Review

Pathogenesis and treatment of HTLV-I associated myelopathy

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Background

The first description of what is now termed HAM/TSP has been attributed to Strachan's 1888 paper on Jamaican peripheral neuritis.[1] In 1956, Cruikshank described patients with spasticity (tropical spastic paraparesis, TSP) including a minority with ataxia (tropical ataxic neuropathy) which he termed Jamaican neuropathy.[2] In 1985 Gessain and colleagues, investigating the seroprevalence of human T cell lymphotropic virus type I (HTLV-I) among haematology patients in Martinique, chose neurology patients as controls and unexpectedly found that 59% of patients with tropical spastic paraparesis had anti-HTLV-I antibodies.[3] In Japan, where adult T cell leukaemia was first described in 1977[4] and associated with HTLV-I in 1981,[5] Osame *et al* independently described the association of HTLV-I with a spastic paraparesis which they called HTLV-I associated myelopathy (HAM).[6] While seronegative TSP has been described,[7] by definition all patients with HAM are infected with HTLV-I.

HTLV-I is a type C retrovirus, closely related to other human and primate lymphotropic viruses and the bovine leukaemia virus. Like all retroviruses the genome of HTLV-I contains *GAG*, *POL*, and *ENV* genes flanked by two long terminal repeats (LTR) which contain the transcription initiation sequences (Fig 1). In addition, HTLV-I has another gene, pX with four open reading frames of which *TAX* and *REX* (the transactivating and regulating genes of the X region) have been best characterised. The protein product of the *TAX* gene is important not only for activating viral transcription but because it is able to transactivate a large number of human genes (Table 1). For this reason *TAX* is considered to play a critical role in the development of adult T cell leukaemia/lymphoma (ATLL).[8] No sequence differences distinguishing HTLV-I found in patients with HAM and patients with ATLL have been identified.[9]

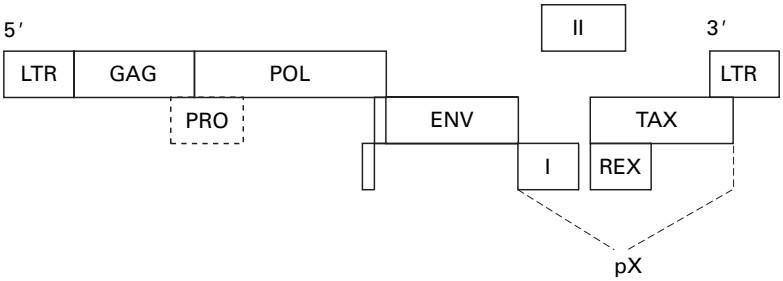

*Figure 1 Schematic representation of the HTLV-I genome (modified from Franchini et al, Blood 1995;**86**:3619–39 with permission). LTR=long terminal repeat; GAG=group antigen (nuclear proteins); PRO=protease; POL=polymerases (RT, RNaseH, integrase); ENV=envelope proteins (transmembrane and surface); REX=regulating gene of pX region; TAX=transactivating gene of pX region.*

Like HIV-1, HTLV-I infects $CD4^+$ T lymphocytes although CD4 is not the receptor. This has not yet been identified but has been localised to chromosome 17q and may be a member of the VCAM family.[10] The life cycle of HTLV-I is similar to other retroviruses. Infection requires interaction between the viral envelope and the cellular receptor following which the nuclear content is released into the cytoplasm and transported to the nucleus. The hallmark of a retrovirus is reverse transcription of viral RNA to produce proviral DNA which is then integrated into the cellular genome. In the case of HTLV-I integration occurs randomly. Following an unspecified period the proviral DNA is transcribed. Translation of spliced RNA produces the viral nucleocapsid proteins, enzymes, and envelope glycoproteins. The production of viral proteins is under the control of TAX and REX, with TAX upregulating transcription and REX exerting a negative feedback by reducing splicing of the precursor RNA which results in reduced production of viral proteins including TAX. The production of both full length viral RNA and the constituent proteins results in a new infectious virion which buds from the surface of the cell ready to infect a new target.

HTLVs are also able to replicate without use of reverse transcription which is error prone. Once integration has occurred transactivation of cellular genes results in cell proliferation and at each cell division a new copy of the integrated HTLV provirus is made. This

Table 1

(A) *Cellular transcription factors which interact with HTLV-I TAX*	
CREB	Chrivia *et al*, 1993, Kwok *et al*, 1996
bZIP	Baranger *et al*, 1995
CREM	Zhao and Giam, 1992
NF-KB	Suzuki *et al*, 1994
SRF	Fujii *et al*, 1992
(B) *Cellular genes transactivated by HTLV-I TAX*	
IL-2	Siekevitz *et al*, 1987
IL2-Rα	Inoue *et al*, 1986
IL-3	Wolin *et al*, 1993
Act-2 cytokine	Napolitano *et al*, 1991
β globin	Fox *et al*, 1989
Vimentin	Lilienbaum *et al*, 1990
Class 1 MHC	Sawada *et al*, 1990
GM-CSF	Miyatake *et al*, 1988
NGF	Green, 1991
TGF-β1	Kim *et al*, 1990
PTHr-P	Watanabe *et al*, 1990
c-fos	Fujii *et al*, 1988
c-sis	Pantazis *et al*, 1987
egr-1	Fujii *et al*, 1991
egr-2	
PCNA	Ressler *et al*, 1997
MDR1	Lau *et al*, 1998

Table 2 Cerebrospinal fluid findings in HAM

Mild lymphocytosis	
Normal or increased protein	
Oligoclonal bands with evidence of local synthesis	
Anti-HTLV-I antibodies	
β_2 microglobulin	↑
Neopterin	↑
TNF-α	↑
IFN-γ	↑
IL-1	↑
IL-6	↑

Table 3 Cytokines released by TAX specific CTL

Cytokine	*Associated with:*
TNF-α, IFN-γ	demyelination
MIP-1α, MIP-1β	transendothelial migration of leucocytes
IL-16	attracts CD4 lymphocytes
MMP-9	facilitates crossing of blood–brain barrier

proliferation results in expansion of the infected cells. The ultimate example of this clonal expansion is seen in ATLL but polyclonal expansion of HTLV-I infected cells has been observed in patients with HAM/TSP and in carriers.[11]

HTLV-I and the related virus, HTLV-II, are transmitted by sexual intercourse, especially from males to females; parenterally through cellular blood products and the reuse of injecting equipment; and from mother to child, predominantly through breast feeding. Although Europe is not an endemic area for HTLV-I infection it is found among immigrants from high prevalence areas, their partners, and sporadically in the native population. HTLV-II is common among intravenous drug users in a number of European cities.[12]

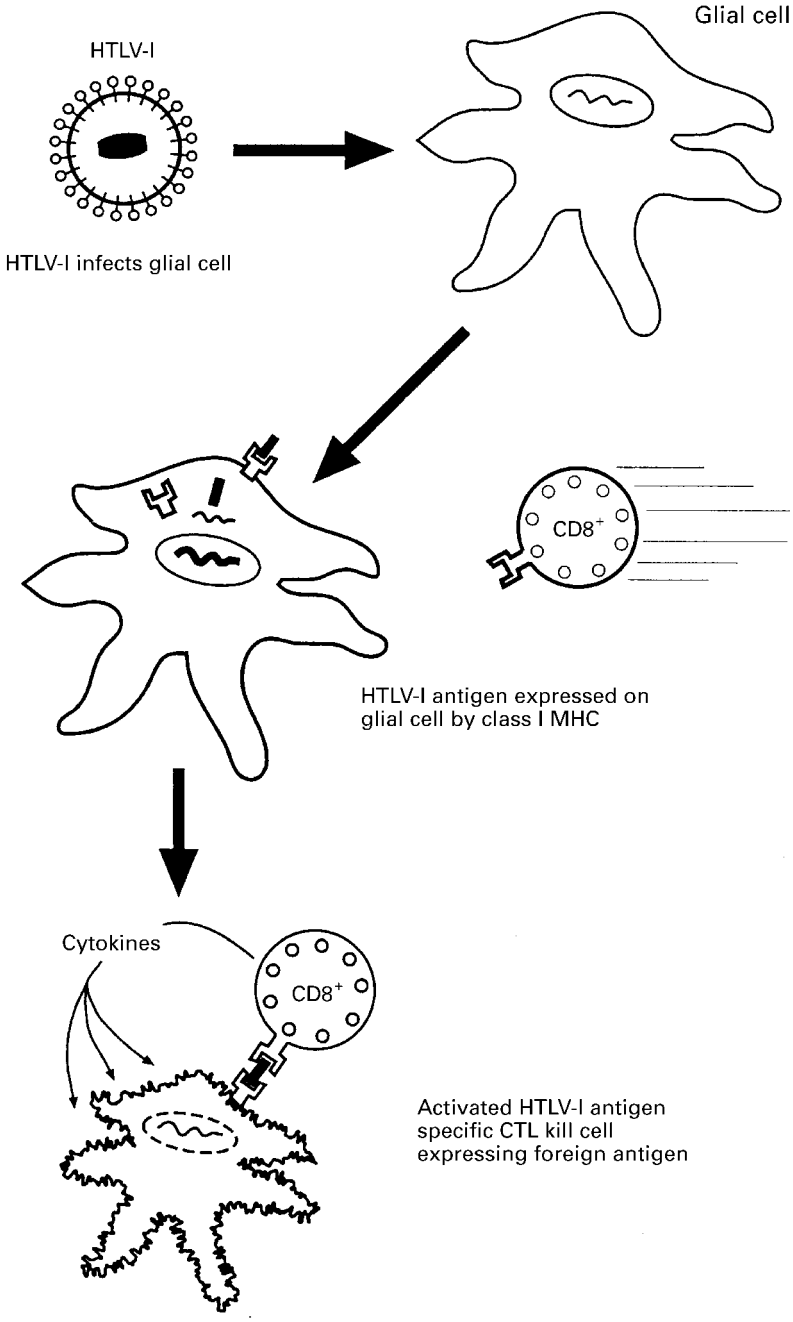

Figure 2 Direct toxicity theory of HAM pathogenesis: HTLV-I infects glial cells which are lysed by cytotoxic T lymphocytes.

Clinical and pathological features of HTLV-I associated myelopathy

HAM/TSP is generally a slowly progressive disease; indeed patients often have had symptoms for years before diagnosis. The characteristic features are low back pain, urinary dysfunction, impotence, and spastic paraparesis. Remissions and relapses are not a feature, and the condition tends to plateau followed by stability or slow deterioration. With the average age at onset only 30–40 years and with up to 50% of patients becoming wheelchair dependent this is a disease of considerable morbidity.[13] Unlike Japan where the life time risk of a HTLV-I infected person developing HAM has been calculated to be 0.25%[14] HTLV-I carriers in the United Kingdom seem to have a much higher probability of HAM more similar to the 1.7–7% reported from Africa,[15] the Caribbean,[16] and the United States.[17] In addition to the characteristic clinical features, the diagnosis of HAM/TSP is made by excluding other pathology, particularly spinal cord compression, and confirming the presence of HTLV-I antibodies in serum and CSF. Computerised tomography is usually normal and magnetic resonance imaging may be normal or reveal high T2 weighted signal abnormalities in the white matter similar to those seen in multiple sclerosis. Although mild, there is evidence of inflammation in cerebrospinal fluid (Table 2) and cytokines may be implicated in pathogenesis.

At the postmortem examination of a 59 year old woman with HAM of 3 years' duration, who died of mixed mitral and aortic valve disease, Akizuki *et al* found proliferation of capillaries, perivascular cuffing with lymphocytes, loss of myelin and axons, proliferation of gemistocytic astrocytes, and infiltration with foamy macrophages. These changes were most severe in the lateral and anterior columns of the thoracic spinal cord but were also observed in the medulla, pons, and white matter of the cerebrum and cerebellum. They also found evidence of vasculitis and arachnoiditis with lymphocytic

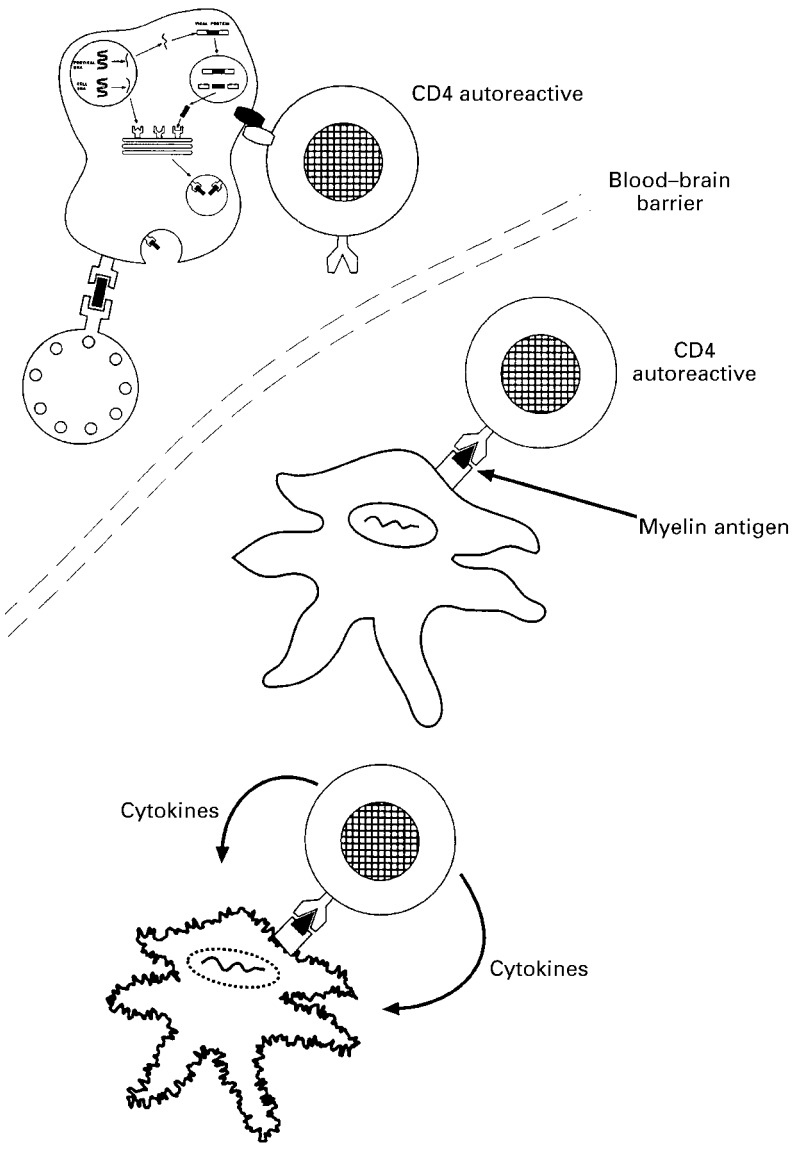

Figure 3 Autoimmunity theory of HAM pathogenesis: CD4 lymphocytes which recognise HTLV-I peptides mistake a "self" antigen expressed by glial cells as "foreign".

infiltration.[18] These findings are similar to those of others including Montgomery *et al* in 1964.[19] After many years of HAM/TSP atrophy and gliosis, rather than inflammatory changes, predominate.[20] The clinical stability of patients with long standing HAM/TSP and this evolution of neuropathology have important implications when we come to consider the pathogenesis of HAM/TSP and responses to treatment.

The lymphocytic infiltrate in patients with a short history of HAM/TSP is composed predominantly of $CD4^+$ T cells.[21] Later the population is more mixed with both $CD4^+$ and $CD8^+$ lymphocytes and macrophages, with the production of interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). In patients with long standing HAM/TSP the infiltrate comprises predominantly $CD8^+$ lymphocytes, and cytokine expression is rarely noted.[22] HTLV-I provirus can be found in the spinal cord; however, it remains uncertain whether HTLV-I infects astrocytes in vivo[23] or is only present in the cord within migrating lymphocytes.[24]

Pathogenesis of HTLV-I associated myelopathy

In cross sectional studies HTLV-I proviral load has been found to be at least 10-fold higher in patients with HAM/TSP than in carriers although the ranges of proviral load overlap. In patients with TSP/HAM this viral burden was relatively constant over several months.[25] In a prospective study HTLV-I proviral load, whether high or low, remained relatively constant over 2–3 years in most patients and carriers. Multiple measurements of proviral load in a carrier who developed HAM revealed a constant high proviral load, more than the average for a patient with HAM, that predated by at least 2.5 years the onset of symptoms.[26]

Jacobson *et al* reported that HTLV-I specific cytotoxic T lymphocytes (CTL) were present in patients with HAM/TSP but not in carriers,[26] but Parker *et al* found anti-HTLV-I specific CTL in carriers and in HAM/TSP.[27] The immunodominant peptides are invariably found in the TAX protein. Recently, Biddeson *et al* reported that anti-TAX specific $CD8^+$ CTL produce a variety of cytokines which may be implicated in the pathogenesis of HAM/TSP (Table 3).[28] In particular, TNF-α and IFN-γ are associated with demyelination.[29]

Pathogenesis hypotheses

There are three main hypotheses; direct toxicity, autoimmunity, and bystander damage.[30] In the first hypothesis it is presumed that HTLV-I infects glial cells in vivo, which then present HTLV-I antigens on their cell surface. Circulating $CD8^+$ cytotoxic T cells specific for a HTLV-I antigen cross the blood–brain barrier, encounter the infected cell, and release cytokines which cause cell death (Fig 2).

The second hypotheses presumes that a glial cell "self" antigen is similar to a viral antigen. $CD4^+$ helper cells encounter this viral antigen in the periphery and upon crossing the blood–brain barrier, mistake the glial cell for an infected cell triggering autoimmune activity with death of the glial cell. Alternatively, $CD4^+$ "helper" cells which by chance recognise "self" antigen are stimulated to proliferate by infection with HTLV-I. The chance of infection of such a cell would be related to the infectious burden of virus (Fig 3). In the third hypothesis, HTLV-I infected $CD4^+$ and anti-HTLV-I specific $CD8^+$ lymphocytes migrate across the blood–brain barrier, meet in the CNS and the innocent glial cells are damaged by cytokines released against the infected lymphocyte (Fig 4). While there are few in vivo data to support the first hypothesis, either or both of the others may play a role in the pathogenesis.

Treatment of HTLV-I associated myelopathy

A summary of reports of the treatment of HAM is presented in Table 4. Most treatments have been directed at reducing inflammation in the affected tissues either directly, as with corticosteroids, or indirectly—for example, heparin, while interferon-α has both antiviral and immunomodulatory capacity. The only published studies of specific antiretroviral

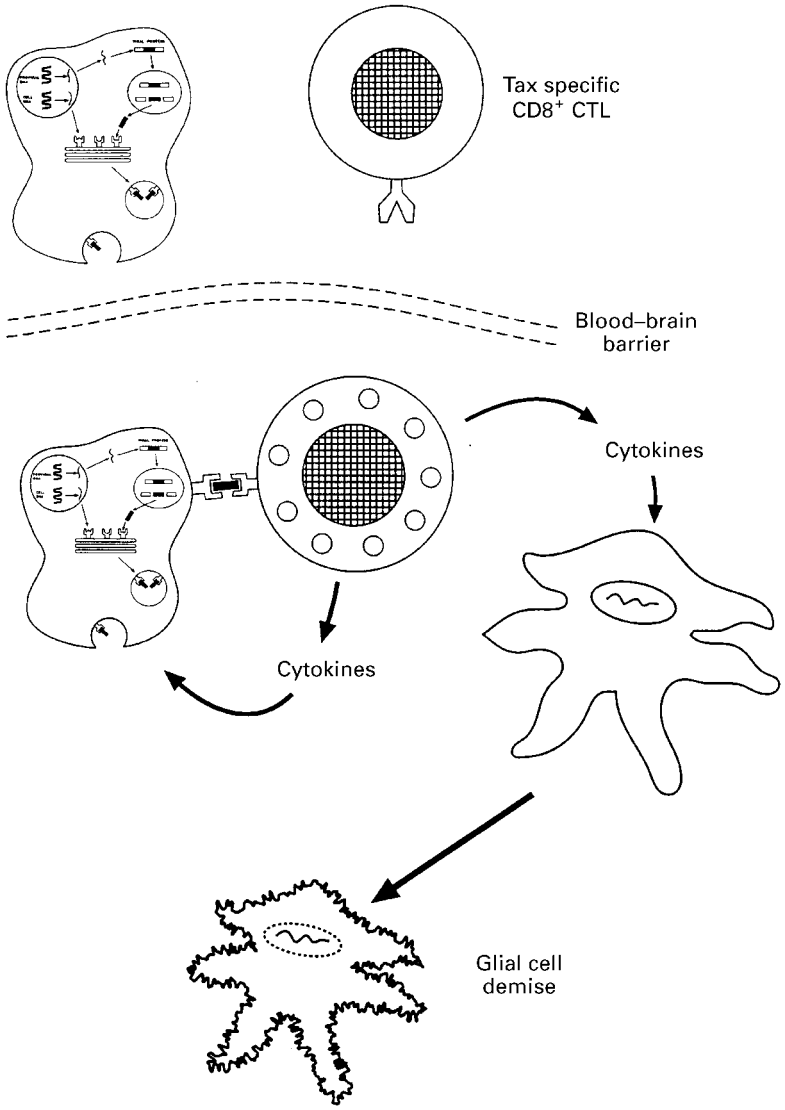

Figure 4 Bystander theory of HAM pathogenesis: circulating anti-TAX specific cytotoxic T lymphocytes migrating through the spinal cord or cerebrum encounter an HTLV-I infected CD4+ lymphocyte. Cytokines directed against the infected lymphocyte cause "collateral damage" to glial cells.

therapy are of zidovudine and lamivudine. With a single exception all reports have been of open preliminary studies, limited by small numbers of patients and the possibility of placebo effect. Earlier studies used HTLV-I antibody titres (or in one case the numbers of atypical lymphocytes) as a surrogate for proviral load and focused on spontaneous lymphocyte proliferation (an ex vivo phenomenon) and T cell subsets to measure change in the immune response. In a number of studies both treatment and follow up have been of short duration and longer studies of the same treatment modality have been less encouraging. Thus, Matsuo *et al* reported a rapid but transient improvement with plasmapheresis for 14 days[31] but approximately 2 years later none of their patients were improved and 6/18 had deteriorated.[32] Similarly, although Osame *et al* reported improvement in 58 of 65 patients treated with high dose prednisolone,[33] symptoms often worsen again as the dose is reduced, and Kira *et al* reported that 33% of their patients had further deteriorated from baseline during 20–33 months of follow up.[36] Nakagawa *et al* observed that while 69.5% of 131 patients had an excellent or moderate response to oral prednisolone, the benefits were transient and the complications of steroids would limit their use particularly in post-menopausal females for whom interferon-α might be more appropriate.[47] The steroid responsiveness of HAM has not been confirmed outside Japan. There have been several favourable reports relating to short duration therapy with interferon-α.[34 38 40 45 46] More significantly, Yamasaki *et al* recently reported clinical, immunological, and virological improvement when treatment was continued for 6 months.[48] Although the reduction in proviral load was modest this is the first treatment study to report HTLV-I proviral load measurements and is at variance with previous studies which concluded that interferon-α did not have any anti-HTLV-I effect because the anti-HTLV-I antibody titres did not change. However, this study, like those using steroid sparing cytotoxics[33 43] and the anabolic steroid danazol,[37] is limited by small numbers and its open nature. The limited nature of the benefits of treatments such as interferon-α and plasmapheresis is indicated by the following comment from the Nagasaki group. Referring to their earlier studies they conclude that "these modalities are . . . plagued with problems of high cost and the high frequency of side effects."[41] In 1992 this group reported that the adherence of T cells to endothelial cells ex vivo was significantly increased in patients with HAM compared with controls.[49] Although they initially tried daily intravenous infusions of heparin in HAM[41] they have recently suggested that oral pentoxifylline may, by reducing the migration of activated T lymphocytes across the blood–brain barrier, be a safe and beneficial treatment.[46]

Gout *et al* treated five patients with HAM with zidovudine and concluded that they did not get worse. Their patients had long standing disease and no measurement of viral burden was made.[39] Sheremata *et al* treated 10 patients with HAM with zidovudine and reported improved mobility in some. They did not report proviral load measurements because both HTLV-I and β globin DNA were reduced in their patients' peripheral blood during treatment.[42] Recently five patients with HAM/TSP and high proviral load were treated with lamivudine monotherapy. The median proviral load reduction during 6 months of therapy was greater than 1 $\log_{10}$ although by 6 months proviral load had returned to baseline in three subjects. In the only patient with recent onset of symptoms clinical improvement was associated with a reduction in anti-TAX CTL frequency which fell with the decline in proviral load.[50]

Clinical benefits in up to 50% of patients have been reported with a variety of other agents including the antibiotics erythromycin and fosfomycin, which may have immunomodulating effects, as well as agents used in inflammatory disease such as salazosulphapyridine.

Table 4 Reports of treatment of HAM/TSP

Intervention	Year	Centre	Duration HAM		No of patients		Duration of past history	Follow up	Immunology	Authors' comments	Ref
			Range (years)	Mean	Treated	Improved					
Plasmapheresis	1988	Nagasaki	2–40	14	18	11	14 days		No change CSF HTLV-I Ab titre Decreased serum HTLV-I Abs	Rapid but transient improvement	31
	1989							1.8–2.5 years		No improvement. 6 worse	32
Prednisolone	1989	Kagoshima	0.3–48		65	59	9 months	15 months		Prednisolone is an effective therapy	33
Intrathecal hydrocortisone					3	4					
Azathioprine					4	4	7 months				
Interferon-α 1.5–9 MU	1990	Nagasaki	1–28	13.8	5	4	1–4 weeks	4 weeks	No change: T cell subsets; HTLV-I Ab titre Decreased lymphocyte proliferation to PHA	Clinically effective in HAM	34
High dose IV Ig	1991	Saga	2–31	12	14	10	5 days	30 days	No change: T cell subsets; HTLV-I Ab titre Decreased lymphocyte proliferation to PHA	Temporary suppression of progression of HAM	35
Prednisolone 40–60 mg	1991	Fukuoka	1–37	12	16	*	1–4 months	20–33 months		Does not alter chronic progressive nature of HAM/TSP	36
Methyl prednisolone 1 g IV					3						
Danazol 200 mg three times daily	1991	Miami	ns	ns	7	5	4–16 weeks	4–16 weeks		Useful agent in HAM	37
Interferon-α 1.5–9 MU	1991	Nagasaki	1–40	13.2	17 includes 5 patients from 1990	11	4 weeks		No change: T cell subsets; HTLV-I Ab titre Decreased lymphocyte proliferation to PHA	Efficacy comparable to plasmapheresis Safety and efficacy in all patients	38
Zidovudine 0.5–1 g daily	1991	Paris	2-13	4.6	5	0	6 months		HLA-DR+ lymphocytes	No benefit	39
Interferon-α 3 MU	1992	Saga	2–34	11.4	16	10	4 weeks	4–6 weeks	No change: T cell subsets; HTLV-I Ab titre; SPL Decreased IgG, IgA, IgM	Effective in HAM. Unlikely to have antiviral effect as no change HTLV-I Ab titre	40
Heparin 5-10 000 U	1993	Nagasaki	1–45	14.5	10	7	9–93 days	~ one month	No change HTLV-I Ab Decreased SPL No change PBL subsets	Unable to draw any conclusion about therapeutic efficacy	41
Zidovudine 1g	1993	Miami	ns	6	10	7	24 weeks			Appears to be safe in HAM	42
Vitamin C 35–40 mg/kg daily 3–5 days, 2 days off	1993	Oita			7	7		9.7 months	Decreased serum immunosuppresive acidic protein and CSF IgG index. No change PBL subsets or HTLV-I Ab.	Improved muscle power	43
Cyclophosphamide 2 mg/kg, prednisolone	1994	Los Angeles	6	—	1	1	12 months	12 months	Improved CSF	Remarkable clinical improvement in single patient	44
Interferon-α 0.3 MU	1996	Kagoshima	<5 >5	17	15	0	28 days	56 days	No change; Igs; HTLV-I Ab; T- ell subsets	Favourable clinical effects	45
1.0MU				31	17	3					
3.0MU					16	6				50% had safety and efficacy	
Corticosteroids	1996	Kagoshima	1–60	15.1	146	117	Variable		CSF neopterin levels	Oral prednisolone the most effective. Effects transient and patients' motor disabilities worsened over several months with all treatments After effects limit use of steroids in older women A placebo effect could have accounted for the positive responses	46
Lymphocytopheresis					9	7					
Plasmapheresis					7	3					
Interferon -α					43	29					
Azathioprine					9	6					
High dose vitamin C					20	14					
Erythromycin					25	12					
Salazosulphapyridine					24	12					
Mizoribine					17	8					
Fosfomycin					14	11					
Thyrotrophin releasing hormone					16	6					
Pentoxifylline 300 mg	1997	Nagasaki	2–24	10.3	15	13	4–48 weeks	4–52 weeks	Decreased SPL No change PBL subsets No change HTLV-I Ab or TNF-α	May be a safe and beneficial agent in HAM	47
Interferon-α 3 MU	1997	Furuoka, Tokyo			7	6	6 months	12 months	Decreased SPL Decreased CD8/DR + cells Decreased s IL-2 receptor	Benefits from long term IFN due immunomodulation and antiviral effect	48

*Subjective improvement during therapy with recurrence of gait and sphincter abnormalities as steroids reduced. 33% deteriorated during long term follow up.
Overlap between 1989 and 1996 reports from Kagoshima?
PHA=phytohaemaglutinin; SPL=spontaneous proliferation of lymphocytes; s IL-2=soluble interleukin-2.

The transient nature of the benefits in many of these open studies and the wide range of therapies which have given similar results suggests that a placebo response may be contributing to the positive findings. However, since the majority of patients participating in these studies have had symptoms of HAM for many years, sometimes decades, and are likely to have a considerable degree of irreversible neurological damage, failure to produce significant permanent improvement does not necessarily imply that these treatments are inappropriate for all patients with HAM/TSP. Future studies should aim to include patients with more recent onset of symptoms as well as those who are progressing and should include direct measurement of viral burden as well as the immune response.

Summary

That HTLV-I is not a latent infection is indicated by the detection of mRNA in the peripheral blood and CNS of patients with HTLV-I infection and by the persisting humoral and cellular immune responses. Indeed the frequency of anti-HTLV CTL is extremely high. The reduction in anti-TAX CTL frequency following reduction in proviral load suggests that removal of viral antigen may result in a reduced inflammatory response at least in peripheral blood and although the clinical data should be interpreted with caution, perhaps in the CNS. Patients with more advanced disease, and possibly fixed deficits may not benefit from either anti-inflammatory or antiretroviral treatment. The patients with most to gain are those with least deficit in whom early diagnosis and treatment will depend on raising awareness of HTLV-I beyond the neurological community. Many patients with HAM first present to a urologist or gynaecologist with bladder dysfunction or may have been seen in the genitourinary clinical with impotence or positive treponemal serology, which in the older patient is often the result of childhood infection with *Treponema pallidum pertenue*. Investigation of these patients should include HTLV-I serology and further investigation of HTLV-I positive patients should include proviral load measurements as well as markers of inflammation. Treatments whether antiviral or anti-inflammatory should be assessed for their effect on both as well as a clinical response.

Further reading

IARC monographs on the evaluation of carcinogenic risk to humans. Vol 67. Human immunodeficiency viruses and human T-cell lymphotrophic viruses. Lyons: International Agency for Research on Cancer, 1996.

A highly referenced resource on HTLV-I and HTLV-II especially, but not only for ATLL references.

Human T-cell lymphotropic virus type I. Eds Hollsberg and Haffler. Chichester: Wiley, 1996.

A very readable, up to date, text onHTLV-I and HTLV-II including chapters on cellular immune responses, virology, and HTLV-I associated myelopathy.

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Daenke S, Bangham CRB. *Do T-cells cause HTLV-I associated disease?: a taxing problem (editorial). Clin Exp Immunol 1994;***96***:179–81.*

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Describes the interaction between HTLV-I and host cell proteins particularly the effects of Tax.

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