thigh (EDSS 7.0). After 10 months of IFN-α2b treatment, she had markedly increased weakness and intolerable pain, leading to another course of corticotropin treatment and physical therapy. After this, she was able to walk short distances with a cane (EDSS 6.5). Despite continuing IFN-α2b for another 18 months, neurological deterioration continued unabated with progressive disability to EDSS 8.5. There was no neurological improvement as of eight months after discontinuing IFN-α2b treatment (Figure 1C).

DISCUSSION

In the United States there is no FDA-approved treatment for HAM/TSP, but in Japan, the reported efficacy of treatment with human lymphoblastoid-derived human IFN-α as studied in the 1990s led to its approval for use in HAM/TSP since 2000 [10–13]. Almost three decades ago, “natural” human lymphoblastoid IFN-α (Sumiferon, Sumitomo Pharma Co. Ltd, Osaka, Japan) was reported to be effective in the treatment of HAM/TSP in an open therapeutic trial of 5 patients given 3 MIU daily injected intramuscular (IM) for 28 days [10]. The overall response was beneficial in 4 of 5 patients, primarily in motor and ambulation outcomes. A double-blind, multicenter, dose-ranging study by Izumo et al. published in 1996 reported favorable therapeutic response in 66.7% (10 of 15) of HAM/TSP patients treated with 3.0 MIU daily of lymphoblastoid interferon-alpha (IFN-α1; Wellferon®, Sumiferon®) for 28 days [11]. Significant improvement was noted in motor function [as assessed by the Osame Motor Disability Score (OMDS)], urinary and bowel disturbances, sensory disturbance, and tremor. “Excellent to good” responses were maintained in 48 (61.5%) patients in the 3.0 MIU daily group at four weeks after treatment completion, even in cases...
with severe motor dysfunction. Side effects of natural IFN-α were reported to be “minimal,” with fever being the most commonly reported AE. Additional evidence describing the beneficial effect of IFN-α on HAM/TSP disease progression came from a study published in 1997 of 7 patients treated with high dose (6 U) natural IFN-α (Sumiferon) for a total of 22 weeks (daily for two weeks, then three times weekly) [12]. Five of the 7 patients showed improvement in neurologic symptoms best seen with the OMDS, and measures of the time or steps required to walk 5 or 10 meters. The EDSS was not significantly affected. Clinical improvement correlated with a reduction in HTLV-1 viral load in the early course of the therapy. These studies led to the approval of natural IFN-α as the first drug for the treatment of HAM/TSP in Japan in 2000, after which an extended surveillance study was established there to monitor the drug’s efficacy and adverse events. The surveillance study was reported in a review of 167 cases published in 2007 [13]. Adverse effects were observed in 87.4% (146/167) of patients, most frequently leukopenia (80/167), thrombocytopenia (42/167), and fever (110/167). Of these, 46 AEs in 24 patients were considered serious. Efficacy was evaluated in 152 patients, with mild or modest to marked improvement at four weeks in 66.2%. The majority of patients were treated less than 35 days. But of 61 patients treated greater than 35 days, 35 were improved (mild or modest to marked) at withdrawal. Efficacy ratios were not affected by treatment with corticosteroids or muscle relaxants. While longer term administration (greater than six months) had demonstrated benefit in 9 of 14 patients, the most suitable dosing protocol was not concluded. Withdrawal of medication appeared to result in a clinical rebound (relapse within one month) in 20% of a cohort of 30 patients who were followed for more than six months after treatment. An additional 17% of treated patients relapsed from 1 to 5 months of withdrawal, while 7% relapsed at five or more months of withdrawal. However, 30% of treated patients never relapsed.

Given the favorable treatment results reported for HAM/TSP patients in Japan, we used human leukocyte derived IFNαn3 at 3.0 MIU/day to treat 3 HAM/TSP patients with clinical worsening of their illness. The 3 patients, 2 women and 1 man, all living in the Caribbean, were initially treated with this purified form of natural interferon-α product for a mean of 20 months. The mean age of onset for the HAM/TSP patients was 49 ±10.6 years (Table 1). The pretreatment duration of illness ranged from 15 to 24 months. Their pretreatment disability ranged from an EDSS of 3.5–7.0. All patients tolerated the treatment well, with no patients withdrawing from the treatment due to adverse events and all exhibited subjective and objective neurological improvement over time as indicated by a decrease in the EDSS score. Our clinical experience with the commercially available form of purified natural interferon-alpha (IFN-αn3; Alferon-N®) serves to support and extend the reports from Japan regarding the treatment efficacy of “natural” IFN-α. Limited availability of IFN-αn3 led to the decision to treat patients with recombinant IFN-α2b despite documented clinical benefit with IFN-αn3.
What caused this different clinical response to IFN-α2b treatment remains unclear. The most obvious difference is that our 3 patients were treated initially with human leukocyte-derived IFN-α3, then changed to recombinant IFN-α2b treatment, after which they experienced deterioration in neurological function. The alteration in the molecular structure of the IFN-α might have generated a neutralizing immunological response to IFN-α2b after the IFN-α3 treatment. In a meta-analysis of 21 independent studies using type 1 IFN, Strayer and Carter compared patients with multiple diseases, including MS, hepatitis, and malignancies treated with natural (n-IFN) and recombinant interferon (r-IFN) [15]. They found that a large range of patients treated with r-IFN-α developed neutralizing antibodies (NABs), ranging from 15% to 100%, depending on the disease process [15], while the incidence of antibodies induced against n-IFN was very low (<0.2%). In their review, patients who did not develop NABs had a sustained response to treatment, as would be expected. Interestingly, they found that those patients who either relapsed or had no response to the r-IFN in the setting of NABs, still responded to n-IFN treatment 50% of the time after they were switched [15]. In an older study of patients treated with n-IFNα for condylomata acuminata, 48 patients were treated and none developed NABs [16]. Perhaps in our HAM/TSP patients, the neurological decline observed during r-IFN administration may have been due to the development of neutralizing or binding antibodies. Unfortunately, specific anti-IFN-α antibody testing to address this question directly was not available for these patients. Another possible explanation is the patients’ geographic environment, that is, the Caribbean basin. This could produce differing epigenetic influences or differences in the endemic HTLV-1 viral subspecies that in turn influenced the response to IFN-α2b treatment compared to IFN-α3.

In a longitudinal study in the United Kingdom, Martin et al. reported that the patients of Afro-Caribbean ethnicity and those living far from urban centers had the highest mortality associated with HTLV-1 infection [17]. Also, patients from Martinique had a longer time interval to diagnosis (mean 5.3, median 3 years) compared to patients from the United Kingdom (mean 3.8, median 2 years) [17]. This might be explained by the differences in access to healthcare between countries. Although the prevalence of HTLV-1 infection among US donors has declined since the early 1990s, a Florida blood transfusion study reported in 1991 a relatively high (0.4%) seroprevalence for HTLV-1 among donors in a South Florida area settled by Caribbean immigrants [18]. The high worldwide incidence of HTLV-1 makes HAM/TSP a significant factor contributing to neurological morbidity. The HTLV Outcomes Study (HOST) followed a large cohort of HTLV-1-infected patients over 15 years, and observed a risk greater than the previously reported 4% cumulative risk of acquiring HAM [19]. The frequency of infection and central nervous system (CNS) disease,
as well as a lack of awareness of this viral infection by practitioners in some areas, could result in misdiagnosis (e.g., multiple sclerosis). The true HTLV-1-infected population may be underestimated on a worldwide basis and the disease may have an even larger socioeconomic impact in areas of higher prevalence [18].

Different mechanisms have been proposed to explain the immunopathogenesis of HAM. One of the most relevant mechanisms is the “bystander model” where peripheral CD4 T-cells and CD8 T-cells activated by HTLV-1 cross the blood-brain barrier and penetrate the CNS. Then HTLV-1-specific CD8 T-cells respond to antigen expressed by CD4 T-cells and infected glial cells, and release myelotoxic cytokines such as Interleukin-1, Interleukin-6, TNF-α and interferon γ, causing CNS damage [4]. Interferon-alpha (IFN-α), a type 1 interferon, counters the pro-inflammatory response by inhibiting HTLV-1 infection through the action of an interferon-stimulated gene, PKR, on posttranscriptional stages of viral replication [20].

Overall, however, there is a lack of mechanistic understanding of how IFN-α can reduce or halt long-term disability in HAM/TSP. The main demonstrated marker of efficacy of IFN-α is the reduction in the HTLV-1 proviral load. It is believed that this effect correlates with the decrease of the central memory CD8 T-cell population [21]. This supports the role of the CD8 T-cell population in the pathogenesis of the neurological pathology through a “bystander” damage mechanism. Skillman et al. studied IFN-α3 in 20 patients with HIV-1 infection and found that it was safe and well tolerated [22]. It had potent antiviral effects, decreased viral replication, and inhibited the spread of infection by producing defective gp120 [22]. In a series studying HAM/TSP, Saito and coworkers reported that IFN-α1, not surprisingly, decreased viral load during treatment [23]. This has correlated with clinical improvement since there is a correlation between higher viral loads and the development of HAM/TSP [23]. The median proviral load is 16 times higher in HAM/TSP patients than in asymptomatic HTLV-1 carriers [24]. However, sustained clinical improvement following treatment cessation has also been observed with IFN-α1, despite the observation that viral loads return to pretreatment levels within 2-4 weeks of drug withdrawal. Sustained clinical improvement may possibly be related to a persisting decrease in CD4+ cell proliferation [12]. Interferon-α also exhibits other immunomodulation effects such as complex fluctuations of T cell subsets including alterations in the balance of Th1/Th2 subsets and their chemokines [12, 23, 25, 26].

**CONCLUSION**

This case report of 3 patients presented here illustrates an interesting observation of clinical neurological improvement in HAM/TSP patients treated with highly purified, leukocyte-derived, “natural” human IFN-α. But this is also a cautionary tale in that clinical deterioration occurred in the same patients after treatment was switched to recombinant IFN-α2b. Treatment with natural IFN-α was well-tolerated for prolonged periods of time while more adverse events were documented in the 3 patients during treatment with recombinant IFN-α2b. Currently, there are more than 20 million HTLV-1-infected people worldwide. The symptomatic TSP/HAM subpopulation of HTLV-1-infected people represents a large unmet need for safe and effective disease modifying therapy. Further investigation is needed to identify the factors and suitable surrogate markers that are predictably and meaningfully associated with neurological benefit from natural IFN-α. These include the duration of treatment, stage of illness, viral load response, and antibody formation. Additionally, a placebo-controlled trial would be highly desirable to determine optimal treatment for HAM/TSP patients given the unrelenting progressive disability associated with this viral infection and widespread socioeconomic impact of this disease.

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Author Contributions
Chao Zheng – Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Guarantor of Submission
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Consent Statement
This case report was prepared according to the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals given by the International Committee of Medical Journal Editors (ICMJE).” Identifying information for each patient has been excluded. Prior to submission, the report was reviewed and approved by the Office of HIPAA Privacy and Data Security, University of Miami Miller School of Medicine.

Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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