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Interventions for the treatment of Human T-lymphotropic virus type-I-associated myelopathy: A systematic review of randomised controlled trials

Olalekan A Uthman, Rashidah T Uthman

Center for Evidence-Based Global Health, SAYIN, Ilorin, Nigeria

Abstract

Objective: To evaluate the effectiveness and safety of various interventions for treating Human T-lymphotropic virus type-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Methods:* The data sources were MEDLINE, EMBASE, AMED, CINAHL, PSYCHLIT, The Cochrane Library (2007 Issue 2), and bibliographies of included trials. Predefined criteria were used to select randomised controlled trials comparing use of any intervention aimed at treating HAM/TSP with placebo or another intervention in any language. Two assessors independently reviewed each trial, and disagreements were resolved by consensus. *Result:* Three small trials with a total of 68 participants are included in this review. Two trials demonstrated a significant difference. Therapeutic benefit in the 3.0 MU human lymphobastoid interferon (HLBI) group was significantly higher than in the 0.3-MU group. No significant changes in pain score (weighted mean difference (WMD) 0.02; 95% CI -2.55 to 2.59), urinary day frequency (WMD 0.08; 95% CI -1.34 to 1.50), nocturia (WMD 0.63; 95% CI -0.79 to 2.05), and disability (Osame's score WMD 0.01; 95% CI -2.55 to 2.59) was shown in the trial that investigated zidovudine and lamivudine. There was no significant difference in the incidence of symptomatic side effects between groups in the three trials.
Conclusion: There is no clearly defined best treatment for HAM/TSP. High dose HLBI offer high efficacy with acceptable side-effects profile. There is no evidence of benefit of zidovudine plus lamivudine for treating HAM/TSP. These data are limited because of their small size, relatively short study duration, and some compromises in study design.

INTRODUCTION

Human T-lymphotrophic virus 1 (HTLV-1) was among the first human retroviruses discovered in the early 1980s.[1] An estimated 10 to 20 million individuals are carriers worldwide.[2] It is the causative agent of HTLV-1–associated myelopathy/ tropical spastic paraparesis (HAM/TSP).[3] The lifetime cumulative risk of carriers' developing HAM/TSP is about 2%.[4] Endemic areas of HTLV-I are in southern Japan, Central and West Africa, the Caribbean, Central and South America, the Middle East, Melanesia[5], and there are also smaller foci in the aboriginal populations of Australia, Papua New Guinea, and northern Japan. In Europe and North America, the virus is found chiefly in immigrants from these endemic areas and in some communities of intravenous drug users.[5]

The clinical and laboratory guidelines for the diagnosis of HAM/TSP have been formulated based on the recommendation of the World Health Organization guidelines.[5] Clinically, HAM/TSP is characterized by muscle weakness, hyperreflexia, spasticity in the lower extremities, and urinary disturbance associated with preferential damage of the thoracic spinal cord.[5] HAM/TSP is a chronic immune-mediated neurologic disease[6], whose main pathological feature is a chronic inflammation of the spinal cord, characterized by perivascular lymphocytic cuffing and parenchymal lymphocytic infiltration.[7] In parallel, DNA provirus is also implicated in the HAM/TSP pathogenesis, since these patients show higher HTLV-1 proviral load than asymptomatic carriers.[8-10] Inflammatory cytokine production, such as interferon gamma (IFN-γ), interleukin-15 (IL-15) and tumoral necrosis factor-alpha (TNF-α) are important in the inflammatory process in TSP/HAM development[8], and cytotoxic T lymphocytes activity (CTLs) may also be involved in the TSP/HAM pathogenesis.[10,11]

There is no generally agreed standard treatment regimen for HAM/TSP. An evidence-based approach to the practice of medicine has

Address correspondence to: Olalekan A. Uthman, Center for Evidence-Based Global Health, P. O. Box 5146, Ilorin, Kwara State, Nigeria; e-mail: uthlekan@yahoo.com

become more important in the face of increasing pressures to maintain quality care in the context of significant cost containment. Proper understanding of the evidence for interventions and treatment of HAM/TSP requires a systematic, comprehensive, and appropriate analysis of all currently available data. We evaluated the evidence from available randomised controlled trials in order to assess the effectiveness of various interventions for HAM/TSP.

METHODS

Search strategy to identify studies

The following databases were searched: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PSYCHLIT, Allied and Complementary Medicine Database (AMED), Database of Abstracts of Reviews of Effectiveness (DARE), and the Cochrane Controlled Trials Register (CCTR). Reference lists for all primary and other pertinent articles identified were searched. The time period searched was from 1980 to July 2007. No language restrictions were placed on the search. Key words used included: Human T-lymphotropic virus type-I, myelopathy, tropical spastic paraparesis, and added a sensitive filter to identify all possible reports of relevant randomised trials.[12]

Selection of trials

Only randomized, placebo-controlled trials investigating Human T-lymphotropic virus type-I-associated myelopathy published in any language were eligible for inclusion in this study. The two authors of this study independently assessed the titles and abstracts of all reports of studies identified by the search. We obtained full text hard copies of studies that fulfilled the inclusion criteria and for studies where there was some doubt. We then applied the inclusion criteria using an eligibility form and resolved any disagreements through discussion. We prepared a QOUROM[13] statement flow diagram to describe how we processed the references identified through the search results.

Assessment of methodological quality

Two authors independently assessed the methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, and inclusion of all randomized participants in the analysis.[14] We reported who was blinded in each trial, such as the participant, care provider, or outcome assessor. Any disagreements were resolved by discussion. Trials were also graded using the Jadad scale, a clinical trial quality instrument scored from 0 to 5 with higher scores correlating with better quality studies.[15] This validated score lies in the range 0-5. Studies are scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals. For example, the score is two if appropriate methods of randomization are described, one if the study is merely described as 'randomized' and zero when no details are provided to evaluate randomization. Two points can be given for blinding in the study: a score of two is allocated if patients and investigators are made blind by appropriate methods, one if the study is described merely as double blind and zero if details about blinding are not provided. The third item to be scored is the reporting of withdrawals. The study receives a score of one if all patients are accounted for in the analysis and reasons for withdrawals are provided. A score of zero is given when information regarding withdrawals is incomplete.

Data extraction

The two authors independently extracted data on trial characteristics including methods, participants, interventions, and outcomes. Any disagreements were resolved by discussion.

Data analysis

OU used Review Manager 4.2 for data analysis. For dichotomous outcomes, we calculated relative risks (RR) with 95% confidence intervals (CI) using a fixed-effect model. We analysed these data on an intention-to-treat basis.

RESULTS

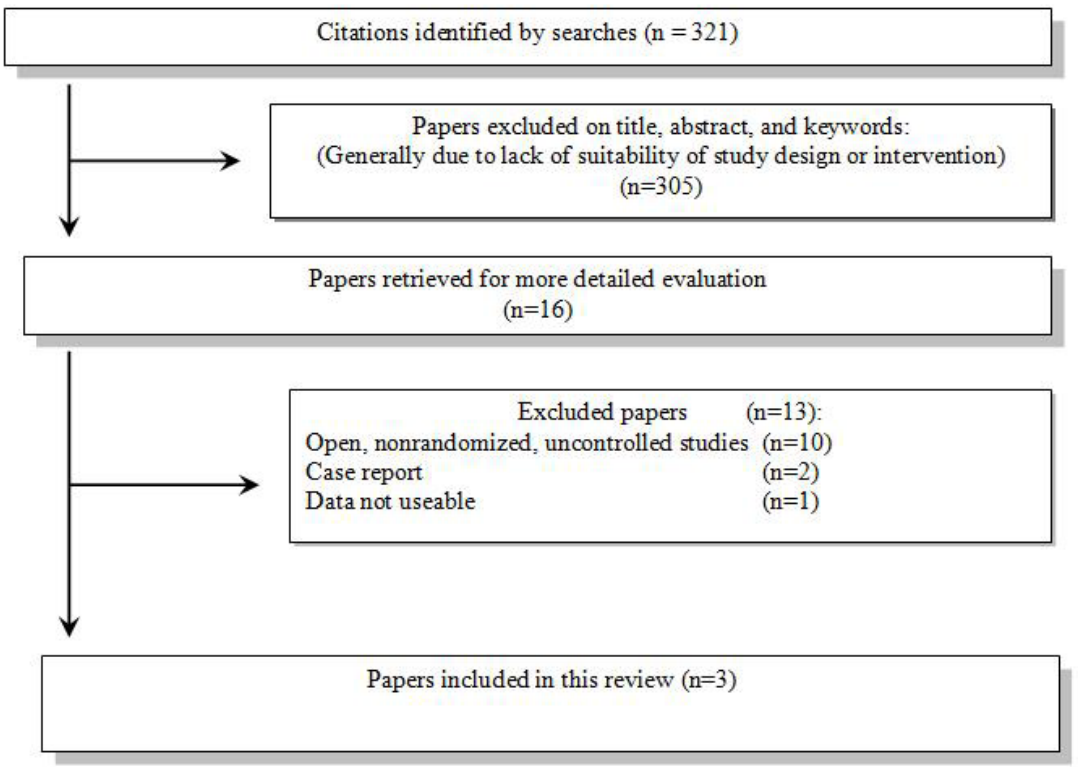
Description of studies

The literature searches yielded 321 titles of potentially relevant articles. After scanning titles and abstracts, a total of 16 potentially relevant articles were identified and full-text copies were assessed independently against the inclusion criteria by the two authors (figure 1). The reference lists of these studies were scanned. Thirteen papers were excluded because they were either open, nonrandomised, uncontrolled studies[16-25] (n=10) or case reports[26,27] (n=2) (see Table 1). One study[28] was excluded because the trial included both idiopathic and Human T-lymphotrophic virus 1

Table 1: Characteristics of excluded studies

Study ID	*Agent*	*Participant*		*Reason for exclusion*
Matsuo 1988[27]	Plasmapheresis	18	Produced a temporary improvement	Case reports
Matsuo 1990[26]	Plasmapheresis			Case reports
Nagasato 1993[16]	Heparin	10	In 7 patients, motor dysfunction improved	Open, nonrandomised, uncontrolled study
Matsuzaki 2005[17]	Lactobacillus casei strain Shirota (from fermented milk)	10	Improvements in spasticity (modified Ashworth Scale scores) and urinary symptoms	Open, nonrandomised, uncontrolled study
Oh 2005[18]	Interferon one alpha	12	Some measures of motor function were improved	Open, nonrandomised, uncontrolled study
Shirabe 1997[19]	Pentoxifylline	15	In 13 of the 15 patients, motor disability, especially spasticity, improved substantially.	Open, nonrandomised, uncontrolled study
Yamasaki 1997[20]	Interferon-alpha	7	Five patients showed a sustained improvement in motor performance during and up to 6 months after the completion of IFN-alpha	Open, nonrandomised, uncontrolled study
Cartier 1996[28]	Nucleus CMP	46 (29 HTLV-1)	Neurogenic bladder improved in 10 of 22 receiving the drug and 4 of 24 receiving placebo	Included both idiopathic and HTLV-1 associated. Unable to extract data for HAM subjects
Sheremata 1993[21]	Zidovudine	10	Safe and time gait improved by at least 50%	Open, nonrandomised, uncontrolled study
Araujo 1993[22]	Intravenous methylprednisolone	23	Only one patient showed a sustained benefit	Open, nonrandomised, uncontrolled study
Kataoka 1993[23]	Vitamin C	7	All HAM patients responded well to intermittent high-dose vitamin C therapy	Open, nonrandomised, uncontrolled study
Shibayama 1991[24]	Interferon-alpha	17	4 patients showed a marked clinical response, 7 showed a moderate response and the others did not show any clinical response.	Open, nonrandomised, uncontrolled study
Gout 1991[25]	Zidovudine	7	The patients showed good compliance with zidovudine therapy. No systemic side effect was noted	Open, nonrandomised, uncontrolled study

Figure 1 – Trial flow



QUOROM statement flow diagram of the process of identifying and including references for the systematic review

(HTLV) associated progressive spastic paraparesis and it was not possible to decipher the data for HAM/TSP patients from the study.

Three trials[29-31] met the inclusion criteria. One trial[30] was carried out in 11 different medical centers in Japan in 48 participants to assess three different doses of human lymphoblastoid interferon (HLBI). In Kuroda[31], two patients were randomised to receive 3.0-million in international unit (MU) per day human interferon, one to receive 1.0-MU and one to receive a dose of 0.3 MU. The other trial[29] was conducted at two sites, The HTLV clinic at St. Mary's Hospital London, UK and the 3rd Department of Internal Medicine, University of Kagoshima, Kagoshima, Japan in sixteen participants to assess zidovudine plus lamivudine against placebo.

The length of follow up was eight weeks in Izumo[30] and 28 days in Kuroda.[31] The participants were randomised to start 24 weeks treatment with zidovudine 300mg plus lamivudine 150mg twice daily or matching zidovudine and lamivudine placebo tablets. This was followed by 24 weeks open therapy with the active compounds for all study participants.

The change in gait, disability, pain, bladder function, and change in HTLV-I viral DNA from baseline were the main outcomes assessed in the included trials.

Methodological quality

Izumo[30] and Kuroda[31] were weak methodologically (Jadad score 2), while Taylor[29] was of a good methodological quality (Jaded score 4). They were relatively small. The trials were randomised and double-blind. The three trials did not describe their methods of allocation sequence generation. Taylor[29] used adequate method for concealing allocation – central allocation method. Allocation concealment was inadequate in Izumo[30] – patients were treated in ascending order with the next case supply and unclear in Kuroda [31]. Participants, pharmacist, and clinicians were masked to the treatment allocation in Taylor.[29] The blinding methods were unclear in the other two trials.[30,31]

The three trials[29-31] did not report sample size

calculations. The trialists reported the number of participants lost to follow up and all randomised participants were included in analysis. The withdrawal rate in Taylor[29] was 6% (1/16). The reason for withdrawal was described as continuing deterioration in medical condition in one active arm participant. The withdrawal rate in Izumo[30] was 4% (2/48). The reasons for withdrawal were not described. No patient was lost to follow up in Kuroda.[31]

Efficacy and safety outcomes

The studies could not be combined for meta-analysis due to heterogeneity in interventions tested. Results for individual comparisons are, therefore presented by outcome.

Zidovudine plus lamivudine[29]

No significant changes in pain score (weighted mean difference (WMD) 0.02; 95% CI -2.55 to 2.59, p = 0.99), urinary day frequency (WMD 0.08; 95% CI -1.34 to 1.50, p = 0.93), nocturia (WMD 0.63; 95% CI -0.79 to 2.05, p = 0.41), and disability (Osame's score WMD 0.01; 95% CI -2.55 to 2.59, p = 0.99) in patients treated with zidovudine plus lamivudine compared to placebo. No significant change in proviral load was seen in the active arm compared with the placebo arm (mean difference (SD); 0.02 (0.48), p = 0.92). No side effect was reported in the first 24 weeks of the double blind phase. There were no significant biochemical abnormalities.

Human lymphoblastoid interferon (HLBI)[30,31]

Two trials[30,31] compared three different doses of human lymphoblastoid interferon (HLBI): 0.3 million international units (MU), 1.0 MU, and 3.0 MU. Patients treated with 0.3 MU exhibited only a minimal clinical improvement in motor dysfunction during therapy and 4 weeks after completion of therapy. In contrast, in the patient group receiving 1.0 MU, three of 17 patients (17.6%) improved clinically by one or more grades. The most striking clinical benefit was seen in the 3.0 MU group. Six of the 16 patients (37.5%) improved one or more grades during the study period. The 3.0 MU group therefore showed a significantly higher improvement of motor dysfunction than the 0.3 MU group (p < 0.051), only 2 weeks after starting therapy, and also exhibited a tendency to maintain this improvement for at least 4 weeks after starting therapy (p = 0.10). Similar trends were observed for those described above for motor dysfunction. Side effects occurred dose-dependently. There was no significant difference in the incidence of symptomatic side effects between groups: 3.0-MU versus- 0.3-MU group (relative risk (RR) 1.67; 95% CI 0.62 to 4.46), 1.0-MU versus 0.3-MU group (RR 1.10; 95% CI 0.36 to 3.37), and 3.0-MU versus 1.0-MU group (RR 1.51; 95% CI 0.61 to 3.71). In Kuroda[31], therapeutic responses were observed in two patients receiving a dose of 3.0MU.

DISCUSSION

This review of interventions for treating Human T-lymphotropic virus type-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) has brought together evidence from three randomised placebo controlled trials[29-31] of zidovudine plus lamivudine and human interferon from the last sixteen years incorporating 68 subjects. Efforts were made to identify all relevant studies and no study was excluded due to language. It is possible that some studies were missed but we feel that it is unlikely that we missed any higher quality published studies such as randomised controlled trials.

Sequence generation is often improperly addressed in the design and implementation phases of controlled trials, and often neglected in their published reports, which causes major problems in assessing sequence generation.[32] Although all studies were randomised, only one study actually described the method used for randomization.[29] Similarly, all the studies were blinded; only one described the blinding method.[29] Therefore, while the studies were all randomised, placebo-controlled, they were only mediocre in quality overall, as reflected in the median Jadad score of 2. There was no indication that power calculations were used to determine the number of patients needed for an expected effect size which in essence renders the studies inappropriate. It is not possible to draw firm conclusions from this review, as it contains only three small trials and the confidence intervals for all outcomes are wide.

Several open, nonrandomised, uncontrolled trials and case reports of plasmapheresis[26,27], heparin[16], lactobacillus casei strain Shirota (from fermented milk)[17], alpha interferon[18,20,24], pentoxifylline[19], zidovudine[21,25], methyprednisolone[22], and vitamin C[23] resulted in only short-term improvement.

In conclusion, there is no clearly defined best treatment for Human T-lymphotropic virus type-I-associated myelopathy/tropical spastic paraparesis

(HAM/TSP). We found limited evidence from two trials that high dose human lymphoblastoid interferon is more effective in the treatment of HAM/TSP compared to low dose with acceptable side-effects profile. We found no evidence of benefit of zidovudine plus lamivudine for treating HAM/TSP. These data are limited because of their small size, relatively short study duration, and some compromises in study design. As a result, their power to detect important differences was limited and their results imprecise. Current clinical practice in treatment of HAM/TSP is based on case series and open, nonrandomised uncontrolled studies. This is a weak evidence base. To avoid bias, future trials need to pay more attention on the methodological requirements for randomized controlled trials. More trials with adequate power would also be helpful.

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