資料 1

The management of HAM/TSP ：Systematic review and consensus-based recommendations 2019

Abelardo Araujo MD, PhD[1], Charles RM Bangham BM, PhD[2], Jorge Casseb MD, PhD[3], Eduardo Gotuzzo MD[4], Steve Jacobson PhD[5], Fabiola Martin MD, MD(Res)[6], Augusto Penalva Oliveira MD[7], Marzia Puccioni-Sohler MD, PhD[8], Graham P Taylor MB, DSc[9], Yoshihisa Yamano MD, PhD[10].

[1]Laboratory for Clinical Research in Neuroinfections, Evandro Chagas National Institute of Infectious Diseases, FIOCRUZ, Rio de Janeiro, Brazil.

[2] Section of Immunology of Infection, Department of Infectious Disease, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK

[3]Faculdade de Medicina da Universidade de São Paulo/Institute of Tropical Medicine of Sao Paulo, Sao Paulo, SP, Brazil[4]Instituto de Medicina Tropical "Alexander von Humboldt", Universidad Peruana Cayetano Heredia, Lima-Peru

[5]Viral Immunology Section, National Institutes of Health, Bethesda, MD, USA
[6] Stonewall Medical Centre, 52 Newmarket Rd, Windsor QLD 4030, Australia.

[7]Instituto de Infectologia Hospital Emilio Ribas, Sao Paulo University, Sao Paulo, SP Brazil

[8]Federal University of the State of Rio de Janeiro (UNIRIO)/ Federal University of Rio de Janeiro (UFRJ) – Rua Mariz e Barros 775, Rio de Janeiro, RJ 20270-004, Brazil

[9] Section of Virology, Department of Infectious Disease, Imperial College London, St Mary's Campus, Norfolk Place, London W2 1PG, UK

[10]Yoshihisa Yamano, Department of Rare Diseases Research, Institute of Medical Science, St Marianna University School of Medicine, Kanagawa, Japan.

List of abbreviations

AE	Adverse event
sc	subcutaneous
DMT	Disease modifying therapy
g	gram
HAM/TSP	HTLV-1-associated myelopathy/tropical spastic paraparesis
HIV	Human immunodeficiency virus
HTLV-1	Human T-lymphotropic virus type 1
im	intramuscular
IRVA	International Retrovirology Association
IV	intravenous
kg	kilogram
µg	microgram
mg	milligram
MIU	million international units
MRI	magnetic resonance imaging
OMDS	Osame Motor Disability Score

Abstract

PurposePurpose of Review: To provide an evidence-based approach to the clinical management of HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) – a rare disease.

Recent Findings: all**A**ll 41 articles the onclinical outcome of disease-modifying therapy for HAM/TSP were included in a systematic review by members of the International Retrovirology Association; we report here the consensus assessment and recommendations. The quality of available evidence is low, being based for the most part on observational studies, with only one double-masked placebo-controlled randomised trial.

SummarySummary: There is evidence to support the use of both high-dose pulsed for methylprednisolone for induction and low-dose (5mg) oral prednisolone as maintenance therapy for progressive disease. There is no evidence to support the use of antiretroviral therapy. There is insufficient evidence to support the use of interferon-α as a first-line therapy.

Introduction

At a conservative estimate 5 – 10 million persons are infected with HTLV-1 globally(1). HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) occurs in ~3% of HTLV-1 carriers. The risk varies between different endemic regions: the lowest reported life-time risk is 0.25% from Japan, whiledata from Brazil indicate a risk much higher than 3%%, with an incidence of 1.47% over a median of 3 years in one cohortcohort(2, 3).

Although the range of symptoms can be extensive, there are five cardinal symptoms: lower limb stiffness and/or weakness; lumbar pain with or without radiation; bladder dysfunction (spastic or flaccid); bowel dysfunction, usually presenting as constipation; and sexual dysfunction. The neurological findings are reported in detail elsewhere(4). Natural history studies indicate a chronic progressive deterioration, resulting in 50% of patients with HAM/TSP becoming wheelchair-dependent within 20 years of first symptoms. Rates of progression vary widely, with a subset remaining stable over many years while a small minority become rapidly bedbound(5).

Although symptomatic management and physical therapies can improve function and quality of life in HAM/TSP, they do not alter the natural history of the condition. In this guideline, published on behalf of the International Retrovirology Association (IRVA) for the management of patients with HAM/TSP, the potential of disease-modifying therapies (DMT) is reviewed. The term DMT will be used in this review to refer to any therapy which targets the disease process, be it anti-inflammatory or anti-viral, rather than symptomatic treament. A broad range of compounds have been examined over the last three decades, but there are few systematic studies and no published guidelines on their use.

Methods

An international panel of physicians and clinical scientists from neurology and infectious diseases, experienced in the management of patients with HAM/TSP, was convened from the membership of the International Retrovirology Association, the association for research, education and training on HTLVs and associated diseases.

Two approaches were taken. First, a literature review was conducted by searching PubMed in January 2017 using the terms *HTLV-1-associated myelopathy, tropical spastic paraparesis, therapy and treatment.* Second, the biennial conference proceedings of IRVA were systematically reviewed. The disposition of articles is presented in Figure 1. Studies were included if they reported an observational cohort, an open treatment study or a randomised controlled study (masked or unmasked), with one or more clinical outcome measures. Case reports and studies of surrogate markers were excluded. The outcomes of interest were changes in disability, mobility, pain, bladder or bowel function in relation to therapy directed at the underlying disease, rather than symptomatic management. The preferred measure of effect was the time taken to walk a fixed distance (typically 10 m). None of the studies presented confidence intervals and only two studies were prospective randomised studies, both of small size. Important clinical effects were any measured change in time taken to walk 10 m, change in validated disability scale, or change in pain as measured on a visual analogue scale. The findings of the systematic review were presented for consultation at an open workshop held during the 18th International Conference on Human Retrovirology: HTLV and related viruses (March 2017) Kamakura, Japan. Thereafter panel members met on two occasions to formulate recommendations. The draft recommendations were circulated to and commented on by all panel members with the addition of any eligible

studies publish since the original literature search. The resulting recommendations, made in accordance with the GRADE Guidelines(6), recommendations represent the consensus reached by discussion among the panel members.. The draft recommendations were presented at the IRVA Tokyo Conference and International Symposium 13th July 2018 and then published on the International Retrovirology Association website for public consultation. The final recommendations were presented at the 19th International Conference on Human Retrovirology: HTLV and related viruses (Lima, Peru, 24-26 April 2019).

Data Availability Statement. All data used to inform these recommendations are published and referenced.

Recommendations and context

1. **It is recommended that clinical studies of therapy for HAM/TSP should pre-define patients into the following categories: Rapid progression, slow progression, and very slow or non-progressing, and report outcomes separately for each category.**

HAM/TSP has a broad spectrum of severity and consequently the potential benefit of therapies varies considerablyconsiderably. The natural history of HAM/TSP ranges from a disease that renders the patient bed-bound within months to minor disturbances of gait or abnormalities of bladder function that remain stable over many years.

There is increasing evidence that responsiveness to therapy (reduced symptoms, increased mobility) correlates with the duration and stage of disease. Since current therapies which aim to alter the course of HAM/TSP all have notable risks, it is important to select those patients who are most likely to benefit. Patients with rapidly progressing disease should be treated immediately. In addition, patients with rapid disease may require more intense treatment to modify disease progression. Clinical experience suggests that more aggressive therapy that would not be considered for patients with slowly-progressing disease can restore mobility in rapidly progressing patients. However, this suggestion needs to be verified through clinical studies.

The optimal management of the milder forms of HAM/TSP will be discussed in detail. However, the relative merits of treatment needs to be determined for each clinical subgroup of patients, to ensure that the risks and benefits are appropriately assessed.

Rapid progression:

In the ongoing randomised controlled study HAMLET-p, comparing placebo with prednisolone, patients are defined as rapid progressors if they present with or display one or more of the three deterioration criteria in the 'clinical history' or all four deterioration criteria in the 'clinical examination' at screening visit or during the three-month assessment period:

Criteria of Rapid Deterioration

1. Clinical History

A) In the preceding three months:

- Loss of ability to run.
- Loss of ability to climb stairs unaided (now needing to use at least one banister to climb up or downstairs).

- First symptoms of HAM/TSP during the preceding three months and already needs a walking aid (unless this need is unrelated to HAM/TSP).

B) In the preceding two years:

- Progression from walking unaided to wheelchair-dependent or bedbound within two years of onset of symptoms

2. Documented clinical examination during the following three months, one or more of the following:

    - Additional walking aid needed
    - Increase in 10 m timed walk (s) by ≥ 30%
    - Decrease in 6 minute timed walk (m) ≥ 30%
    - Increase in timed up-and-go (s) ≥ 30%

Slow progression:

Patients are defined as slow progressors if they meet none of the rapid progression criteria listed above, but one or more of the three clinical examination criteria for slow progression, at any point during the assessment period:

Criteria of slow progression:

Documented by clinical examination over a three month period, one or more of the following:

- Increase in 10 m timed walk (s) by ≥ 10%
- Decrease in 6 minute timed walk (m) ≥ 10%
- Increase in timed up-and-go (s) ≥ 10%

Outside a clinical trial clinicians may choose to estimate the rate of progression from the history but this can make interpretation of the clinical response more difficult.

Very slow progression (or no progression):

Patients who do not meet any of the clinical history or clinical examination criteria of slow or rapid progression listed above.

A few patients show very slow progression of motor disability. For example, a patient may lose the ability to run at 10 years or more after the onset of motor symptoms, but still can climb up or downstairs without any support(5).

Conclusion/Expert Opinion. While these definitions require international validation in multiple settings before becoming standardised in clinical trials, they are non-invasive and easily assessed. The definitions are presented here to identify patients who would benefit from the treatments outlined below, while recognising that local variations are used. It is helpful to us more than one clinical measure: for example, in patients with HAM/TSP the 10 m timed walk has been shown to detect change but underestimate fatigue, which is identified with the 6 minute timed walk (7).

2. All patients with HAM/TSP should be *considered for* and *offered* disease-modifying therapy within the context of a clinical study, regardless of severity and duration of disease.

Currently clinical trials for patients with HAM/TSP are uncommon. However, there is an urgent need for higher quality evidence to support any recommendations because, as is shown below, the evidence base for guiding treatment for patients with HAM/TSP is extremely limited. Since the potentialeffect on any patient of the current (and future) therapies is uncertain, the safety and efficacy of any therapy need to be tested across the spectrum of disease severity.

3. Therapy for patients with slowly progressing HAM/TSP

3.1 Use of Corticosteroids

Before starting any immunosuppressive therapy, patients with HTLV-1 infection should be screened for HIV, hepatitis B and C, syphilis, *Strongyloides stercoralis* (if they are or were resident in an endemic region) and tuberculosis, and treated as appropriate. Other clinical contraindications to the use of corticosteroids in the short or long term must also be considered and Adult T-cell Leukaemia/Lymphoma must be excluded.

3.1.1 Treatment with pulsed methylprednisolone (1g daily for 3 – 5 days) should be considered for patients with progressing disease either as a standalone treatment or as an induction therapy before starting HAM/TSP disease-modifying therapy.

The use of pulsed intravenous methylprednisolone (500mg daily for 5 days) was reported in 1990 by Duncan and Rudge. Pain and paraesthesia improved in 4/7 patients, spasticity in 3/8 and lower limb weakness in 5/9. Noeffect on urinary symptoms or paraesthesia was observed. However, with one exception the benefit lasted no more than six weeks and the utility of this treatment was considered limited(8). Araujo *et al* similarly treated 21 patients and observed improvement in only one, who had symptoms for only five months when first treated, but had sustained benefit(9). Nakagawa *et al* reported that 1g methylprednisolone IV daily for 3 days was effective in 6 of 10 rapidly progressing HAM/TSP patients(10). More recently Croda *et al* reported on repeated treatments with 1 g methylprednisolone IV daily for 3 days, every 3 – 4 months in 39 patients. Concurrent anti-spasmodic treatment and physiotherapy were administered, and the mean number of therapies was 3.4. No statistically significant changes were seen at follow up in either of two disability scales, the Disability Status Scale and the Osame Motor Disability Score (OMDS), but a statistically significant improvement in Incapacity Status Scale was observed following the first two treatments. Numbers were too small after subsequent therapies to achieve statistical significance in ISS although broadly the change from baseline was similar. The response to treatment was not correlated with either the severity of disability at baseline or the number of therapies administered. Fifty-eight percent of patients were already using a walking aid at baseline(11). Buell *et al* reported improvement in pain scores following a single three-day course of pulsed methylprednisolone (1g daily) which persisted to 24 weeks, whereas improvements in the 10 m timed walk observed by the time of the 3rd infusion were no longer detected at the 4 week review. However, an improved 10 m timed walk was seen in patients with less than 2 years of disease. Urinary symptoms were unaltered. Twenty-four of 25 patients completed the course(12).

Conclusion/Expert Opinion: Pulsed methylprednisolone is well tolerated, but is associated with only transient clinical improvement, mainly in movement or pain. The effects are seen within days, and persist for several months in a proportion of patients. One study indicated that the benefits may be maintained by repeated courses, but more data are required on treatment with more than two courses (11). Treatment in earlier disease tends to achieve

better results. The expert panel considered that pulsed methylprednisolone can be an effective approach to initiating disease-modifying therapy for slowslowly progressing HAM/TSP.

3.1.2 For patients with HAM/TSP who are ambulant and have evidence of *progressive disease,* treatment with low dose (~5mg daily) prednisolone[1] can be offered unless they are rapid progressors.

Where this is tolerated, this can be given long-term (up to 4 years) as maintenance therapy.

3.1.3 Higher doses of prednisolone (<60 mg daily) are sometimes indicated with titration of the dose according to the clinical response.

Although little good-quality evidence of efficacy is available, the best current evidence relates to the use of corticosteroids. Five studies have addressed this: all are observational and four are retrospective analyses.

In 1990 Osame et al reported the results of treating 65 patients with oral prednisolone: mean age was 52 years, duration of HAM/TSP 4 months to 48 years (median not stated), dose was initially 60-80 mg daily on alternate days for 2 months, tapered to 10 mg alternate days over 6 months, then maintained on 5 mg alternate days for 3 months and then stopped. Fifty of the 65 patients were ambulant at baseline; an improvement in mobility was documented in 59 (91%) patients, ranging from an improvement in the 10 m timed walk within a disability grade (Fair response, 33.8%) to an improvement of at least 2 grades in the Osame Motor Disability Score (Excellent response, 20%). Treatment responses had maximal effect at 1-3 months and were less with greater severity of disease. Following treatment discontinuation the symptoms worsened again but did not reach the pre-treatment baseline by the end of the 1 – 6 months follow up. In addition to the improvement in motor function, 51% of patients with bladder dysfunction reported improvement, as did 51% of patients with impaired vibration sense. Hand tremor improved in 52% of the 25% of patients in whom it was present. Important treatment side effects were observed in 20% of cases, including Cushingoid appearance, steroid myopathy, paravertebral abscess, osteoporosis and compression fractures. In 9%, no clinical improvement was noted (13).

Kira et al (1991) reported on 16 patients with HAM/TSP treated with 40-60 mg prednisolone daily for 1 – 4 months, following which prednisolone was tapered and then stopped. The mean age and disease duration of these 16 patients was not reported, but in the larger group of patients with HAM/TSP in the MRI study, the mean age was 50 years and the duration of disease was 12 years. During the first 3-12 weeks of prednisolone treatment, ~70% of patients subjectively improved, albeit with no change in Kurtzke disability score or in brain MRI. The authors summarised that there was a modest improvement in spastic gait and sphincter disturbance during high-dose corticosteroid therapy which was not maintained once the steroids had been tapered. After 20 – 33 months of follow up, 15/16 patients reported deterioration, and in the group as a whole there was either no change or a deterioration in both the Kurtzke scale and brain MRI(14).

One hundred and thirty-one patients treated with oral 40-80 mg prednisolone daily or on alternate days for 1-2 months between 1986 and 1993 were included in Nakagawa's retrospective analysis of the outcome of treatment of more than 200 patients with HAM/TSP

[1] Or prednisone where prednisolone is not available

with a variety of agents. Prednisolone was tapered by 5-10 mg every other day or was stopped after 6 – 12 months of therapy. Using an 11-point motor ability scale the mean value pre-treatment was 5, representing the use of a unilateral walking aid. An improvement in OMDS of 2 grades or more was observed in 16/131; of 1 grade in 75/131, and improvement within a grade was seen in 16, giving an overall response rate of 82%. Five patients experienced fractures, five bronchitis, fourfour osteoporosis, fourfour Cushingoid features, three each had urinary tract infection, gastro-duodenal ulceration, hypertension and glucose intolerance, and various other adverse events were reported in individual patients(10).

Despite this paucity of data and inconsistency of effect, oral prednisolone has been used extensively in Japan. Where disease severity was mentioned in a published report, patients were more likely to respond if they had less disability at baseline, and 20% reported adverse events. A recent retrospective study sheds more light on the potential of low dose oral prednisolone. Coler-Reilly *et al* conducted a retrospective multicentre case-note reviewin Japan(15). One hundred and fourteen patients were included in the study; 57 were taking oral prednisolone at a median dose of 4.8 mg daily and 29 were not taking any potentially disease-modifying therapy. Of the remaining 28 patients, 12 had discontinued prednisolone and 14 had taken both prednisolone and interferon. The median duration of follow-up was 3.4 years and during this period 79% of untreated patients deteriorated by at least one OMDS grade. Patients on prednisolone had an averaged of 0.12 grade/year improvement in OMDS, whereas untreated patients deteriorated by an average of 0.13 grade/year. Patients who had been treated with prednisolone for less than 4 years either improved (52%) or remained stable (35%), stability here being defined as no change in OMDS grade.A. Amongst those not treated with prednisolone no patient reported an improvement in OMDS grade, and 87% reported clinical deterioration. Amongst patients treated with prednisolone for > 4 years the **most common outcome** was to remain within an OMDS grade (44%), whereas most (79%) of those untreated deteriorated.

Boostani *et al* conducted an open study in 13 patients with a combination therapy for 25 weeks of pegylated interferon 180 μg sc weekly, sodium valproate 10-20 mg/kg daily, and prednisolone 5 mg/day. Disability improved in 11/13 as measured by OMDS but no follow-up after the treatment period was reported(16).

Conclusion/Expert Opinion. The most recent evidence emphasises the on-going deterioration seen in untreated slowly progressing HAM/TSP, and suggests that low-dose (~ 5 mg) prednisolone daily for at least 4 years can give clinical benefit. There remains considerable uncertainty over the optimal duration of treatment, and long-term studies of adverse events are required. In these non-randomized studies, there might have been a bias towards treatment, especially if patients were deteriorating at baseline, which might mask some of the benefits; and higher-risk patients (those with osteopenia, diabetes mellitus, hypertension etc.) might have been less likely to receive treatment. The consensus was that there is sufficient evidence, albeit of low quality, to consider 5 mg prednisolone daily for up to 4 years as first-line therapy for patients with slowly progressing HAM/TSP and without contraindications. This recommendation is weak, and individual circumstances may require alternative management. Since a benefit is seen at 5 mg daily, patients started on higher doses should aim to reduce to this dose as far as possible.

The benefits of prednisolone for very slow progressors or non-progressors are unknown, and a watchful waiting approach is recommended. First-line therapy for patients who are progressing rapidly is addressed in Section 4.

3.2 Therapies other than corticosteroids

3.2.1 Where treatment with prednisolone is not considered appropriate the offer of steroid-sparing, anti-inflammatory, disease-modifying maintenance treatment for HAM/TSP should be considered.

Ciclosporin. A prospective proof-of-concept study of ciclosporin was conducted in seven patients with either recent onset of disease (< 2 years) or progressive disease (>50% deterioration in 10 m timed walk over 3 months). Ciclosporin was prescribed at 2.5 mg/kg/day in two divided doses and the dose was adjusted to maintain 12 hour plasma concentrations between 80-100 mg/ml. Five patients completed the planned 48 weeks of treatment. Objective improvement was reported in all patients; one patient discontinued treatment because of recurrent UTIs and depression and another discontinued for headache. Two patients requested to recommence ciclosporin during the follow-up phase due to motor deterioration after discontinuation of ciclosporin (17).

Azathioprine. Two retrospective studies reported on the use of azathioprine. Osame et al treated four patients for a total of four months. Treatment was initiated at 25 mg daily for two weeks then 50 mg daily for two weeks and maintained at 100 mg daily for two months, after which the dose was tapered. Clinical improvement was documented in all four patients with ≥ 1 grade improvement in OMDS in 3 of the 4 patients. Duration of effect and toxicity were not reported(13). Nakagawa et al treatednine patients with 50-100 mg daily of azathioprine for 1-3 months. Follow-up was reported for eight patients, of whom two demonstrated a one grade improvement in a ten-point motor disability scale grade and three were reported to have motor improvement within a grade. Duration of effect was not reported. Three were unchanged (10). An increase in serum transaminase concentrations was reported in one patient, and worsened dysaesthesia of the lower limbs in another patient.

Salazopyrine. Nakagawa et al reported retrospectively on 24 patients treated with Salazopyrine 1000 – 1500 mg per day for 1 – 3 months. Twelve patients improved by 1 grade in the ten point motor disability scale. Duration of effect was not reported. A range of side-effects were noted in six patients although the severity and influence on duration of therapy was not recorded(10).

Methotrexate. There are no peer-reviewed data on treatment of HAM/TSP with methotrexate although this is routinely used in the UK as maintenance therapy following 3 days of pulsed methylprednisolone. Ahmed et al reported improvement in 10 m timed walks within 4 weeks of starting methotrexate (7.5 mg – 12.5 mg weekly, plus 5 mg folic acid the next day) in a retrospective analysis of 13 patients(18).

Conclusion/Expert Opinion: Theeffect of various steroid-sparing, anti-inflammatory therapies has been reported in patients with HAM/TSP in a mixture of retrospective and prospective studies. The studies generally report a favourable clinical response but the numbers are small and, with the exception of ciclosporin, which was given for 48 weeks, the duration of treatment was short (1 – 3 months). More studies are required to determine the role of steroid-sparing therapy in the treatment of patients with HAM/TSP, particularly in patients with contraindications to prednisolone or where a response is not maintained at 5 – 10 mg daily. In such patients,steroid-sparing immunosuppressive therapies should be considered case-by-case.

3.2.2 There is insufficient evidence to recommend the offer of Interferon-alpha (IFN-α) as a first-line therapy.

Type-1 interferons have anti-viral and immune-modulating effects, providing a rationale exploringto explore their potential in the treatment of HAM/TSP. The initial studies of interferon were observational, short duration and used small sample sizes. In 1990 Nakamura *et al* reported improvement in gait in 3/5 patients following 4 weeks therapy with interferon-alpha, administered as a daily intramuscular injection at a dose of 3 MIU in three patients and at various doses between 1.5 and 9 MIU in two patients. Neither the duration of effect nor tolerability were reported (19).

Shibayama *et al*, reporting on in-patient treatment of 17 ambulant patients with 3 MIU interferon-α daily for 4 weeks, observed no improvement in six cases,moderate improvement in seven and seven, and marked improvement in four, although only in two did the disability grade improve. (20). Duration of effect was reported for only two participantsat 3 months. Concurrent physical therapies during the inpatient stay were not reported. All patients reported fever and almost two thirds reported fatigue, nausea and anorexia, with neutropenia in 50%. The first fiveparticipants in Shibayama's paper (20)appear to be the same patients that were reported in Nakamura's paper(19).

Kuroda *et al* reported clinical benefit in 8/12 patients similarly treated with daily intramuscular 3 MIU interferon- α as inpatients. After 2 weeks of interferon, extensor femoris muscle strength improved by 33 – 171% and 20 m timed walk by ≥10% in the 'responders'. Concurrent physiotherapy, duration of effect after final dose and adverse effects were not reported (21).

Saito *et al* treated 25 patients with intramuscular interferon-α: 12 received 3 MIU daily for four weeks and and all patients were able to walk > 10m at baseline assessment. Although responses were reported in patients with up to 11 years' duration of illness, patients appeared more likely to respond if their symptoms were of short duration; indeed 3 of 4 patients with ≤ 2 years symptoms improved and the 4th had mild gait disturbance and no bladder symptoms. The authors reported that shorter disease duration (<10 years vs. >10 years) was statistically associated with improvement. Concurrent physiotherapy, duration of effect after final dose and adverse effects were not reported (22).

Yamasaki *et al* studied the effect of 6 MIU interferon-α IM daily for 2 weeks and twice weekly for 22 weeks in 7 patients. Two did not complete the therapy - one developed depression and another withdrew following deterioration. Gait improved in fivefive patients at 1 month, with sustained improvement at 6 months after completing therapy. Objective improvement in cystometry in two patients was not reflected subjectively. Fever occurred in all patients, responded to NSAIDS and was self-limiting. Other common symptoms were fatigue, anorexia and headache, especially during the first few weeks of therapy (23).

In an open prospective study in Iran, Rafatpanah *et al* examined the effect of subcutaneous interferon-α -2b 3 MIU daily for 1 month, three times weekly for two months, twice weekly for two months and finally once per week during the 6th month of the study. The final assessment was 6 months after discontinuing therapy. Fifty-six patients were recruited; 6 (11%) discontinued the study within the first month because of toxicity and one was lost to follow-up. Forty-nine patients completed six months therapy of whom nine (16%) were considered to have had an excellent response (≥ 2 grade improvement in OMDS), ten (18%) a good response (1 grade improvement in OMDS); 16 (29%) had a fair response (some improvement but no change in OMDS) and the remainder either did not improve (21%) or deteriorated (16%). Clinical gains in OMDS, spasticity and bladder function were apparent at

four weeks and persisted at six months but were either lost (OMDS) or less marked (urinary symptoms and spasticity) six months after discontinuing treatment. Muscle strength improved at four weeks but was worse after six months on therapy than at baseline and continued to weaken at the 12 month visit, six months after the last dose. In this study, duration of disease or severity of disability did not affect response rates. Patients continued with physiotherapy during the study and took anti-pyretics as required. AA decrease in neutrophil count was observed during therapy (24).

Arimura *et al* conducted post-marketing surveillance on the use of interferon-α (3 MIU sc or im daily) following its approval for the treatment of HAM/TSP in Japan in January 2000. Over a 5 year period, until end March 2005, 273 patients were commenced on interferon, and efficacy data (based on case note review) were reported on 152 patients (25). The majority of patients were ambulant. After 4 weeks on interferon- α at baseline. 29% of patients were determined to have improved by at least one gradein OMDS; 37% had improvement in urinary or sensory symptoms without change in OMDS; 28% showed no clinical change; 3% had worsening of symptoms without change in OMDS and 2% experienced a deterioration in OMDS. Safety data were available on 167 patients, amongst whom 24 had serious adverse drug reactions (resulting in or prolonging hospitalisation (n=38 events) or considered medically serious (n=8 events), including one fatality. Milder adverse events (AEs) were common: pyrexia (66%); leucopenia (48%); thrombocytopenia (25%). At least one AE was reported by 87% of patients. Forty-eight evaluable patients continued interferon for longer than 35 days of whom 85% had been classified as showing improvement at four weeks. The duration of treatment beyond 35 days was not stated but 15 patients continued interferon beyond six months, with nine maintaining improvement. At the time of withdrawal of interferon 35 (74%) remained improved, 6 (12.5%) were stable and 7 (15%) had deteriorated. Where evaluated (n = 30) amongst patients who had a documented improvement in OMDS at time of interferon withdrawal, this improvement persisted in 11 (37%) for at least 5 months. Improvement was most likely to be reported in patients with least motor disability, shorter duration of symptoms or active progression.

Randomised studies

Kuroda *et al* reported on the randomisation of 4 patients to 3 interferon-α doses with the two responders receiving 3 MIU and the two non-responders receiving 0.3 or 1 MIU IM daily(21).

Izumo *et al* randomised 48 patients to 3 MIU; 1 MIU or 0.3 MIU daily for 4 weeks. After 4 weeks' therapy the response rates were as follows: >1 grade improvement in OMDS 2/15, 1/17, and 0/14 respectively; 1 grade improvement in OMDS or no improvement in OMDS but improvement in motor and two other parameter (urinary, and other unspecified neurological) 4/15, 2/17 and 0/14 respectively; no change in OMDS but improvement in at least one measured parameter 6/15, 8/17; 6/14; no improvement 3/15; 6/17, 8/14. Forty patients were evaluated fourfour weeks after discontinuing interferon, with similar patterns of responses. Adverse events were reported in 50% of patients on 3 MIU daily and in ~25% of patients on the lower doses. The authors concluded that the 66.7% response rate was better than previously reported for prednisolone. The outcomes at 4 weeks on treatment ($p = 0.02$) and 4 weeks after treatment (p 0.0) were statistically different between the 0.3 and 3 MIU doses(26).

Other interferons: A 12-patient observational study of interferon-beta1A given for 24 weeks reported stability in the patients' condition(27)..

Conclusion/Expert Opinion. Clinical improvement is observed in some patients treated with 3 MIU interferon- α for up to four weeks. However, side effects are common. There are insufficient data on treatment beyond fourfour weeks, and data from two studies suggest that even where improvement at fourfour weeks is maintained at sixsix months, the benefit is gradually lost once treatment is discontinued. Although interferon-α has been licensed for the treatment of HAM/TSP in Japan since January 2000 (whereas prednisolone is not licensed), in a recent survey only 2-3% of patients with HAM/TSP are currently treated with interferon (unpublished data). The panel concluded that the quality of the evidence on efficacy was low, that intolerance was high and that although one RCT showed moderately good evidence of short-term improvement, the current data do not support the use of interferon-α in patients with HAM/TSP either as first-line therapy or in long-term treatment.

Although not consistently reported, in a number of studies response rates appear to be better with milder disease and shorter duration of symptoms. Future studies should be powered to include disease severity categories to ensure that potential benefits are not missed through treating patients too late, and that patients with late-stage disease are not unnecessarily exposed to potential toxic therapies.

3.2.3 There is insufficient evidence to support the offer of antiretroviral therapy (treatment targeting HTLV-1 enzymes) for the treatment of HAM/TSP.

HAM/TSP is associated with a high HTLV-1 viral burden. Given the similarities in life-cycle of HTLV-1 to HIV, the potential of antiretroviral therapy to reduce HTLV-1 proviral load, with the anticipated prospect of reduced inflammation, has been tested. Gout *et al* reported no clinical benefit in five patients treated with zidovudine for six months(29) whereas Sheremata *et al* reported that 7/10 patients with HAM/TSP improved, again following six months of therapy(30). Taylor *et al* reported clinical improvement in 1/5 patients treated with lamivudine for six months (31). To address these conflicting observations, Taylor *et al* conducted a placebo-controlled random trial of zidovudine plus lamivudine for six months followed by six months of open therapy (8 patients per arm). No clinical or immunological improvement was detected. Since the anticipated benefit is through reduction in HTLV-1 proviral load it is important to note that there was no change in HTLV-1 proviral load despite 12 months' treatment(32) and drug resistance did not develop (33). The advent of integrase inhibitors with broad antiretroviral activity and excellent potency in HIV infection prompted further investigation. Trevino *et al* reported no effect on HTLV-1 proviral load infive patients treated with raltegravir, of whom two had HAM/TSP and three were asymptomatic carriers (34). Billioux *et al* presented an interim analysis of 17 patients with HAM/TSP treated with raltegravir. No change in expanded disability status score was observed, nor was there a systematic change in HTLV-1 proviral load (35). The investigation of HTLV-1 replication in vivo clearly identifies the importance of virus-driven proliferation of infected cells in both primary (36) and chronic infection (37). Whilst some degree of infectious spread is likely to continue in chronic infection, its relative contribution to proviral load is small, accounting of the lack of effect of antiretroviral therapy. Laydon *et al* have estimated that there are ~6 x 10^4 HTLV-1-infected T cell clones contributing to the 2 x 10^7 infected cells in a typical infected subject (37); each day ~100 to 200 new clones are infected, and a similar number of infected clones are lost (Laydon et al, submitted). If this analysis is correct, a therapy that blocks infectious spread would take a minimum of 5 years to reduce the proviral burden by 1%, assuming that clones of all sizes disappear at the same rate and that drug resistance does not develop. The distinct potential role of antiretroviral therapy to prevent infection is not addressed here. The combination of antiretroviral therapy with a histone deacetylase

inhibitor, sodium valproate, which markedly reduced STLV-1 proviral load in baboons (38), has not been tested in humans.

3.2.4 Where patients have not responded adequately to corticosteroid therapy there is insufficient evidence to offer the addition of an anti-CCR4 monoclonal antibody

The potential of therapies targeting HTLV-1-infected cells, such as an anti-CCR4 monoclonal antibody, has also been considered for the treatment of patients with HAM/TSP.. In a phase 1/2a study of 21 patients with HAM/TSP (and already taking 5 mg oral prednisolone daily) and treated with the anti-CCR4 monoclonal antibody mogamulizumab, up to 80% reduction in HTLV-1 proviral load was observed, which was sustained for the 12 weeks of observation after one infusion of mogamulizumab 0.3 mg/kg (39). This reduction in proviral load was associated with reductions in CSF lymphocytes and inflammatory markers as well as clinical improvement. Better symptomatic recovery was seen in patients with a shorter duration of disease. Spasticity was reduced, with the number of patients graded 2 or higher on the modified Ashworth scale decreasing from 48% at baseline to <10% after 4 weeks. Motor improvement was also documented, with a reduction in the number of patients requiring a walking aid from 71% to 52% after 4 weeks. Such benefits were maintained in the phase 2a component of the study: 79% of patients had improved muscle tone and 32% had an improved OMDS score. The main adverse events were Grade 1/2 rash and reductions in the counts of white blood cells and lymphocytes.

Conclusion/Expert Opinion. While further clinical studies, both in Japan and elsewhere, are required to confirm the safety, efficacy and durability of this therapy, the initial findings are promising. There are, however, insufficient data at present to recommend this therapy outside clinical trials and the treatment is not widely available.

3.2.5 There is insufficient evidence to recommend the offer of alternative therapies (See table 2) as first-line therapy outside of a clinical study.

A wide range of additional therapies has been reported which are not in current practice. These include anti-CD25 monoclonal antibody (40)erythromycin (10), heparin (44), immunoglobulin (45), *Lactobacillus casei strain Shirota (46)*, the heparinoid, pentosan polysulfate sodium (47), pentoxifylline (48), prosultiamine(49, 50) plasmapheresis(51), sodium valproate(52), intermittent high dose Vitamin C (53).

Three studies have explored the potential of Danazolthe anabolic steroid danazol (41-43), The first two observational reported improvement in mobility in 5/6 and 7/8 patients whilst the most recent report on danazol is a randomised placebo-controlled study reporting statistically significant improvement in mobility, pain, spasticity and bladder function. However, insufficient data are included in the publication to recommend this therapy(43). Further study of danazol is merited.

4. Treatment of rapidly progressing HAM/TSP

4.1 Induction therapy with pulsed methylprednisolone (1g daily for 3 – 5 days) should be offered.

4.2 Alternatively, the induction treatment may include high dose prednisolone (0.5 mg/kg daily per oral) for up to 14 days.

4.3 After the induction therapy with high dose steroids, maintenance therapy as per section 3 should be offered.

Rapidly progressing HAM/TSP may result in such severe bilateral lower limb paraparesis, with or without spasticity, that the patient will become totally wheelchair-dependent within a few months. In such circumstances the panel recommends early initiation of HAM/TSP disease-modifying therapy with high-dose (1 g) pulsed intravenous methylprednisolone for up to five days. Where this is not readily available, high-dose oral prednisolone can be substituted. Where no response or limited response is seen after IV pulsed methylprednisolone, further treatment with high-dose oral prednisolone for 2 weeks can be added followed by a gradual, clinically responsive reduction in dose. Panel members have observed that some patients are quite steroid sensitive and that exacerbations occur as the dose is reduced, even at doses as high as 15 mg prednisolone daily. The panel recommends that all patients with rapid progression continue with maintenance therapy and that steroids are not stopped abruptly. This can be low dose (5 to 10 mg daily) of oral prednisolone or steroid-sparing agents as described in Section 3. In the ciclosporin study of early or progressing disease, treatment was given for 48 weeks and then discontinued, following which some patients quickly deteriorated while others maintained the clinical improvement for the 24 weeks' scheduled follow up. In unpublished long-term follow-up all patients eventually recommenced a disease-modifying agent due to further progression.

5. Treatment of very slow or non- progressing HAM/TSP

There is insufficient evidence to recommend that disease modifying drug therapy be offered to patients with very slow or non-progressing HAM/TSP, who have no biological evidence of disease activity.

The expert panel considered that there was insufficient evidence to warrant the offer of treatment with steroids or steroid-sparing agents at this time and that a watchful waiting approach, with symptomatic management and physical therapies, was sufficient. The prognostic use of biomarkers of disease activity, especially CSF cytokines, has recently been published and may become an additional decision-making tool.(5)

Appendix 1

Names	Locations	Roles	Contributions
Abelardo Araujo	Rio de Janeiro, Brazil	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Charles RM Bangham	London, UK	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Jorge Casseb	Sao Paulo, Brazil	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Eduardo Gotuzzo	Lima, Peru	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Steve Jacobson	Bethesda, USA	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Fabiola Martin	Brisbane, Australia	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Augusto Penalva Oliveira	Sao Paulo, Brazil	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Marzia Puccioni-Sohler	Rio de Janeiro, Brazil	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript
Graham P Taylor	London, UK	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, writing first draft, revision of manuscript

Yoshihisa Yamano	Kanagawa, Japan	Member of HAM/TSP guideline writing group	Review of data, drafting of recommendations, revision of manuscript

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Table 1. Summary of Recommendations

		Strength of Recommendation/ Strength of Evidence
1	**Classification of HAM/TSP sub-types**	
	Clinical studies of therapy for HAM/TSP should pre-define patients into the following categories: Rapid progression, slow progression, and very slow or non-progressing and report outcomes separately.	Strong Recommendation (1)
2.	**Clinical trials**	
	All patients with HAM/TSP should be *offered/considered for* HAM/TSP disease-modifying therapy[2] within the context of a clinical study regardless of severity and duration of disease	Strong (1)
3	**Treatment for slow progressing HAM/TSP outside of clinical trials** (see definitions below)	
3.1	**Corticosteroids**	
3.1.1	Treatment with pulsed methylprednisolone (1g daily for 3 – 5 days) should be considered for patients with progressing disease either as a standalone treatment or as an induction therapy prior to initiating HAM/TSP DMT. (For rapid progressors – see Section 5 below) *Rationale - Transient clinical improvement has been observed with 3-5 days IV pulsed methyl-prednisolone in patients with HAM/TSP. Published data indicate that after 2 such courses clinic gains are usually much less.*	Weak (2) Very Low (D)
3.1.2	Where no clinical trial is available, for patients with HAM/TSP who are ambulant and have evidence of *progressive disease,* treatment with low dose (~5mg daily) prednisolone[3] should be considered unless they are rapid progressors. Where this is tolerated, this can be given long-term (>2 years) as maintenance therapy. *Rationale - low level evidence that patients on 5mg prednisolone have higher function long term. Prevention of deterioration is also desirable where improvement is not seen*	Weak (2) Weak (C)
3.1.3	Higher doses of prednisolone (<60mg daily) are sometimes indicated with titration of the dose according to the clinical response.	Weak (2) Very Low (D)

[2] Disease Modifying Treatment (DMT) is defined, in the context of HAM/TSP, as therapy targeting the pathogenic process of HAM/TSP, and not symptomatic therapy. Currently these agents mostly target the inflammation or heightened inflammatory activity of HAM/TSP but also include therapies to reduce the antigen burden (proviral load).

[3] Or prednisone where prednisolone is not available

	Rationale (clinical experience)	
3.2	**TTherapies other than steroids for slow progressing HAM/TSP**	
3.2.1	Where treatment with prednisolone is not considered appropriate steroid-sparing, disease-modifying maintenance treatment for HAM/TSP should be considered. *Rationale (clinical experience)*	Weak (2) Very Low (D)
3.2.2	There is insufficient evidence to recommend the use of Interferon-alpha (IFN-α) as a first-line therapy**.** *Rationale (clinical experience)*	Strong (1) Weak (C)
3.2.3	There is insufficient evidence to support the use of antiretroviral therapy (treatment targeting HTLV-1 enzymes) for the treatment of HAM/TSP. *Rationale (published data including RCT with placebo)*	Strong (1) Moderate (B)
3.2.4	There is insufficient evidence to recommend the addition of or switch to an anti-CCR4 monoclonal antibody to/from oral steroid therapy outside of a clinical trial. (currently *available in Japan and USA only*)	Strong (1) Moderate (B)
3.2.5	There is insufficient evidence to recommend the use of alternative therapies (See table 2) as first line therapy outside of a clinical study. *Rationale (limited clinical experience)*	Weak (2) Very Low (D)
4	**Treatment for Rapidly Progressing HAM/TSP**	
4.1	Where no clinical trial is available, induction therapy with pulsed methylprednisolone (1g daily for 3 – 5 days) should be offered. *Rationale (published observational data)*	Strong (1) Low (C)
4.2	Alternatively **induction treatment may also include** high dose prednisolone (0.5 mg/kg daily per oral) for up to 14 days	Strong (1) Low (C)
4.3	After the induction therapy with high dose steroids, maintenance therapy as per section 3 should be offered. *Rationale (clinical experience)*	Weak (2) Weak (C)
5	**Treatment for very slow or non-progressing HAM/TSP**	
	There is insufficient evidence to recommend that disease modifying drug therapy be offered to patients with very slow or non-progressing HAM/TSP, who have no biological evidence of disease activity. *Rationale (lack of data, uncertain benefit)*	Weak (2) Very Low (D)

Table 2. Alternative therapies (see 3.2.5)

Compound	Number Treated	Duration	Outcome
Danazol 200mg tds(41)	6	Up to 16 weeks	2 wheelchair dependent became ambulatory 3 walked further with walking aids
Danazol 200mg tds(42)	8	>4 weeks	7/8 improved motor and bladder function
Erythromycin(10)	25	?	4 improved by >1 grade on motor disability scale
Heparin 5-10,000 units daily(44)	10	9-93 days	7/10 improved. Improved mobility in 6/7 ambulant patients
Immunoglobulin IV 10g/day or 400mg/kg/day(45)	14	5 days	10 'temporary improvement' within 7 days and up to 30 days in gait and power No side effects
Lactobacillus casei(46)	10	4 weeks	Improvement in spasticity and bladder function No adverse effects
Pentosan polysulfate sodium sc weekly(47)	12	8 weeks	8/8 improved spasticity 10mTW improved for <5 weeks
Pentoxifylline 300mg daily (48)	15 4/15	4 weeks 48 weeks	2 improved by >1 grade in OMDS 6 improved walking times within a grade 10 had reduced spasticity Safe Improvements maintained
Plasmapheresis (4 – 6 sessions) (51)	18	2 weeks	11 'temporary improvement' 2- 4 weeks gait, sensory, and/or sphincter disturbance improved 5 improved by >2 grades on MDS Nearly all required prednisolone to maintain improvement.
Prosultiamine 300mg daily(49)	24	12 weeks	Improvement in spasticity and bladder function 10m timed walk improved in 11 and worsened in 7
Prosultiamine 300mg daily(50)	16	12 weeks	Open, prospective, study comparisons to baseline. Improvement in OABSS (Total) p 0.004 Improvement in QoL score p 0.013 No change in mobility (OMDS) p 0.25
Sodium Valproate 20mg/kg/day(52)	16	<2 years	Transient worsening of gait No improvement
Vitamin C oral 35 -40mg/kg/day (53)	7	3-5 days	Mean FU 9.7 months 6 improved by > grades on OMDS; 1 by 1 grade.

Figure 1. Flow diagram documenting the disposition of articles during the systematic review