Pilot Study of Intravenous Immunoglobulin in HIV-Associated Myelopathy

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Abstract

There is no effective treatment for HIV-associated myelopathy (HIVM). The introduction of highly active antiretroviral therapy (HAART) has made little difference to its natural history. Spinal cord pathology reveals vacuolization and inflammation. Intravenous immunoglobulin (IVIg) is used successfully in a number of inflammatory conditions associated with HIV. In view of the potential for reversibility of the inflammatory response in HIVM, we treated 17 patients with IVIg twice over a 56-day study period. There was improvement in composite Medical Research Council (MRC) strength scores 28 days following the first infusion (increase in score: 3.94; $p = 0.021$). The second infusion did not produce further improvement, however there was little reduction from peak strength. These pilot data suggest that further investigation of the use of IVIg in HIVM is warranted.

Introduction

HIV-ASSOCIATED MYELOPATHY (HIVM) is the most common cause of spinal cord disease in HIV/AIDS. While the prevalence of clinical HIVM is unknown, autopsy studies report pathological evidence of HIVM of between 22% and 55%.^{1,2} Although more commonly found in advanced disease, it can be present at any stage of HIV infection³ and can progress despite relatively good immune status.⁴ Unlike many conditions associated with HIV, which improve with highly active antiretroviral treatment (HAART), reports of improvement of HIVM are rare.^{5,6}

HIVM is characterized by white matter vacuolization predominantly of the posterior and lateral columns of the thoracic spinal cord, often associated with pathologic evidence of inflammation.^{2,3,7,8} Clinical and pathologic features of HIVM are similar to subacute combined degeneration of the spinal cord. However, there is no associated reduction of serum B₁₂ levels in patients with HIVM and supplementation with vitamin B₁₂ or L-methionine (a constituent of the B₁₂ transmethylation pathway) does not affect the course of the disease.⁹

The presence of inflammation in HIVM suggests the possibility of partial reversibility with anti-inflammatory agents. IVIg has been used successfully in a number of inflammatory conditions associated with HIV (e.g., HIV-associated myopathy; acute and chronic inflammatory demyelinating polyneuropathies¹⁰), in addition to the myelopathy associated

with human T-lymphotropic virus (HTLV)-1.^{11,12} Although the pathology is different in these conditions, IVIg appears to reduce the inflammatory response and result in clinical improvement. These observations provide the rationale to undertake a pilot study to evaluate the safety and efficacy of IVIg treatment in patients with HIVM.

Methods

Seventeen patients (16 men, 1 woman; ages 22 to 59 years; mean 44.4 ± 8.6) with HIVM were recruited through referrals from neurologists, primary care physicians, and AIDS service providers. Consecutive patients who fulfilled inclusion criteria, defined below, were invited to participate. The demographics and baseline characteristics of the study group are outlined in Table 1 and Table 2 provides details concerning individual clinical and virologic status.

Prior to entry into the study, exclusionary blood studies were performed for other causes of myelopathy, including vitamin B₁₂, Venereal Disease Research Laboratory (VDRL), HTLV-1, toxoplasma titers and cryptococcal antigen. Subjects underwent contrast-enhanced magnetic resonance imaging (MRI) of the cervical, thoracic, and lumbar spine to exclude other causes of myelopathy. Inclusion criteria were: (1) documented history of HIV infection, (2) 18 years of age or older, (3) adequate baseline organ function (normal liver and renal function and normal serum vitamin B₁₂ level

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Patient numbers
Number of patients treated	17
Age (yrs)	
Mean	44.4
Range	22–59
Gender	
Male	16
Female	1
CD4 count (cells/m ³)	
Mean	300
Range	20–1200
Viral load (copies/ml)	
Undetectable / < 50	5
50–1000	2
1000–10,000	4
10,000–50,000	2
50,000–750,000	4
Time with HIV infection (yrs)	
Mean	7
Range	1–12
Risk factors for HIV acquisition	
Male-to-male contact	11
IDU drug use	5
Blood products	1
Other neuro-HIV conditions	
Peripheral neuropathy	10
HIV-associated dementia	1 (mild)
History of AIDS-defining illnesses	3
Concurrent	
HBV infection	2
HCV infection	1
HTLV-1 infection	0

IDU, injection drug use; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T-lymphotrophic virus.

(200–1000 pg/mL), and (4) a diagnosis of HIV-associated myelopathy based on history and examination by a neurologist, experienced in neuro-AIDS.⁹

Clinical evidence of progressive myelopathy was based on: (1) Presence of at least four of the following symptoms for a minimum of 6 weeks: weakness of the lower extremities; unsteady, stiff, or uncoordinated gait; stiffness or spasms in the lower extremities; paresthesias or numbness in the lower extremities; urinary frequency, urgency, or incontinence; and erectile impairment in men. (2) Presence of at least three of the following signs: weakness of the lower extremities; spastic gait; extensor plantar response; and reduction in vibratory or position sensation in the lower extremities. (3) Hyperactive deep tendon reflexes or clonus in the lower extremities. (4) Absent or minimal weakness and pyramidal signs in the upper extremities. Exclusion criteria included active opportunistic infections, confounding neurological disorders, major psychiatric disorders, those whose myelopathy were attributable to other causes, pregnancy, IgA deficiency, and previous hypersensitivity to immunoglobulin. Patients who fulfilled these criteria signed informed consent to participate. The study was approved by the Institutional Review Board, and all subjects signed informed consent prior to participation.

Participants were followed for 56 days. On days 1, 2, 29, and 30, each participant received an infusion of 1 g/kg per day of IVIg. Infusions were administered at the participants'

homes by a nurse who monitored the patients throughout the infusion period. They were seen for clinical evaluation at 2-week intervals on days 0, 14, 28, 42, and 56. Neurologists performed the clinical evaluations to assess spasticity (modified Ashworth score), strength (Medical Research Council [MRC] strength score; range, 0–5), deep tendon reflexes, sensation, urinary function (range, 0 [normal]–3 [severe urinary symptoms with incontinence or frequency >15 per day]),⁹ and clinical disability (Hillel disability scale).¹³ Whenever possible, the same neurologist examined the patient serially.

Since the predominant involvement in HIVM is in the thoracic spine, strength scores were obtained in the legs. A composite muscle score was established with summation of lower extremity MRC scores (0–5) on both sides, including the mean results from hip flexors, hip extensors, knee flexors, knee extensors, foot dorsiflexors, and foot plantar flexors. The total score could range from 0–30.

The Student's *t* test for paired samples was used for statistical analysis. Significance was taken at a value $p \leq 0.05$.

Results

All 17 patients had IVIg on days 1 and 2 and were assessed at 28 days. All but 2 patients had their second IVIg infusion on days 29 and 30. Of the 2 patients who did not have the second infusion of IVIg, 1 patient's health rapidly declined with progressive dementia, and the other patient was hospitalized for primary pulmonary hypertension. Both events were considered to be unrelated to the study drug. Twelve patients presented for assessment on day 42 and 10 of the 17 patients completed the study from baseline to exit at 56 days. Five patients were lost to follow-up (1 patient lost insurance coverage for IVIg and declined to return, and 4 patients missed day 42 or day 56 appointments and could not be reached for follow-up).

The results from all 17 patients were included for assessment at 14 and 28 days. The results at days 42 and 56 included all patients who could be evaluated (day 42, $n = 12$ and day 56, $n = 10$). Subgroup analysis of only the 10 patients who completed the study from baseline to exit at 56 days did not alter the level of significance of the results at 14 and 28 days. Therefore, it did not appear that there were any characteristics associated with the patients who dropped out that altered the data at days 28 and 42.

Composite MRC strength scores for the lower limbs significantly improved from baseline to day 28 (mean improvement: 1.97; $p = 0.021$; Fig. 1). Improvement in composite strength scores from day 0 to 14 followed this trend, approaching significance (mean improvement of 1.32; $p = 0.053$). The change in composite strength scores from baseline to day 56, or from day 28 to day 56 was not significant. Spasticity, deep tendon reflexes, sensation, urinary function, and clinical disability scores did not change significantly from baseline to exit (data not shown).

There were no major adverse effects of IVIg during infusion or throughout the weeks following infusion. The only adverse event, which was considered to be definitely related to treatment, was swelling at the IV site in one patient. Other adverse events included headache, sore throat, mild increase in blood-urea-nitrogen (BUN) and creatinine, which subsequently returned to normal, and back pain, each in one patient, and were cited as possibly related to study treatment.

TABLE 2. INDIVIDUAL CLINICAL CHARACTERISTICS, MEDICATIONS, AND BLOOD INDICES

Patient number	Clinical status	HAART medication	CD4 count (cells/mm ³)	Viral load (copies/mL)
001	Walking with aids; moderate spasticity	Stavudine; ritonavir; saquinavir	35	247,000
002	Unsteady; independent; mild spasticity	Zidovudine; lamivudine; indinavir	199	UD
003	Mild gait difficulty; independent; no spasticity.	Lamivudine; nelfinavir; zidovudine	204	81,000
004	Long leg braces and walker; moderate spasticity	Nil	116	318,801
005	Moderate gait difficulty; occasional falls; no aids	Ritonavir; nevirapine; stavudine; lamivudine	150	20,000
006	Mild gait difficulty; independent	Didanosine; abacavir; ritonavir	22	136
007	Wheelchair-bound	Delavirdine; nelfinavir; abacavir; didanosine	274	8900
008	Moderate gait difficulty; moderate spasticity; independent	Didanosine; ritonavir; abacavir	105	42,616
009	Uses cane; moderate spasticity	Nelfinavir; stavudine; nevirapine; lamivudine	228	UD
010	Uses cane and walker; mild spasticity	Saquinavir; nelfinavir; abacavir; efavirenz	190	5000
011	Normal gait; independent; mild spasticity;	Combivir; efavirenz	1200	6000
012	Uses walker	Nelfinavir; Combivir	1022	565
013	Wheelchair-predominant; few steps with walker	Nevirapine; combivir; indinavir	386	UD
014	Uses walker	Combivir; nelfinavir; efavirenz; saquinavir	600	UD
015	Mild gait difficulty; uses cane	Amprenavir; lamivudine; ritonavir; efavirenz	23	500,000
016	Mild gait difficulty; mild spasticity; independent	Didanosine; tenofovir; kaletra; lamivudine	20	750,000
017	Uses cane	Nevirapine; combivir	342	UD

UD, undetectable.

Discussion

The cause of HIVM is unknown. It can occur at any stage of HIV infection. In addition to vacuolization, there is often evidence of inflammation.^{2,3,7,8} The use of HAART does not seem to have altered the natural history of this condition¹⁴ and progression of symptoms can continue despite good CD4 counts and low viral loads.⁴ In our patient group, CD4 counts ranged from 20 to 1200 and there were no direct correlations between severity, clinical progression and CD4 count.

Currently no treatment is effective for HIVM. In the current study, all 17 patients had improvement in strength following infusion of IVIg at a total dose of 2 g/kg infused over 2 days. By 14 days the increase from baseline in composite strength scores approached, and by 4 weeks, reached statistical significance. Although this pattern of improvement was not seen following a second course of IVIg, there was little reduction from the peak strength seen at 28 days (Fig. 1). The analyses subsequent to the second infusion were confounded by loss to follow-up. There was no difference in the outcome and level of significance in strength scores at 28 days, when the results of only those patients who completed the study were analyzed. Therefore, it did not appear that there were any characteristics associated with the patients who dropped out that altered the data at days 28 and 42.

FIG. 1. Mean composite Medical Research Council (MRC) strength scores for patients with HIV-associated myelopathy treated with intravenous immunoglobulin (IVIg). Adjusted data set, all evaluable patients at each assessment day.

The lack of improvement in scores for spasticity, deep tendon reflexes, sensation, urinary function, and clinical disability may result from insensitivity of these scales in reflecting change in this relatively small number of patients. Such functions may recover more slowly and could not be measured over the 56-day study period, or alternatively may be irreversible.

The improvement in strength demonstrated in this study warrants further investigation of the use of IVIg in the treatment of HIV-associated myelopathy a condition with no current treatment options.

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References

- Artigas J, Grosse G, Niedobitek F. Vacuolar myelopathy in AIDS: A morphological analysis. *Pathol Res Pract* 1990;186: 228–237.
- Petito CK, Navia BA, Cho E-S et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with Acquired Immune Deficiency Syndrome. *N Engl J Med* 1985;312:874–879.
- Dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV-1-associated vacuolar myelopathy: An autopsy-based case-control study. *Neurology* 1994;44:2159.
- Aboulafia DM, Taylor L. Vacuolar myelopathy and vacuolar cerebellar leukoencephalopathy: A late complication of AIDS after highly active antiretroviral therapy-induced immune reconstitution. *AIDS Patient Care STDs* 2002;12:579–584.
- Staudinger R, Henry K. Remission of HIV myelopathy after highly active antiretroviral therapy. *Neurology* 2000;54:267–268.
- Di Rocco A, Geraci A, Tagliati M. Remission of HIV myelopathy after highly active antiretroviral therapy. *Neurology* 2000;55:456.
- Tan SV, Guilloff RJ, Scaravilli F. AIDS associated Vacuolar myelopathy. A morphometric study. *Brain* 1995;118:1247–1261.
- Rottnek M, Di Rocco A, Laudier D, Morgello S. Axonal damage is a late component of vacuolar myelopathy. *Neurology* 1995;58:479–481.
- Di Rocco A, Wener P, Bottiglieri, et al. Treatment of AIDS-associated myelopathy with l-methionine: A placebo-controlled study. *Neurology* 1997;63:1270–1275.
- Malamut RI, Leopold N, Parry GL. The treatment of HIV-chronic inflammatory demyelinating polyneuropathy (HIV-CIDP) with intravenous immunoglobulin (IVIg). *Neurology* 1992;42(Suppl 3):335.
- Johnson RT, McArthur JC. Myelopathies and retroviral infections. *Ann Neurol* 1987;21:113–116.
- Kuroda Y, Takashima H, Ikeda A, et al. Treatment of HTLV-1-associated myelopathy with high-dose intravenous gammaglobulin. *J Neurol* 1991;48:312–314.
- Hillel AD, Miller RM, Yorkston K, et al. Amyotrophic lateral sclerosis severity scale. *Neuroepidemiology* 1989;8:142–150.
- Banks LT, Geraci A, Liu M, Gobold G, et al. A natural history of HIV myelopathy in the HAART era [Abstract PO6.037]. *Neurology* 2002;(Suppl 3):A441.

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