An SSRI May Enhance Immune Function in HIV

In depressed HIV patients, natural killer cell activity returned to normal when the depression resolved.

BY DAMIAN McNAMARA
Miami Bureau

SAN JUAN, P.R. — A selective serotonin reuptake inhibitor can enhance killer lymphocyte activity against HIV infection, according to preliminary study findings.

Depression may raise the risk of morbidity and mortality in patients with many medical conditions, including HIV infection. In addition, depression has been linked to immune function deficits, such as decreased natural killer cell activity, according to a presentation at the annual meeting of the American College of Psychiatrists.

In normal physiology, natural killer cells defend against viral infections and eliminate neoplastic cells. Natural killer cells are a focus of the ongoing HIV in Women: Depression and Immunity study, funded by the National Institute of Mental Health.

In this study of 40 women, a blood sample was obtained from each subject, and the researchers then treated the sample with citalopram and/or a substance P antagonist (an experimental agent); they then measured natural killer cell activity in vitro. They found that such treatment could reverse the detrimental effect of HIV on natural killer cell activity.

These preliminary data are "hot off the press," Dr. Dwight L. Evans said. "Next we need to look at this in a real in vivo situation."

These findings "suggest that killer lymphocyte antiviral activity is enhanced by an SSRI and the substance P antagonist," said Dr. Evans, the Ruth Meltzer Professor and chair of psychiatry at the University of Pennsylvania in Philadelphia.

"The reason we focused on natural killer cells—or killer lymphocytes as they are now known—is they kill or lyse HIV-1 infected cells and secrete chemokines and cytokines," Dr. Evans said.

Cytotoxic T lymphocytes also lyse HIV-infected cells and secrete HIV-suppressive factors. Severe life stress decreases both these natural killer cells and cytotoxic T lymphocytes, he added.

In another study, Dr. Evans and his associates found that resolution of major depression was associated with increased natural killer cell activity in HIV-seropositive women (Am. J. Psychiatry 2005;162: 2125-30).

The investigators assessed 57 women over 2 years and found that variations in natural killer cell levels corresponded to changes in depression status and ratings on the 17-item Hamilton Depression Rating Scale. Major depression in 11 participants resolved over time, with a simultaneous and significant increase in natural killer cell activity, which returned to normal levels.

'This study suggests that depression may impair certain aspects of innate cellular immunity relevant to delaying the progression of HIV disease.'

"This study suggests that depression may impair certain aspects of innate cellular immunity relevant to delaying the progression of HIV disease and that these alterations are reversible with the resolution of a depressive episode," the authors wrote. "We don't know if this is a resolution of depression or if it's a direct effect of the treatment on the immune system," Dr. Evans added.

Researchers are assessing other potential mechanisms that may influence immunity and HIV disease progression, including hyperactivity of the hypothalamic-pituitary-adrenal axis and increases in substance P. Studies have shown that HIV-positive men have elevated substance P levels, compared with HIV-negative men, Dr. Evans said.

"Depression is really bad for the brain, bad for the body," Dr. Evans said. The physiologic changes that have been associated with depression include suppression of cell-mediated immunity, decreased neurogenesis in the brain, decreased heart rate variability, increased platelets, hyperactivity of the hypothalamic-pituitary-adrenal axis, and increased insulin resistance.

Dr. Evans has published an article on the topic titled, "Mood Disorders in the Medically Ill: Scientific Review and Recommendations" (Biol. Psychiatry 2005;58: 175-89). "We're trying to get this issue in front of our other colleagues in medicine," he commented. ■

Acute Hepatitis C Infections May Be Growing Challenge in HIV Patients

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Acute hepatitis C infections among individuals who are HIV positive have been documented in four countries, and treatment of this coinfection remains controversial, Dr. Marion G. Peters said at a meeting on HIV management sponsored by the University of California, San Francisco.

The largest outbreak was documented in the United Kingdom, where 210 individuals from London and surrounding cities were found to be infected. Cases also have been reported in Germany, France, and the United States.

Dr. Peters of the University of California, San Francisco, and her colleagues documented 11 cases of acute HCV infection in the San Francisco Bay Area among men who have sex with men. Presentations varied greatly, ranging from incidental elevations of aspartate aminotransferase and alanine aminotransferase levels to severe liver dysfunction.

Ten of the 11 patients had adequate CD4 counts. Five patients were treated with interferon and ribavirin, and four of them achieved sustained virologic responses. Six patients were untreated; three of them developed chronic hepatitis C and three seroconverted spontaneously, losing their hepatitis C RNA.

Among the 210 patients with acute hepatitis C documented in London, 64% were on antiretroviral therapy, and their mean CD4 count was 552 cells/mm^3, which Dr. Peters described as "perfectly adequate."

Subtyping identified five clusters of patients. The patients in each of the clusters apparently acquired the virus from a single individual or small set of individuals. One of the clusters contained 43 patients. Genotype 1a was found in 78% of the cases overall.

A case-control study involving 60 of the 210 patients documented significant levels of high-risk behavior. Patients with acute hepatitis C were more likely than were controls to be users of intravenous drugs, and they reported a larger median number of sexual partners.

Most authorities recommend treating these coinfected patients with interferon and ribavirin, but controversy remains over when to begin that treatment.

Studies of monogamous couples in which both partners have hepatitis C show that their viruses are rarely identical, and that sexual transmission occurs in only 1 case in 500. This suggests that blood-to-blood transmission, perhaps due to traumatic sexual practices, is likely to account for the transmission of hepatitis C in patients who are HIV positive.

Most authorities recommend treating these coinfected patients with interferon and ribavirin, but controversy remains over when to begin that treatment. Many patients seroconvert on their own, so the question is how long to wait.

"There's a big argument in the world literature [over] whether you should wait 12 weeks, 24 weeks, [or some other length of time]," Dr. Peters said. "We know that if you wait too long the patient will become chronic and then [his or her] chances of responding are very low. So we are fairly aggressive, and if we have a pinpoint of when they acquired [the infection], I would wait 12 weeks. If we don't have a pinpoint, it's doctor-patient preference." ■

Parkinsonism Recognized as Common HIV Complication

WASHINGTON — Treating the HIV infection may ease the symptoms of Parkinson's disease in patients with both conditions, one expert said at the World Parkinson Congress.

Using levodopa to treat Parkinson's symptoms in an HIV-positive individual "may in fact accelerate the HIV infection and it definitely can exacerbate the psychosis that is associated with the infection," said Dr. Cynthia L. Comella.

Parkinsonism is "increasingly recognized as being one of the neurologic complications of HIV," said Dr. Comella, a neurologist at Rush University Medical Center in Chicago. As many as 5% of patients with HIV meet U.K. criteria for Parkinson's disease, according to the literature, and an additional 10% exhibit parkinsonian features.

Typically, parkinsonism is seen in HIV patients with the most severe immunosuppression—with CD4 cell counts less than 40, Dr. Comella said.

Parkinsonism associated with HIV is described as symmetric and mostly bradykinetic. Rigidity is also seen, as are early gait and postural instabilities. "Particularly, it's associated with other neurological or psychiatric manifestations, such as associated myoclonus and associated dystonia," Dr. Comella said.

The etiology of parkinsonism in individuals with HIV arises from two mechanisms: direct HIV infection and opportunistic infections of the basal ganglia. HIV-infected patients are also very susceptible to drug-induced parkinsonism.

"The HIV virus seems to have a propensity to invade the basal ganglia, causing nigral degeneration," Dr. Comella said.

There is a loss of as much as 25% of nigral neurons, even in asymptomatic patients with HIV. It has also been shown that there is a reduction of dopamine in the cerebral spinal fluid in HIV patients, even in those without neurocognitive deficits.

The highly active antiretroviral drug regimens that are effective against HIV infection are also the most effective treatment for HIV-associated parkinsonism, Dr. Comella said.

In some patients parkinsonian symptoms may resolve with effective treatment of underlying opportunistic infections. The atypical neuroleptics are recommended for psychiatric abnormalities seen in these patients, particularly because these patients are more susceptible to the development of drug-induced parkinsonism with the typical neuroleptics.

—Kerri Wachter