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Treatment of HTLV-I-Associated Myelopathy / Tropical Spastic Paraparesis: Towards Rational Targeted Therapy

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INTRODUCTION

Human T cell lymphotropic virus type I (HTLV-I) is the etiologic agent in a progressive neurological disease termed HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)^{1, 2}. HAM/TSP is a chronic inflammatory disease of the central nervous system (CNS) characterized by unremitting myelopathic symptoms such as spastic paraparesis, bowel/bladder dysfunction and lower limb sensory changes. Our understanding of the pathogenesis of HAM/TSP has advanced since its first characterization in the mid 1980's. This review discusses the current and future approaches to the treatment of HAM/TSP within the context of our current understanding of the underlying pathogenic mechanisms.

HTLV-I is the first human oncogenic retrovirus to be identified and isolated^{3, 4}. In the peripheral blood, HTLV-I preferentially infects CD4+ T-cells and to a lesser extent CD8+ T cells *in vivo*^{5,6}. A wider range of vertebrate cells are susceptible to HTLV-I infection *in vitro*⁷, and the localization of HTLV-I RNA in astrocytes suggests a broader tropism that may include resident cells of the CNS⁸.

HTLV-I is transmitted via three major routes: (1) transmission from mother to child through breast milk (2) transmission by sexual contact (3) transmission by way of infected blood. In endemic areas, maternal-child transmission via breast milk is a major mode of transmission of HTLV-I, followed by sexual contact. Transmission also occurs through unscreened blood transfusions and the use of contaminated intravenous needles.

Approximately 20–40 million people are infected worldwide. Endemic areas of HTLV-I infection include the Caribbean, southern Japan, Central and South America, the Middle East, Melanesia and the equatorial Africa^{9, 10}. The majority of infected individuals remain lifelong asymptomatic carriers. Approximately 0.25–3.8% develop HAM/TSP. Another 2 – 3% of

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infected individuals develop an aggressive mature T-cell malignancy termed adult T-cell leukemia (ATL). In Japan, the lifetime risk of HAM/TSP among the nearly one million infected individuals is 0.25%¹¹. The lifetime risk of HAM/TSP in the estimated 22,000 infected individuals in England is 3%¹². Seroprevalence of HTLV-I in US blood donors is 1 per 10,000. A recent study estimates that approximately 266,000 individuals are infected with HTLV-I or -II, and that there are likely more than 3,600 people in the United States with unrecognized HAM/TSP¹³. HTLV-I infections has also been associated with other inflammatory disorders including myositis^{14, 15}, peripheral neuropathy^{16, 17}, uveitis^{18, 19}, arthritis²⁰, Sjogren syndrome²¹ and alveolitis²².

Understanding the pathogenesis of the virus within the host has important implications for therapies directed against the virus itself. The maintenance of HTLV-I may occur through several, non-mutually exclusive, mechanisms. Proliferation of infected cells is likely a major mechanism by which the expansion of the number of HTLV provirus copies occurs. Alternatively, new infection may occur through virion production or through the formation of a virus induced synapse²³. Reverse transcriptase activity is required for the latter two mechanisms of viral propagation. The contribution of reverse transcriptase activity to maintaining HTLV-I proviral load *in vivo* is controversial. Conflicting data from clinical studies with regards to the efficacy of nucleoside analogues to reduce proviral load in HAM/TSP leaves this issue unsettled^{24, 25}.

Among the HTLV-I encoded viral genes, the *Tax* gene encodes a protein that activates viral transcription and also transactivates a large number of human genes²⁶. The Tax protein also contains immunodominant epitopes for MHC class I restricted cytotoxic cellular immune responses²⁷. Thus the transactivating Tax protein is not only the target but also modifies the host immune response. The Tax protein and its down-stream effects have been implicated in the persistent immune activation that contributes to the pathogenesis of HAM/TSP, and therefore represents an important target for therapy in HAM/TSP²⁸.

RISK FACTORS FOR DEVELOPMENT OF HAM/TSP

An elevated HTLV-I proviral load is the best marker of symptomatic neurologic disease in individuals infected with HTLV-I. In cross-sectional studies, the HTLV-I proviral load, determined by real-time PCR, was consistently higher in individuals with HAM/TSP than in asymptomatic carriers^{29, 30}. In practice, the typically low proviral loads (mean of ~2% of peripheral blood leukocytes in our cohort) of asymptomatic carriers tend to be reassuring, but the occasional asymptomatic carrier who demonstrates intermediate range proviral load presents a prognostic challenge. Often, such carriers are family members of individuals with HAM/TSP²⁹.

A number of host susceptibility genes have been identified that modify the risk of HAM/TSP. Many of these genes play a role in the host immunologic response and support the hypothesis that host immune response to the virus is a critical determinant in the development of HAM/TSP. The presence of HLA-A*02 allele has been reported to be protective where as the HLA-DRB1*0101 appears to confer susceptibility³¹. Polymorphisms in the genes for the inflammatory cytokines TNF- α and Interleukin-15, and in the SDF-1 has been reported to confer susceptibility³².

In practice, the most reassuring data to the individual with incidental finding of positive HTLV-I serology are that the over 90% of HTLV-I infected individuals are asymptomatic carriers and that the lifetime risk of developing HAM/TSP is likely less than 1%¹¹

DIAGNOSIS

The diagnosis of HAM/TSP is seldom in doubt in a seropositive individual who presents with a chronic progressive spastic paraparesis in the setting of elevated HTLV proviral load. The initial symptoms are typically back pain, gait disturbance, bladder/bowel or sexual dysfunction which are usually insidious but occasionally abrupt over weeks. Sensory symptoms including paresthesias and neuropathic pain, typically of the lower extremities, are often present in older patients. When subacute (relatively rapid) progression occurs, it is typically seen in the first two to three years of symptomatic disease. Clinical signs include weakness of the legs, spasticity, hyperreflexia, gait ataxia and loss of vibratory sensation. Most experience slowly progressive disease thereafter, but some remain stable for years or rarely improve to milder disability. Less common signs and symptoms include cerebellar signs, optic neuritis and atrophy, nystagmus and depressed ankle reflexes. In general, the burden of disability tends to be high with a majority of symptomatic individuals requiring assistance with ambulation³³.

Diagnosis is often delayed due to slow development of the full constellation of symptoms or misdiagnosis. The WHO diagnostic guidelines for HAM/TSP outline the full spectrum of disease without codifying levels of ascertainment³⁴. A recent recommendation proposes to refine the WHO diagnostic guidelines by formulating levels of ascertainment as “definite”, “probable” and “possible” HAM/TSP, where a patient with “definite” HAM/TSP manifests non-remitting progressive spastic paraparesis, positive serology and / or detection of proviral HTLV-I DNA and the exclusion of other disorders³⁵.

The differential diagnosis for HAM/TSP includes primary progressive multiple sclerosis, primary lateral sclerosis, hereditary spastic paraplegias, subacute combined degeneration secondary to vitamin B12 deficiency, HIV vacuolar myelopathy, syphilis and Lyme disease. Some have reported higher prevalence of positive HTLV-I serology in patients with Sjogren syndrome, and the findings of some elements of Sjogren syndrome may not be mutually exclusive with the diagnosis of HAM/TSP²¹.

Differentiating HAM/TSP from primary progressive MS is occasionally a diagnostic challenge, since the two are clinically indistinguishable and the mere presence of positive HTLV-I serology does not always lead to neurological disease. The difficulty is compounded by the fact that it is not unusual to find white matter abnormalities on brain magnetic resonance images (MRI) of patients with HAM/TSP^{36–38} (Figure 1). CSF pleocytosis, when present, typically falls within a similar range and oligoclonal bands are present in both. A recent study suggests that a high ratio of CSF to peripheral blood proviral load may distinguish HAM/TSP from individuals with MS³⁹. In general, HTLV-I proviral loads measured in the cerebrospinal fluid of individuals with HAM/TSP are typically greater than twice their load in the peripheral blood⁴⁰, whereas the ratio of CSF to peripheral blood HTLV-I proviral loads are typically lower in asymptomatic carriers^{39, 41}, reflecting either recruitment or expansion of HTLV-I infected cells in the CNS.

PATHOLOGY

Examination of the spinal cord demonstrates degeneration of the lateral columns, with variable damage to the anterior and posterior columns⁴², with the thoracic cord being typically most severely affected⁴³. Inflammatory changes are prominent histopathologic features of the HAM/TSP spinal cord (Figure 2), characterized by perivascular and parenchymal lymphocytic infiltrates in the white and grey matter along with activated microglia/ macrophages and severe degeneration and gliosis of the white matter⁴⁴. The lymphocytic infiltrates in the spinal cord is a mixture of CD4+ and CD8+ T-cells in early disease leading to a predominance of CD8+ T-cells, later in disease^{44–46}. Similar perivascular inflammatory infiltrates are observed in the brains of patients with HAM/TSP⁴⁷. Infiltrating cells include HTLV-I-specific CD8+ T

cells⁴⁸, demonstrated in the spinal cord of HAM/TSP patients by the use of Tax₁₁₋₁₉ peptide loaded HLA pentamers (Eiji Matsuura, MD, Kagoshima, Japan, personal communication). The HTLV-I-specific cytotoxic T cells appear to be preferentially recruited or expanded in the CNS⁴⁸. HLA class I and II expression is upregulated on endothelial cells and microglia⁴⁹. Pro-inflammatory and potentially neurotoxic cytokines such as IL-1 β , TNF- α and INF- γ are detected in perivascular infiltrating macrophages, microglia and astrocytes^{50, 51}.

PATHOGENESIS

The striking CNS inflammatory changes demonstrated in HAM/TSP favor immune mediated mechanisms of pathogenesis. Several hypotheses have emerged. HTLV infection of glial cells could lead to direct lysis by HTLV-specific cytotoxic CD8+ T cells. Alternatively, the target of immune attack may be HTLV infected activated lymphocytes that have migrated into the CNS. *Bystander damage*⁵² is then mediated through the release of neurotoxic inflammatory cytokines during the HTLV-specific cellular immune response. In addition, evidence has been put forth for the presence of anti-HTLV antibodies that, by *molecular mimicry*⁵³, cross-react with self-antigens (hnRNP-A1) in the CNS, leading to neuronal dysfunction and damage⁵⁴.

The sequence of events leading to *bystander damage* may be as follows²⁸. Activation of T cells following HTLV infection allows the activation and migration of CD4+ and CD8+ T cells across the blood-brain barrier from the peripheral blood to the central nervous system (CNS). HTLV-I-specific CD8+ T cells are preferentially recruited or expanded in the CNS, and respond to HTLV-I antigen expressing cells, most likely HTLV-I infected CD4+ T cells or possibly HTLV-I infected glial cells. HTLV-specific immune responses that occur in the CNS then lead to release of neurotoxic cytokines and subsequent CNS damage.

THERAPY

No therapy has been conclusively shown to alter long-term disability associated with HAM/TSP. Clinical improvements have been reported for a number of agents in open-label studies including corticosteroids, plasmapheresis, danazol⁵⁵, pentoxifylline⁵⁶ and interferon. With the exception of interferon- α , however, these drugs lack the quality of evidence required to merit a strong recommendation for their use in HAM/TSP. The role of interferon- α in HAM/TSP also remains in question, as no study has conclusively shown long-term benefit.

Although significant challenges to the development of effective disease modifying therapy for HAM/TSP remain, therapeutic trials for HAM/TSP, collectively, continue to advance our understanding of this disease, setting the stage for better qualification of biomarkers and refinement of specific therapeutic targets.

HAM/TSP relevant biomarkers

The lack of sensitive measures of disease activity remains a challenge for assessing the effect of therapy in a chronic progressive neurological disease such as HAM/TSP. Progression of clinical disease in HAM/TSP may be subtle, especially later in disease, and difficult to quantify even over the course of a year. Biomarkers that reflect the progression or activity of underlying pathogenic mechanisms would hold great potential with respect to diagnosis and prognosis as well as screening and evaluation of novel therapeutics in a timely, effective manner in HAM/TSP.

There are no validated surrogate markers in HAM/TSP. Among the number of potential relevant biomarkers studied, *HTLV-I proviral load* has the most data supporting its relationship with disease course. HTLV-I proviral load is determined as the amount of integrated HTLV provirus, measured by a real-time polymerase chain reaction (PCR) assay

and typically expressed as the number of copies of HTLV-I proviral DNA per number of peripheral blood mononuclear cells (PBMC). There is little, if any, cell-free virus found in plasma of HTLV infected individuals⁵⁷. Evidence from clinical studies suggests HTLV-I proviral load is potentially a marker of disease activity. Analysis of observational studies showed a relationship between HTLV-I proviral load and disability^{33, 40, 58, 59}. Analysis of the interferon- α studies showed concordance between reduced proviral load and clinical benefit⁶⁰. Full validation of HTLV-I proviral load as a marker of disease activity will require data from prospective controlled trials that demonstrate correlation between change in HTLV-I proviral load and clinical impairment/disability.

A related biomarker is the **HTLV-I Tax mRNA load** measured by real-time quantitative RT PCR. One study showed correlation between HTLV-I Tax mRNA load and disease severity, and showed higher ratio of Tax mRNA load to the proviral load (mRNA/DNA) in HAM/TSP than in healthy volunteers⁶¹. The reduction in HTLV-I Tax mRNA load corresponded to the reduction in the frequency of **Tax-specific CD8+ T cells** following interferon- β therapy, suggesting that Tax mRNA load identifies a transcriptionally active fraction of HTLV-I infected cells that disproportionately influence host cellular immune response⁶². Tax-specific CD8+ T cells has been implicated as a key cellular element contributing to *bystander damage* in HAM/TSP²⁸. The availability of peptide/MHC tetrameric and pentameric complexes allows the direct identification of Tax-specific CD8+ T cells for individuals with the HLA A*0201 and HLA A*2404 alleles. The high frequency of Tax-specific CD8+ T cells distinguished HAM/TSP from asymptomatic carrier within an HTLV-I infected cohort⁶³. Further characterization of these cells with respect to effector/memory phenotype, cytokine production and function is likely essential to understanding their role in HAM/TSP^{64–66}.

Spontaneous lymphoproliferation indicates *ex vivo* proliferation of peripheral blood leukocytes from patients with HAM/TSP in the absence of exogenous stimulation. The observation of spontaneous lymphoproliferation is often interpreted as a marker of persistent immune activation in HAM/TSP. The upregulation of Interleukin-2 (IL-2) and Interleukin-15 (IL-15) by the HTLV-I encoded Tax protein underlie the autocrine/paracrine loops driving spontaneous lymphoproliferation in HAM/TSP^{67, 68}. Thus inhibition of spontaneous lymphoproliferation reflects the ability to modulate key inflammatory cytokines dysregulated in HAM/TSP^{69, 70}.

Novel biomarkers currently being examined include CD4+CD25+ regulatory T cells and its marker Foxp3, which are impaired in HAM/TSP^{71, 72}, altered TGF- β receptor expression in HAM/TSP (Christian Grant et al, manuscript in preparation) and the spontaneous degranulation (CD107a mobilization) demonstrated by of HTLV-I-specific CD8+ T cells in HAM/TSP (Yoshimi Akahta et al, manuscript in preparation).

Corticosteroids

The evidence for supporting the use of corticosteroids in HAM/TSP is based on uncontrolled case series⁷³. The immunomodulatory effects of corticosteroids⁷⁴ form the rationale for its use in HAM/TSP. One of the earliest reported therapy producing clinical benefit in HAM/TSP⁷³, corticosteroids are now generally considered to confer transient clinical benefit⁷⁵. However, due to the lack of well-designed controlled trials, many questions remain regarding the usefulness of corticosteroids in HAM/TSP. Anecdotal reports suggest corticosteroids may be most efficacious early in disease, in rapidly progressive disease, and that clinical benefit may be prolonged with prolonged course (e.g. monthly pulsed intravenous corticosteroids). But there is no reliable data to guide the clinician with regards to the time of initiation, the dose or the duration of corticosteroid therapy in HAM/TSP.

Plasmapheresis and intravenous gammaglobulin (IVIG)

The rationale for the use plasmapheresis would be to modulate the contribution of the humoral response to the pathogenesis of HAM/TSP. There is some evidence to suggest that anti-HTLV antibodies could potentially be neuronopathic (see above). Limited data from uncontrolled case series showed that plasmapheresis led to transient (2–4 weeks) clinical improvement in more than half the patients treated for HAM/TSP⁷⁶. Anti-HTLV-I-antibody titers were lowered in serum but not in the CSF following plasmapheresis. Future studies analyzing the relationship between changes to the titers of anti-neuronal antibody implicated in HAM/TSP (hnRNP-A1) and clinical response following plasmapheresis may further our understanding of the relative pathogenic contribution of anti-HTLV-I humoral response. A similar transient clinical benefit was reported for IVIG⁷⁷, which has a number of effects on the immune system including neutralization of activated complement, signaling via Fc receptors and modulation of proinflammatory cytokines⁷⁸. It is yet unknown whether periodic plasmapheresis or IVIG treatment could lead to sustained clinical benefit.

Daclizumab (humanized anti-Tac)

HTLV-mediated upregulation of the IL-2 signaling represents a key component of the immune activation observed in HAM/TSP. HTLV encoded transactivating factor Tax upregulates expression of IL-2 as well as CD25, the alpha subunit of the IL-2 receptor in T cells⁶⁸. An expansion of the CD4+CD25+ compartment in the peripheral blood is observed and identifies a major reservoir of HTLV infection⁷⁹. In vitro studies showed that an antibody against CD25 that blocks IL-2 signaling inhibits the characteristic spontaneous proliferation of peripheral blood leukocytes from patients with HAM/TSP⁶⁸. Clinical trials had already demonstrated the potential for anti-CD25 monoclonal antibody humanized anti-Tac to reduce CD25+ cells in adult T cell leukemia/lymphoma^{80, 81}. Thus preliminary studies suggested that a monoclonal antibody therapy against CD25 could reduce HTLV infected cells as well as block HTLV driven immune activation.

Anti-CD25 monoclonal antibody therapy was tested in a single-center open-label trial using humanized anti-Tac (daclizumab)⁸². Anti-CD25 antibody therapy had the anticipated result of reducing the number of CD4+CD25+ cells in subjects with HAM/TSP. Moreover, the anti-CD25 antibody therapy resulted in a significant concomitant reduction in the HTLV proviral load. Analysis of *ex vivo* proliferative capacity demonstrated a partial suppression of spontaneous lymphoproliferation during anti-CD25 antibody therapy. Three out of the nine treated subjects demonstrated clinical improvements by Expanded Disability Status Scale (EDSS). None had clinical progression of disease during the trial. The reduction in HTLV proviral load likely represents loss of HTLV infected CD4+CD25+ cells during humanized anti-Tac therapy, and supports the use of this marker (CD25) to target HTLV infected cells. The reduction in spontaneous lymphoproliferation suggested that the anti-CD25 antibody therapy achieved at least partial inhibition of immune activation in HAM/TSP.

Interferons

Class I interferons (IFN- α and - β), which have cytostatic and antiviral properties, represent an approach for long-term immunomodulatory therapy in patients with HAM/TSP.

Interferon- α , considered a standard of care for HAM/TSP in Japan, demonstrated clinical benefit for subjects with HAM/TSP in a blinded trial⁸³. A dose-effect was demonstrated using human lymphoblastoid interferon with subjects on higher dose interferon- α injections more likely to improve than those on lower dose. The benefit of long-term interferon- α therapy, however, has not been well studied. A small study extending interferon a treatment to 24 weeks reported sustained clinical response⁸⁴.

The main marker of efficacy during interferon- α therapy appears to be a reduction in HTLV-I proviral load⁶⁰. The reduction in HTLV-I proviral load during interferon- α therapy was associated with changes in CD8+ T cells. A reduction in CD8+T cells of the central memory phenotype was observed with interferon- α treatment. In addition, a reduction in CD8+ T cell perforin expression was observed, and a concordance between reduced perforin and clinical improvement was suggested by the analysis. These changes in cellular immune response following interferon- α study lend some support to cytotoxic CD8+ T cell involvement in *bystander damage* postulated to occur in HAM/TSP.

Following the modest success of interferon- α therapy in HAM/TSP, long-term treatment with **interferon- β** was tested in a cohort of HAM/TSP patients. In an open-label, single center trial, 12 subjects who met WHO criteria for HAM/TSP received up to twice weekly injection of 60 μ g interferon- β 1a for 28 weeks. No significant clinical changes were observed during the trial in this cohort whose mean disease duration was 6.5 years (range 2–20). Among the number of biomarker measured during the trial, significant reduction in the frequency of Tax-specific CD8+ T cells was observed along with a reduction in HTLV-I Tax mRNA load and the spontaneous lymphoproliferation. No significant changes were observed in the HTLV proviral loads. These results suggested that interferon- β therapy had an overall immunomodulatory effect in HAM/TSP as evidenced by the relative suppression of spontaneous proliferation, and demonstrated that interferon- β therapy had a profound effect on virus specific cellular immune responses.

The observation that reduction in Tax-specific CD8+ T cell frequencies were more closely tied to HTLV-I Tax mRNA load than to the HTLV-I proviral load following interferon- β treatment suggest that a small transcriptionally active fraction of HTLV infected cells may be largely responsible for the extent of virus specific CD8+ response in HTLV-I infection. Thus changes in HTLV-I transcriptional activity, through increased HTLV-I protein expression, processing, and presentation as peptide in association with the major histocompatibility complex, may profoundly influence HTLV-I-specific cellular immune response. These results also suggest that one could modify the magnitude of the HTLV-I-specific immune response by the altering the transcriptional activity of the HTLV-I provirus.

Nucleoside analogues

Initial observational studies suggested clinical benefit and reduction of HTLV-I proviral load with zidovudine^{85, 86} and lamivudine²⁵, which had demonstrated some *in vitro* activity against the HTLV-I reverse transcriptase^{87, 88}. A randomized, double-blind, placebo controlled study of six months combination therapy with these two nucleoside analogues was conducted in sixteen patients²⁴. No significant clinical changes were observed as a result of zidovudine/lamivudine combination therapy in the measures tested. No significant change was observed in HTLV-I proviral loads. The contribution of reverse transcriptase activity to maintaining HTLV-I proviral load *in vivo* remains controversial, despite this well-designed trial targeting HTLV-I reverse transcription.

Emerging therapies

Hu MiK β 1: Targeting Interleukin-15—Pro-inflammatory cytokines implicated in the pathogenesis of immune-mediated inflammatory diseases represent rational targets for therapy. Interleukin-15 (IL-15) is a pro-inflammatory cytokine that appears to be dysregulated in HAM/TSP, and may play a pathogenic role in this and a number of other immune-mediated inflammatory diseases⁸⁹. The role of IL-15 is particularly relevant in HAM/TSP because the HTLV-I encoded Tax protein promotes the expression of IL-15 and its private receptor (IL-15R α) by transactivating IL-15 and IL-15R α gene transcription⁶⁷. The upregulation of IL-15 contributes to the sustained immune activation in HAM/TSP that can be inhibited *in*

vitro by the administration monoclonal antibodies that block IL-15 signaling⁶⁹. An important function of IL-15 in the immune system is the maintenance of memory CD8+ T cells. The upregulation of the IL-15 paracrine loop may explain the persistent expansion of HTLV-I-specific CD8+ T cells in HAM/TSP⁹⁰. In short, evidence suggests that IL-15 plays a specific role in the immune activation observed in HAM/TSP.

A phase I/II clinical trial is underway to test the safety and provide preliminary efficacy data of a monoclonal antibody, Hu MiK- β 1, that blocks IL-15 signaling. Based on its *in vitro* effects, we hypothesize that the administration of Hu MiK- β 1 in subjects with HAM/TSP will lead to inhibition of spontaneous proliferation and reduction in HTLV-I-specific cellular immune responses. The study of targeted therapies such as Hu MiK- β 1 has the potential to elucidate the contribution of specific pathways to the pathogenesis of HAM/TSP.

Valproic acid

A large fraction of the HTLV-I infected cells in the peripheral blood is transcriptionally quiescent in HAM/TSP, escaping cytolysis by HTLV-I-specific cytotoxic CD8+ cells and the effects of reverse transcriptase inhibitors. Recent work in human immunodeficiency virus (HIV) suggests that histone deacetylase inhibitors such as valproic acid (VPA) may induce expression of HIV from previously quiescent HIV infected CD4+ T cells^{91, 92}, subjecting them to the effects of anti-retroviral therapy.

A single-arm, open-label trial tested the benefit of VPA (20mg/kg/day) in 19 patients with HAM/TSP. Preliminary data suggest VPA administration induced a transient increase then a drop in HTLV-I proviral loads in HAM/TSP patients (Lezin, A et al Abstracts from the 13th International Conference on Human Retrovirology HTLV and related viruses). Clinical measures were stable overall. The authors hypothesized that VPA led to increased viral expression and subsequent destruction by the host immune system.

CONCLUSION

The treatment of HAM/TSP remains a challenge. No agent has shown to significantly modify the long-term disability associated with HAM/TSP. Advances in our understanding of the pathogenesis of HAM/TSP have led to the identification of several biomarkers and therapeutic targets. Clinical trials in HAM/TSP continue to be opportunities for further qualification and refinement of biomarkers and therapeutic targets. The validation of HAM/TSP relevant biomarkers and the identification of new targets remain key challenges in the development of effective targeted therapy in HAM/TSP.

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Figure 1. Magnetic resonance imaging (MRI) findings in HAM/TSP. MRI of the brain and spine in a 39 year old woman with 2 years of gait difficulty and urinary dysfunction showing brain white matter abnormalities (arrow) on FLAIR (A), and T2 signal changes (arrows) in the cervical and upper thoracic cord (B). MRI of the brain and spine in a 58 year old woman with over 20 year history of spastic paraparesis showing brain white matter abnormalities (arrow) on FLAIR (C) and atrophy of the spinal cord (D).

Figure 2. Pathologic findings in HAM/TSP. Hematoxylin and eosin staining of spinal cord section from a subject with HAM/TSP showing perivascular and parenchymal mononuclear cell infiltration (courtesy of Dr. Eiji Matsuura).