International Retrovirology Association guidelines for the management of HTLV-1-associated myelopathy/tropical spastic paraparesis, 2018

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Introduction

HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) occurs in ~3% of HTLV-1 carriers (1). The risk varies between different endemic regions: the lowest reported life-time risk is 0.25% from Japan (2), whilst studies from Brazil indicate much higher risk (3).

Although the range of symptoms can be extensive (4, 5), there are 5 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 (5, 6).

Natural history studies indicate a chronic progressive deterioration of HAM/TSP with 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 whilst a small minority become bedbound within 12 months of onset (7-14).

Whilst symptomatic management and physical therapies are helpful in improving function and quality of life, they do not alter the natural history of the condition. In this guideline, the first to be published on behalf of the International Retrovirology Association (IRVA) for the management of patients with HAM/TSP, we review the potential of disease-modifying therapies (DMT). This term will be used in this guideline to refer to any therapy which targets the disease process, be it anti-inflammatory or anti-viral, rather than managing the consequences of the pathology – e.g. analgesia.

A large number of compounds have been examined over the last three decades but mostly in observational studies (6, 15). The published reports were identified by two means. First, PubMed was searched using the terms HTLV-1-associated myelopathy and tropical spastic paraparesis, therapy and treatment. Second, the conference proceedings of IRVA were systematically reviewed. Reports which addressed changes in disability, pain, bladder or bowel function were included.

The conclusions presented here are based on an open workshop held at Kamakura, Japan during the 18th International Conference on Human Retrovirology: HTLV and related viruses (March 2017) and further in-depth discussions with working party members. The final recommendations were presented at the IRVA Tokyo Conference and International Symposium 13th July 2018.
## Recommendations Summary Table

**Therapies to alter the progression of HTLV-1-associated myelopathy**

<table>
<thead>
<tr>
<th></th>
<th>Classification of HAM sub-types</th>
<th>Strength of Recommendation/Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>It is recommended that clinical studies of therapy for HAM pre-define patients into the following categories: Rapid progression, slow progression, and very slow or non-progressing and report outcomes separately.</td>
<td>Strong Recommendation (1)</td>
</tr>
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<table>
<thead>
<tr>
<th></th>
<th>Clinical trials</th>
<th>Strength of Evidence</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>All patients with HAM/TSP should be offered/considered for HAM disease-modifying therapy within the context of a clinical study regardless of severity and duration of disease</td>
<td>Strong (1)</td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>Treatment for slow progressing HAM/TSP outside of clinical trials (see definitions below)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><strong>Corticosteroids</strong></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>Treatment with pulsed methyl prednisolone (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 DMT. (For rapid progressors – see Section 5 below)</td>
<td>Weak (2)</td>
</tr>
<tr>
<td></td>
<td><strong>Rationale</strong> - 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.</td>
<td>Very Low (D)</td>
</tr>
<tr>
<td>3.1.2</td>
<td>Where no clinical trial is available, for patients with HAM who are ambulant and have evidence of active disease, treatment with low dose (~5mg daily) prednisolone should be considered unless they are rapid progressors. Where this is tolerated, this can be given long-term (&gt;2 years) as maintenance therapy.</td>
<td>Weak (2)</td>
</tr>
<tr>
<td></td>
<td><strong>Rationale</strong> - low level evidence that patients on 5mg prednisolone have higher function long term. Prevention of deterioration is also desirable where improvement is not seen</td>
<td>Weak (C)</td>
</tr>
<tr>
<td>3.1.3</td>
<td>Higher doses of prednisolone (&lt;60mg daily) are sometimes indicated with titration of the dose according to the clinical response.</td>
<td>Weak (2)</td>
</tr>
<tr>
<td></td>
<td><strong>Rationale</strong> - Prevention of deterioration is also desirable where improvement is not seen.</td>
<td>Very Low (D)</td>
</tr>
</tbody>
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1 Disease Modifying Treatment (DMT) is defined, in the context of HAM/TSP, as therapy targeting the pathogenic process of HAM, and not symptomatic therapy. Currently these agents mostly target the inflammation or heightened inflammatory activity of HAM but also include therapies to reduce the antigen burden (proviral load).

2 Or prednisone where prednisolone is not available
### Alternative therapies for slow progressing HAM/TSP

<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Strength</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1</td>
<td>Where treatment with prednisolone is not considered appropriate alternative steroid-sparing, disease-modifying maintenance treatment for HAM should be considered.</td>
<td>Weak (2)</td>
<td>Very Low (D)</td>
</tr>
<tr>
<td>3.2.2</td>
<td>There is insufficient evidence to recommend the use of Interferon-alpha (IFN-α) as a first-line therapy.</td>
<td>Strong (1)</td>
<td>Weak (C)</td>
</tr>
<tr>
<td>3.2.3</td>
<td>There is insufficient evidence to support the use of antiretroviral therapy (treatment targeting HTLV-1 enzymes) for the treatment of HAM.</td>
<td>Strong (1)</td>
<td>Moderate (B)</td>
</tr>
<tr>
<td>3.2.4</td>
<td>There is insufficient evidence to recommend the addition of an anti-CCR4 monoclonal antibody to oral steroid therapy outside of a clinical trial.</td>
<td>Strong (1)</td>
<td>Moderate (B)</td>
</tr>
<tr>
<td>3.2.5</td>
<td>There is insufficient evidence to recommend the use of alternative therapies (See table 2) as first line therapy outside of a clinical study.</td>
<td>Weak (2)</td>
<td>Very Low (D)</td>
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</table>

### Treatment for Rapidly Progressing HAM/TSP

<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Strength</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Where no clinical trial is available, induction therapy with pulsed methyl prednisolone (1g daily for 3 – 5 days) is recommended.</td>
<td>Strong (1)</td>
<td>Low (C)</td>
</tr>
<tr>
<td>4.2</td>
<td>Alternatively the induction treatment may also include high dose prednisolone (0.5 mg/kg daily per oral) for up to 14 days</td>
<td>Strong (1)</td>
<td>Low (C)</td>
</tr>
<tr>
<td>4.3</td>
<td>After the induction therapy with high dose steroids, maintenance therapy as per section 3 is recommended.</td>
<td>Weak (2)</td>
<td>Weak (C)</td>
</tr>
</tbody>
</table>

### Treatment for very slow or non-progressing HAM/TSP

<table>
<thead>
<tr>
<th>Section</th>
<th>Rationale</th>
<th>Strength</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>5</td>
<td>Currently disease modifying drug therapy is not recommended for patients with very slow or non-progressing HAM/TSP, who have no biological evidence of disease activity.</td>
<td>Weak (2)</td>
<td>Very Low (D)</td>
</tr>
</tbody>
</table>
Recommendations

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

HAM has a broad spectrum of severity and consequently the potential benefit of therapies that aim to modify the progression of the disease varies significantly. The natural history of HAM 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 all have significant risks, it is important to select those patients who are most likely to benefit. There is general agreement that 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 slow or very slowing 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 will be discussed in detail. However, the relative merits of treatment need to be determined for each clinical subgroup of patients with HAM, to ensure 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 (was able to run up to three months before the screening visit but cannot run now).
   
   • Loss of ability to climb stairs unaided, (now needing to use at least one banister to climb up or downstairs).
   
   • A patient who first developed symptoms of HAM during the preceding three months and already has to use any walking aid (unless this need is unrelated to HAM/TSP).
   
   B) in the preceding two years:
• Progression from walking unaided to wheelchair dependent or bed bound within two years of onset of symptoms

2. Documented clinical examination during the following three months:
   • Additional walking aid needed
   • Increase in 10 meter timed walk (seconds) by ≥ 30%
   • Decrease in 6 minute timed walk (meters) ≥ 30%
   • Increase in timed up-and-go (seconds) ≥ 30%

Slow progression:
Patients are defined as slow progressors if they meet none of the rapid progression criteria 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:
   • Increase in 10 meter timed walk (seconds) by ≥ 10%
   • Decrease in 6 minute timed walk (meters) ≥ 10%
   • Increase in timed up-and-go (seconds) ≥ 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 above ‘clinical history’ or ‘clinical examination’ criteria of deterioration defined under ‘Slow’ or ‘Rapid’ progression.

Many patients show a 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(16).

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 help identify which patients would benefit from the treatments outlined below whilst recognising that local variations are used. More than one measure is useful as for example, in patients with HAM/TSP 10m timed walk has been shown to detect change but underestimate fatigue, which is identified with the 6 minute timed walk (17).

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 potential impact 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 slow progressing HAM

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 exposure through residence past or current 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 methyl prednisolone (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 DMT.

The use of pulsed intravenous methyl prednisolone (500mg daily for 5 days) was first 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. No impact on urinary symptoms or paraesthesia were observed. However, with one exception the benefit lasted no more than six weeks and the utility of this treatment was considered limited(18). 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(19). Nakagawa *et al* reported that 1g methyl prednisolone IV daily for 3 days was effective in 6 of 10 rapidly progressing HAM/TSP patients(20). More recently Croda *et al* reported on repeated treatments with 1g methyl prednisolone IV daily for 3 days, every 3 – 4 months in 39 patients. Concurrent anti-spasmodic treatment and physiotherapy was administered and the mean number of therapies was 3.4. No significant changes were seen at follow up compared with baseline in regard to 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. Responsiveness did not differ by severity of disability at baseline nor by the number of therapies administered. 58% of patients were already using a walking aid at baseline(21). Buell *et al* reported improvement in pain scores following a single three day course of pulsed methyl prednisolone (1g daily) which persisted out to 24 weeks, whereas improvements in the 10m timed walk observed by the time of the 3rd infusion were no longer detected at the 4 week review. However, an improved 10m timed walk was seen in patients
with less than 2 years of disease. Urinary symptoms were unaltered. 24/25 patients completed the course (22).

**Conclusion/Expert Opinion:** Five studies of pulsed methyl prednisolone indicate that this 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 (21). Treatment in earlier disease tends to achieve better results. The expert panel considered that pulsed methyl prednisolone can be an effective approach to initiating disease-modifying therapy.

### 3.1.2 For patients with HAM who are ambulant and have evidence of **active disease**, treatment with low dose (~5mg daily) prednisolone can be considered 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 (<60mg daily) are sometimes indicated with titration of the dose according to the clinical response.

In an area of clinical practice generally lacking good quality evidence of efficacy 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 4 months to 48 years (median not stated), dose was initially 60-80 mg daily on alternate days for 2 months, tapered to 10mg alternate days over 6 months, then maintained on 5 mg alternate days for 3 months and then stopped; 50/65 were ambulant at baseline; Improvement in mobility was documented in 59 (91%) of these patients. This included improvement in a 10m timed walk observed within a disability grade (Fair response, 33.8%) to an improvement of at least 2 grades of 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 in whom it was present. Twenty percent of patients experienced significant treatment side effects including Cushingoid appearance, steroid myopathy, paravertebral abscess, osteoporosis and compression fractures. In 9% no clinical improvement was noted (23).

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3 Or prednisone where prednisolone is not available
Kira et al (1991) reported on 16 patients with HAM, treated with 40-60mg 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 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, the outcome measurements ~70% of patients subjectively improved albeit with no change in Kurtzke disability score nor 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 observed in both Kurtzke scale and brain MRI. The severity of brain MRI changes at baseline correlated with duration of disease. Kira et al concluded that deep white matter changes observed on MR were related to the duration and severity of HAM and progressed despite 1-4 months therapy with high dose prednisolone(24).

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 also included in Nakagawa’s retrospective analysis of the outcome of treatment of more than 200 patients with HAM 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. Using the same criteria as Osame above an improvement was observed by 2 grades or more in 16/131; by 1 grade in 75/131 and within a grade in 16, giving an overall response rate of 82%. Five patients experienced fractures, 5 bronchitis, 4 osteoporosis, 4 Cushingoid features, three each had urinary tract infection, gastro-duodenal ulceration, hypertension and glucose intolerance, with various other adverse events reported in individual patients (20).

Despite this paucity of data and inconsistency of effect, oral prednisolone has been used extensively in Japan. Where 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. Two recent retrospective studies shed more light on the potential of low dose oral prednisolone. The first by Coler-Reilly et al is a retrospective multicentre case note review conducted in Japan (25). 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 averaged a 0.12 grade/year improvement in OMDS whereas untreated patients deteriorated by an average of 0.13 grade/year in OMDS. 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, whereas amongst those not treated with prednisolone no patient reported an improvement of OMDS grade and 87% reported
clinical deterioration. Amongst patients treated with prednisolone for > 4 years the most common outcome was to have remained within an OMDS grade (44%) whilst the majority of those untreated (79%) deteriorated.

The second new study is a four-year prospective telephone interview conducted amongst patients registered with HAMnet, a patient register in Japan(14). Sato et al reported to the 18th International Conference on Human Retrovirology, Tokyo, March 2017 on 248 registered patients. Of the 107 patients on treatment with oral prednisolone (median dose 5 mg) 26% deteriorated by at least 1 grade on the OMDS whereas 35.7% of the 129 untreated patients had deteriorated (p=0.07) (26).

Conclusion/Expert Opinion. The two most recent studies, by collating data on an untreated comparator group, emphasise the on-going deterioration seen in untreated slow progressing HAM and suggest that low dose (~ 5mg) 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 5mg prednisolone daily for up to 4 years as first line therapy for patients with slow progressing HAM and without contraindications. As this may not apply to all patients due to individual circumstances the recommendation is only weak, allowing individualisation of recommendations. 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 elsewhere.

Since benefit is seen at 5 mg daily, patients started on higher doses should aim to reduce to this dose as far as possible.

3.2 Therapies other than corticosteroids

3.2.1 Where treatment with prednisolone is not considered appropriate alternative steroid-sparing, anti-inflammatory disease-modifying maintenance treatment for HAM should be considered.

Ciclosporin. A prospective proof of concept study of ciclosporin was conducted in 7 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 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 but one patient ‘failed’ treatment due to recurrent UTIs and depression and stopped ciclosporin and another discontinued for headache. Two patients requested to
recommence ciclosporin during the follow up phase due to motor deterioration after discontinuation of ciclosporin (27).

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 25mg daily for two weeks then 50mg daily for two weeks and maintained at 100mg 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 3/4. Duration of effect and toxicity were not reported(23). Nakagawa et al treated 9 patients with 50-100mg 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 (20). An increase in transaminases was reported in one patient, and worsened dysesthesia of the lower limbs in another patient.

Salazopyrine. Nakagawa et al also reported retrospectively on 24 patients treated with Salazopyrin 1000 – 1500mg per day for 1 – 3 months. 12 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 impact on duration of therapy is not recorded (20).

Methotrexate. There are no peer-reviewed published data on treatment of HAM/TSP with methotrexate although this is routinely used in the UK as maintenance therapy following 3 days of pulsed methyl prednisolone. Ahmed et al reported improvement in 10 m timed walks within 4 weeks of starting methotrexate (7.5 mg – 12.5 mg weekly with folate recovery with 5 mg folic acid the next day) in a retrospective analysis of 13 patients.(28).

Conclusion/Expert Opinion: The impact of various steroid-sparing therapies has been reported in patients with HAM 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, particularly in patients with contraindications to prednisolone or where a response is not maintained at 5 – 10 mg daily. In such patients, alternative therapies should be considered on a case-by-case arrangement.

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

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-α, 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. One patient, with relatively mild disability despite 28 years of symptoms, was reported to have marked improvement, based primarily on ‘subjective feeling’. The most striking objective improvement was in a patient with relatively mild disease of 1 year’s duration with documented improvement in 10 m timed walk and a one grade improvement in disability scale. Neither the duration of effect nor tolerability were reported (29). Shibayama et al (30), reporting on in-patient treatment of ambulant patients with 3 MIU interferon-α daily for 4 weeks, observed no improvement in 6/17 and moderate improvement in 7/17. In 2/4 patients with reported to have a marked clinical response an improvement in disability grade was observed: one patient with symptoms of one year and grade 3 disease (on a 10 point scale) and one with 14 years of illness and grade 4 disability. In both patients a 50% reduction in time to walk a fixed distance was documented. In the remaining two, the marked clinical improvement was subjective in one and limited to a decreased frequency of micturition in the other (who had minimal gait disturbance) (30).

Duration of effect was reported for only two subjects at 3 months. Concurrent physical therapies during the inpatient stay were not reported. All patients reported fever and almost 2/3rds reported fatigue, nausea and anorexia, with neutropenia in 50%. The first five subjects in Shibayama’s paper (30)appear to be the same patients reported in Nakamura’s paper (29). 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 (31). Saito et al treated 25 patients with intramuscular interferon-α, 12 received 3 MIU daily for four weeks of which eight were evaluated to have had fair to excellent responses but no significant change in severity on the OMDS. Thirteen patients received 3 MIU for four weeks but at various reduced frequencies of administration. In 8/25 patients OMDS improved by a maximum of two grades. 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 3/4 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 (32).

**Conclusion/Expert Opinion**: Four observational studies reported clinical improvement in some patients, mostly with shorter duration of disease, following four weeks of therapy with daily IM 3 MIU interferon-α. Where reported the rate of side effects was high. Several studies were conducted as inpatients with no mention of concurrent physiotherapy. Neither the duration of effect nor the optimal duration of therapy can be determined from these reports.

Yamasaki et al studied the effect of 6 MIU 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 5/7 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 (33).

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 which 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) 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, took anti-pyretics as required and an overall decrease in neutrophil counts was observed during therapy (34).

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 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 (35). 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 grade improvement in 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 AEs including fever 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 which 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 also reported on the randomisation of 4 patients to 3 interferon-a doses with the two responders receiving 3 MIU and the two non-responders receiving 0.3 or 1 MIU IM daily(31). Izumo et al randomised 48 patients to 3MIU; 1MIU or 0.3MIU 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. 40 patients were evaluated 4 weeks after discontinuing interferon with similar patterns of responses. Adverse events were reported in 50% of patients on 3MIU 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(36).

Other interferons: A 12 patient observational study of interferon-beta1A given for 24 weeks reported stability in the patients' condition(37) whilst improved urinary function has been described in a case report(38).

Conclusion/Expert Opinion. Data from a randomised clinical trial comparing three doses of interferon-α support the findings from observational studies that clinical improvement is observed in some patients treated with 3 MIU interferon-α for up to 4 weeks. However, side effects are common. There are insufficient data on treatment beyond 4 weeks, with data from two studies suggesting that even where improvement at 4 weeks is maintained at 6 months, the benefit is gradually lost once treatment is discontinued. Although interferon-α has been licensed for the treatment of HAM in Japan since January 2000 (whereas prednisolone is not) in a recent survey only 2-3% of patients with HAM are currently treated with interferon (unpublished data). The expert opinion was that the quality of the evidence on efficacy was low, that intolerance was high and that whilst there is moderate good evidence of short-term improvement (one RCT) the current data did not support long term use of interferon-α in patients with HAM. We conclude that there is insufficient evidence to recommend the use of Interferon-alpha as first-line therapy for HAM/TSP.

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, who by virtue of late stage disease, are not unnecessarily exposed to potential toxic therapies.
3.2.3 There is insufficient evidence to support the use of antiretroviral therapy (treatment targeting HTLV-1 enzymes) for the treatment of HAM.

HAM is associated with 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(39) whereas Sheremata et al reported that 7/10 patients with HAM improved, again following six months of therapy(40). Taylor et al reported clinical improvement in 1/5 patients treated with lamivudine for six months (41). 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 and importantly no change in HTLV-1 proviral load despite 12 months' treatment(42). Furthermore the lack of virological impact was not due to the development of drug resistance (43). 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 in 5 patients treated with raltegravir, of which two had HAM and three were asymptomatic carriers (44). Billioux et al presented an interim analysis of 17 patients with HAM/TSP treated with raltegravir. No change in EDSS was observed, nor was there an overall change in HTLV-1 proviral load (45). The investigation of HTLV-1 replication in vivo clearly identifies the importance of virus-driven proliferation of infected cells in both primary (46) and chronic infection (47). Whilst some degree of infectious spread is likely to be occurring even in chronic infection its relative contribution to proviral load appears to be small accounting of the lack of effect on therapy targeting HTLV-1 replication. Laydon et al have estimated that there are ~6 x 10^4 clones contributing to the 2 x 10^7 infected cells per infected subject (47); each day ~100 new clones are infected, and a similar number of infected clones is lost (Laydon et al, in preparation. 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. 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 significantly reduced STLV-1 proviral load in baboons (48), has not been tested in humans.

3.2.4 Where patients have not responded adequately to corticosteroid therapy addition of an anti-CCR4 monoclonal antibody can be considered.

The potential of therapies targeting HTLV-1 infected cells, such as the anti-CCR4 monoclonal antibody, has also been considered for the treatment of patients with HAM. Following in vitro studies demonstrating selective depletion of CCR4+ T-cells (49) and clinical studies demonstrating a degree of efficacy in patients with relapsed or refractory ATL, particularly in leukaemic presentations, treatment with an anti-CCR4 monoclonal antibody was studied in 21 patients with HAM (50). In a phase 1/2a study of 21 patients with HAM (and already taking 5 mg oral prednisolone daily)
up to 80% reduction in HTLV-1 proviral load was observed, which was sustained for the 12 weeks after one infusion of 0.3 mg/kg (50). This improvement was associated with reductions in proviral load 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% 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 white blood counts and lymphocytes.

**Conclusion/Expert Opinion.** Whilst 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 to recommend this therapy outside clinical trials.

### 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.

A wide range of additional therapies has been reported retrospectively. These include anti-CD25 monoclonal antibody (51), Danazol (52, 53), erythromycin (20), heparin (54), immunoglobulin (55), *Lactobacillus casei strain Shirota* (56), the heparinoid, pentosan polysulfate sodium (57), pentoxifylline (58), plasmapheresis (59), sodium valproate (60), daily (20) or intermittent Vitamin C (61) and a case report of using cyclophosphamide(62). Plasma exchange has also been reported in one case, whilst 15 of the 18 patients treated with plasmapheresis subsequently received a variety of additional therapies – interferon n= 2, lymphocytopheresis n= 1, cyclophosphamide n=4. Five had good responses but all but one patient eventually progressed and 14/18 were treated with prednisolone requiring >30 mg/day to prevent recurrence of symptoms (63).
Table 2. Alternative therapies (see 3.2.5)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Number Treated</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol 200mg tds</td>
<td>6</td>
<td>Up to 16 weeks</td>
<td>2 wheelchair dependent became ambulatory 3 walked further with walking aids</td>
</tr>
<tr>
<td>Danazol 200mg tds</td>
<td>8</td>
<td>&gt;4 weeks</td>
<td>7/8 improved motor and bladder function</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>25</td>
<td>?</td>
<td>4 improved by &gt;1 grade on motor disability scale</td>
</tr>
<tr>
<td>Heparin 5-10,000 units daily</td>
<td>10</td>
<td>9-93 days</td>
<td>7/10 improved. Improved mobility in 6/7 ambulant patients</td>
</tr>
<tr>
<td>Immunoglobulin IV 10g/day or 400mg/kg/day</td>
<td>14</td>
<td>5 days</td>
<td>10 ‘temporary improvement’ within 7 days and up to 30 days in gait and power No side effects</td>
</tr>
<tr>
<td>Lactobacillus casei</td>
<td>10</td>
<td>4 weeks</td>
<td>Improvement in spasticity and bladder function No adverse effects</td>
</tr>
<tr>
<td>Pentosan polysulfate sodium sc weekly</td>
<td>12</td>
<td>?</td>
<td>8/8 improved spasticity 10mTW improved for &lt;5 weeks</td>
</tr>
<tr>
<td>Pentoxifylline 300mg daily</td>
<td>15</td>
<td>4 weeks</td>
<td>2 improved by &gt;1 grade in OMDS 6 improved walking times within a grade 10 had reduced spasticity Safe Improvements maintained</td>
</tr>
<tr>
<td>Plasmapheresis (4 – 6 sessions)</td>
<td>18</td>
<td>2 weeks</td>
<td>11 ‘temporary improvement’ 2- 4 weeks gait, sensory, and/or sphincter disturbance improved 5 improved by &gt;2 grades on MDS</td>
</tr>
<tr>
<td>Prosultiamine 300mg daily</td>
<td>24</td>
<td>12 weeks</td>
<td>Improvement in spasticity and bladder function 10m timed walk improved in 11 and worsened in 7</td>
</tr>
<tr>
<td>Valproate 20mg/kg/day</td>
<td>16</td>
<td>?</td>
<td>Transient worsening of gait No improvement</td>
</tr>
<tr>
<td>Vitamin C oral 35 -40mg/kg/day</td>
<td>7</td>
<td>3-5 days</td>
<td>Mean FU 9.7 months 6 improved by &gt; grades on OMDS; 1 by 1 grade.</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>20</td>
<td>4</td>
<td>4 improved by &gt;1 grade on motor disability scale</td>
</tr>
</tbody>
</table>
4. **Treatment of rapidly progressing HAM/TSP**

4.1 Induction therapy with pulsed methyl prednisolone (1g daily for 3 – 5 days) is recommended.

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 is recommended.

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 a setting the panel recommends early initiation of HAM disease modifying therapy with high dose (1 g) pulsed intravenous methylprednisolone for up to 5 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 oral prednisolone for 2 weeks can be added followed by gradual, clinically responsive weaning. 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 whilst 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**

Currently disease modifying therapy is not recommended for 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 treatment with steroids or steroid-sparing agents at this time and that a watchful waiting approach (with symptomatic management and physical therapies) was sufficient.
References

26. Sato TI, E; Yagashita, N; Araya N; Takata A; Yamano, Y., editor Effectiveness of low-dose oral prednisolone to treat and slow progression of HAM/TSP: A nationwide prospective cohort study. 18th International Conference on Human Retrovirology: HTLV and related viruses; 2017; Tokyo, Japan.


