Human Immunodeficiency Virus–Associated Dementia

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Human immunodeficiency virus (HIV) enters the nervous system in the first hours of infection and remains present throughout the infection. Over the past 15 years, much has been learned about the neurologic complications of HIV infection, as well as secondary complications due to the development of opportunistic infections and increased risk of malignant neoplasms associated with the immunodeficient state. The increased risk of previously rare neurologic complications such as cryptococcal meningitis, toxoplasma encephalitis, and progressive multifocal leukoencephalopathy has permitted refinement of therapeutic strategies for the treatment of these complications. While these are important issues, the fundamental neurologic problem is understanding the pathophysiology of the HIV infection in the brain so as to optimally treat this critical manifestation of acquired immunodeficiency syndrome (AIDS). Clinical observations and formal trials are contributing to the increasing knowledge about HIV disease in the brain.

CLINICAL FORMS OF HIV NEUROLOGIC DISEASE

During primary infection, typical “aseptic meningitis” often accompanies the viremia associated with acute infection. Malaise, headache, and rash typical of many viral infections follow a self-limited course as the immune response controls the viral infection. Unfortunately, HIV is well versed in evading the immune system, and eventually undermines it. The next level of clinical neurologic involvement is the minor cognitive motor disorder. This manifestation has a clinically relevant and measurable change in cognitive or motor performance, but the pathophysiological origins of this disorder remain uncertain, as does its prognosis. Development of minor cognitive motor disorder is accompanied by a worse prognosis than HIV infection at a similar stage of disease without it. However, routine progression to more severe dementia or other neurologic changes has not been documented. Exploiting investigations at this stage of the disease seem to be an opportunity for research that could be of great value. The most severe neurologic presentation, HIV–associated dementia (HAD), is well characterized with evidence of cognitive decline and motor slowing that are substantial, often accompanied by a variety of behavioral changes. Even at this stage of clinical presentation it is clear that intervention may be of benefit.

HIV ANTIVIRAL THERAPY AND HAD

While pathologic and clinical studies provided substantial linkage of HAD with the HIV infection itself rather than some other opportunistic infection (eg, cytomegalovirus), perhaps the best evidence associating cognitive performance deficits with this virus comes from treatment trials with antiretroviral drugs. Schmitt et al3 studied the neurologic performance of subjects in the licensing trial for zidovudine. There was concern that zidovudine might produce neurotoxic effects, so a significant psychometric battery was included in the evaluations. Significant improve-
Controlled Trials for Human Immunodeficiency Virus–Associated Dementia

<table>
<thead>
<tr>
<th>Trial/Sponsor*</th>
<th>Test Drug</th>
<th>No. of Patients</th>
<th>Duration of Therapy</th>
<th>Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG1 2005</td>
<td>Zidovudine</td>
<td>43</td>
<td>16 wk</td>
<td>Reverse transcriptase inhibitor</td>
<td>Zidovudine therapy improved neuropsychometric performance</td>
</tr>
<tr>
<td>CNA3001†/Glaxo Wellcome Inc</td>
<td>Abacavir</td>
<td>99</td>
<td>16 wk</td>
<td>Reverse transcriptase inhibitor</td>
<td>No treatment advantage</td>
</tr>
<tr>
<td>NIMH*</td>
<td>Peptide T</td>
<td>143</td>
<td>6 mo</td>
<td>? CCR5 receptor modulation/release of antiviral chemokines</td>
<td>No benefit</td>
</tr>
<tr>
<td>Dana†</td>
<td>OPC-14,117</td>
<td>30</td>
<td>12 wk</td>
<td>Antioxidant</td>
<td>Safe and tolerable</td>
</tr>
<tr>
<td>Dana</td>
<td>Deprenyl and thiocic acid</td>
<td>36</td>
<td>10 wk</td>
<td>Antiapoptotic/antioxidant</td>
<td>Tolerated and verbal memory improved while the patient received deprenyl therapy</td>
</tr>
<tr>
<td>ACTG162</td>
<td>Nimodipine</td>
<td>41</td>
<td>16 wk</td>
<td>Calcium channel antagonist</td>
<td>Safe, no clear benefit</td>
</tr>
<tr>
<td>NARC†</td>
<td>Lexipafant</td>
<td>30</td>
<td>10 wk</td>
<td>Platelet activating factor antagonist</td>
<td>Safe and tolerable</td>
</tr>
<tr>
<td>ACTG301</td>
<td>Memantine</td>
<td>120</td>
<td>16 wk</td>
<td>N-methyl D-aspartate acid antagonist</td>
<td>Closed</td>
</tr>
<tr>
<td>NARC</td>
<td>CPI-1189</td>
<td>60</td>
<td>12 wk</td>
<td>Tumor necrosis factor α antagonist/antioxidant</td>
<td>Open</td>
</tr>
</tbody>
</table>

*ACTG indicates AIDS Clinical Trial Group (trials at 35 sites); NIMH, National Institute of Mental Health, Rockville, Md; Dana, Dana Foundation, Bethesda, Md; and NARC, Neurologic AIDS Research Consortium (trials at 20 sites).

Controlled trials designed to define therapeutic benefit of treatments for HAD are the most convincing means of establishing effective therapy. To design such a trial, a group of subjects confirmed with the diagnosis should be randomized to arms receiving and not receiving the therapy, followed up over an appropriate period taking the therapy without knowledge of whether it is active, and evaluated by investigators similarly “blinded” to therapy. Ethically meeting the requirements for such a trial represents a considerable challenge and has resulted in only a handful of controlled observations of therapy for HAD (Table).

The AIDS Clinical Trial Groups trial, ACTG005, compared 2 high doses of zidovudine with placebo. It was closed after only 43 subjects were enrolled because data became available suggesting that zidovudine was efficacious for treatment of HIV, and thus the placebo arm was no longer ethically acceptable. Remarkably, even with this small group of patients, efficacy was demonstrated by improved neuropsychometric performance in treated subjects. This further established the link of HIV in the pathogenesis of HAD, and reinforced the validity of HIV therapy as a tool in combating it. However, the doses employed were 1000 mg/d vs 2000 mg/d, typical of the very large doses used in the early days of the infection, and have left open the concern that particularly high doses may be required to treat central nervous system disease.

A problem facing investigators since that time has been how to ethically provide a control arm for trials test-
ing antiviral therapies for HAD. Since HAD is a late complication of the infection, subjects have often already received the latest antiviral therapy before they develop dementia, and if they have not, it has been difficult to propose that a clinical equipoise exists without employing the best HIV therapy clinically available. Thus, only one other controlled antiretroviral therapy has been undertaken. This trial of the nucleoside reverse transcriptase inhibitor abacavir was supported by Glaxo Wellcome Inc, Research Triangle Park, NC. The drug is an attractive candidate for treating HAD because it enters the cerebrospinal fluid (and presumably the brain) well and is a potent antiviral. In treatment-naive hosts it is capable of reductions of plasma viral load comparable to the PIs, substantially exceeding the performance of earlier reverse transcriptase inhibitors. This trial used high doses of abacavir (600 mg, twice daily) and compared best conventional antiviral therapy to this plus abacavir, with a double-blinded controlled design. Unfortunately, in this study the addition of abacavir failed to provide significant neuropsychometric improvement. The study illustrates the problems facing investigators. As an antiretroviral therapy, the design of the study minimized the potential improvement that could be hoped for from the subjects. Most patients were on at least triple therapy including PIs, and had markedly suppressed the viral infection. This left little additional benefit virologically to be derived by the additional drug. Second, the patients were highly experienced to therapy including conventional reverse transcriptase inhibitors, and cross-resistance from these therapies reduced the potential benefit that abacavir could provide. Finally, this study was designed before it was firmly accepted that introduction of monotherapy was a clinically suboptimal way to use drugs. Current therapeutic guidelines for HIV strongly support the introduction of multiple new drugs concurrently to avoid speeding development of viral resistance. This clinical requirement will make future tests of individual HIV agents unacceptable, and further complicate the development of antiviral therapy for dementia.

Antiretroviral prescribing for treatment of neurologic disease would ideally be directed by full knowledge of penetration and efficacy of particular drugs in the brain. Unfortunately, the data set to inform this process is incomplete. Based primarily on cerebrospinal fluid–serum distribution ratios, nucleoside reverse transcriptase inhibitors with the most favorable distribution characteristics include zidovudine, stavudine, and abacavir. Nevirapine seems to be particularly able to enter the brain among the nonnucleoside drugs, while indinavir (which is the least protein bound of the approved PIs) may be the theoretically optimal PI for neurologic treatment. However, there is remarkably little evidence suggesting that any particular one of the approved drugs is truly inferior to the rest as a neurologic therapy. Thus, it is my belief that the overriding goal in designing antiretroviral therapy can remain to determine the most effective systemic antiviral therapy. This decision is based on drug exposure history, and increasingly on viral genotypic and/or phenotypic analysis of resistance.

**PATHOPHYSIOLOGICALLY TARGETED THERAPY FOR HAD**

Evaluation of the brains of subjects with HAD consistently reveals HIV, but the correlation of signs of dementia with the viral load in the brain has not shown a close association. This has led most investigators to hypothesize that the development of brain dysfunction is dependent on intermediate processes set in motion by the viral infection, but not quantitatively linked to its extent. Host factors, viral strain difference, and concomitant infections or challenges might play a major role in the development of clinical disease, and might be subject to direct intervention. Active exploration of this possibility continues to drive clinical trials.

Developing an understanding of potential pathophysiological targets has fuelled the development of these trials as evidence accumulates for a variety of potential mechanisms of neurologic injury. Leading candidates have been calcium-mediated neurotoxic mechanisms, excitotoxic processes particularly those linked with N-methyl d-aspartate acid receptors, cytokine-mediated injury, and damage from free radicals.

The Table lists these efforts along with the outcome of the trials. Several clinical trials have evaluated the safety of neuroprotective drugs, while seeking data about the potential efficacy of the drugs. The first such trial used nimodipine in a group of patients with HIV-associated dementia. While nimodipine was well tolerated, the study failed to suggest efficacy, and interest in this approach waned. More novel approaches have included trials of an antioxidant, OPC-14,117,17 deprenyl and thioctic acid,18 a platelet-activating factor antagonist lexicaplan,19 and peptide T.20 The AIDS Clinical Trials Group study of an N-methyl d-aspartate acid antagonist memantine recently was completed and will soon be analyzed. The Neurologic AIDS Research Consortium trial of a functional tumor necrosis factor antagonist CPI-1189 is still in progress. Information regarding available trials in the area of neuro-AIDS may be accessed on the Internet through the Web site of the Neurologic AIDS Research Consortium (http://www.neuro.wustl.edu/narc).

**SUMMARY**

It is clear that optimal control of HIV infection using cocktails of antiretrovirals has an important beneficial effect on the neurologic manifestations of HIV. Research is required to define the pathophysiology of HIV-associated disease in the central nervous system, and to enhance delivery of therapy to this important compartment. Concurrently, trials of potentially neuroprotective agents are needed to optimize central nervous system therapy. No neuroprotective treatment to date has been successfully proven to be beneficial. However, progress has been very rewarding, with rapidly declining incidence of neurologic disease associated with dramatic improvement in HIV therapy. The prolonged life span of patients with HIV leaves the possibility that prevalence of HIV-associated neurologic disease might even increase in coming years. Therapy for HIV in the central nervous system compartment remains potentially the most challenging therapeutic frontier for HIV control.
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REFERENCES