A *G. lamblia* (as opposed to group B *G. lamblia*) among the cases with diarrhea vs. the controls without diarrhea [10]. This result suggests a positive association between group A *G. lamblia* and diarrhea, although it was not statistically significant (*P* = 0.24 by Fisher’s exact test). Future studies testing the association of group A *G. lamblia* with diarrhea would be strengthened by using a larger sample size, ensuring greater homogeneity of the cases in terms of duration of illness, and ensuring greater comparability between cases and controls in terms of gender.

These very preliminary results suggest that *G. lamblia* groups A and B are both present in Chandigarh and that group A *G. lamblia* may cause gastrointestinal disease more frequently. Future studies with larger populations and more appropriate controls in Chandigarh and elsewhere will be needed to confirm or disprove the relative virulence of group A *G. lamblia*.

Ajaib Singh Paintlia, Steven Descoteaux, Bryan Spencer, Anuradha Chakraborti, Nirmal Kumar Ganguly, Ramesh Chander Mahajan, and John Samuelson

Department of Experimental Biology and Biotechnology, Postgraduate Institute of Medical Education and Research, Chandigarh, Punjab, India; and Department of Tropical Public Health, Harvard School of Public Health, Boston, Massachusetts

Successful Resolution of Progressive Multifocal Leukoencephalopathy After Combination Therapy with Cidofovir and Cytosine Arabinoside

Progressive multifocal leukoencephalopathy (PML) is an illness caused by JC virus (a human papovavirus) and affects 2%–4% of individuals with advanced HIV disease [1]. Although no effective treatment for PML has been licensed, we describe the successful resolution of PML in one patient after unprecedented combination therapy with cidofovir and cytosine arabinoside (ara-C).

A 34-year-old homosexual male was found to have HIV infection in 1988. Subsequent therapy with stavudine (600 mg/d) as well as experimental therapy with IL-2 were begun in 1989. Treatment with zidovudine and IL-2 was replaced with stavudine (d4T) in 1994 because the patient developed anemia. In December 1995, lamivudine (3TC) (150 mg b.i.d.) and saquinavir (600 mg t.i.d.) were added to his drug regimen.

In January 1996, the patient noticed that he was having difficulty reading his own writing. At this time his CD4 cell count was 250/mm³. In March 1996, he began experiencing what he described as a sense of impending doom and was having difficulty concentrating. Two weeks later, he developed weakness in his lower right leg and foot and experienced muscle spasms and weakness in his right arm.

References


A preliminary diagnosis of PML, consistent with the appearance of white matter changes on MRIs obtained in March 1996, was made. Results of toxoplasmosis serology and cryptococcal antigen tests were negative. Shortly thereafter, the patient was hospitalized for deep vein thrombosis in his right leg and was treated with iv heparin. He became wheelchair bound, developing complete paralysis in his right lower extremities, and became almost completely aphasic.

CSF and blood samples sent to the National Institutes of Health (Bethesda, MD) for detection of JC virus DNA by PCR were both positive. Because of cidofovir’s demonstrated in vitro activity against JC virus, iv therapy with this drug was begun in April 1996 [2]. Treatment with iv ara-C was also initiated because of its potential activity against JC virus in patients with PML [3–5]. Cidofovir (5 mg/kg) was administered once a week for 2 weeks with probencid, followed by standard maintenance therapy (5 mg/kg once every 2 weeks). Ara-C (5 mg/kg) was administered daily for 5 consecutive days; this treatment was repeated every 14 days.

Approximately 8 weeks later (mid-June), the patient was able to move around using a walker or cane, and his speech had markedly improved. The aphasia and balance problems returned with the cessation of therapy, so a combination cidofovir and ara-C therapy was continued, with cidofovir given at maintenance dosages. His condition once again began to improve when these two drugs were administered in combination.

In August indinavir (800 mg t.i.d.) therapy was added, and by September 1996 the patient was expressing himself clearly without confusion and retained only a residual mild limp in his right lower leg, with a muscle strength of 5/5. The deep vein thrombosis had disappeared, and MRIs obtained in October 1996 showed stabilization of the PML. By this time, the HIV viral load had decreased from 80,000 copies/mL in June 1996 to <400 copies/mL (table 1).
Table 1. Timeline of HIV viral load, CD4 cell count, and antiretroviral therapy for a patient with progressive multifocal leukoencephalopathy.

<table>
<thead>
<tr>
<th>Date</th>
<th>Viral load (copies/mL)</th>
<th>CD4 cell count (/μm³)</th>
<th>Treatment (dosage), patient status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989–1994</td>
<td></td>
<td></td>
<td>Zidovudine (600 mg qd), IL-2 (replaced by d4T in 1994)</td>
</tr>
<tr>
<td>12/95</td>
<td>10,600</td>
<td>111</td>
<td>Saquinavir added (1,800 mg qd)</td>
</tr>
<tr>
<td>1/96</td>
<td>1,940</td>
<td>250</td>
<td>Patient begins to have difficulty reading own writing</td>
</tr>
<tr>
<td>2/96</td>
<td>7,440</td>
<td>231</td>
<td></td>
</tr>
<tr>
<td>3/96</td>
<td></td>
<td>182</td>
<td></td>
</tr>
<tr>
<td>4/96</td>
<td></td>
<td></td>
<td>Cidofovir/ara-C therapy initiated</td>
</tr>
<tr>
<td>6/96</td>
<td>80,000</td>
<td>109</td>
<td>Patient able to walk, showing marked improvement</td>
</tr>
<tr>
<td>7/96</td>
<td>31,000</td>
<td>137</td>
<td>Patient expressing himself clearly without confusion</td>
</tr>
<tr>
<td>8/96</td>
<td></td>
<td></td>
<td>Indinavir (800 mg t.i.d.); delavirdine therapy begun</td>
</tr>
<tr>
<td>9/96</td>
<td>&lt;400</td>
<td>136</td>
<td>Only residual mild limp; muscle strength, 5/5</td>
</tr>
<tr>
<td>11/96</td>
<td>&lt;400</td>
<td></td>
<td>MRI shows stabilization of PML</td>
</tr>
</tbody>
</table>

NOTE. ara-C = cytosine arabinoside; d4T = stavudine; PML = progressive multifocal leukoencephalopathy.

The patient began to show clinical improvement in concordance with cidofovir/ara-C therapy, before indinavir therapy was initiated. Furthermore, the PML had developed and progressed while he was already receiving d4T, 3TC, and saquinavir; thus, his clinical response was not the result of an improvement in immunity secondary to treatment with these drugs. In addition, there was no rise in the CD4 cell count during combination therapy that would indicate the involvement of an immunologic mechanism.

Although isolated anecdotal improvement has been observed with zidovudine and/or ara-C therapy, the recently completed ACTG (AIDS Clinical Trials Group) trial 243 showed that zidovudine alone, intrathecal ara-C plus zidovudine, or intravenous ara-C plus zidovudine were not beneficial for the treatment of PML. The sustained effects seen in our patient are believed to be the result of combination therapy with cidofovir.

The side effects of ara-C included nausea, vomiting, and fatigue and were treated with granisetron and fentanyl patches. There was no renal dysfunction associated with cidofovir therapy, and there were no side effects associated with probenecid.

The patient continues to receive combination cidofovir/ara-C therapy along with d4T (30 mg b.i.d.), 3TC (150 mg b.i.d.), indinavir (800 mg t.i.d.), acyclovir (800 mg b.i.d.), trimethoprim-sulfamethoxazole (once daily), and diflucan (100 mg once daily). He wears a 25-μg fentanyl patch for 72 hours before receiving ara-C infusions, and granisetron is administered once every 12 hours as needed during ara-C infusions.

We believe this case represents the first documented successful treatment of PML, and it is our opinion that the combination of cidofovir and ara-C is responsible for the remarkable turnaround in our patient’s condition. Cidofovir, which was approved in June 1996 for the treatment of CMV retinitis in patients with AIDS, seems to have even greater potential when used in combination with other agents and should be considered as a potential therapy for AIDS-related PML. Cidofovir has been demonstrated to have broad-spectrum activity against a wide variety of DNA viruses, including JC virus, and may well have been the major factor contributing to the improvement in our patient’s condition [2]. Trials are currently being conducted by the ACTG to assess the use of cidofovir and other agents in the treatment of PML and other diseases.

Gary Blick, Mark Whiteside, Paula Griegor, Una Hopkins, Trish Garton, and Lisa LaGravinese
Blick Medical Group, Greenwich, Connecticut; and Old Town Medical Center, Key West, Florida

References