Hemorrhage Warning Added to Aptivus Label

BY KERRI WACHTER
Senior Writer

Reports of fatal and nonfatal intracranial hemorrhage among HIV-1 infected patients taking Aptivus (tipranavir) in combination antiretroviral therapy have prompted the manufacturer to issue new safety information.

Boehringer Ingelheim Pharmaceuticals Inc. has identified 14 reports of intracranial hemorrhage, including eight fatalities, in 6,840 HIV-1 infected individuals receiving Aptivus capsules coadministered with ritonavir (Norvir) (500 mg/200 mg twice daily).

Many of these patients who developed intracranial hemorrhage had other medical conditions—CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcohol abuse—or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events.

Many of the patients who developed intracranial hemorrhage had other medical conditions or were receiving concomitant medications.

The Boxed Warnings, Indications and Usage, Warnings, Precautions, Adverse Reactions, and Animal Pharmacology sections of the label have been changed to reflect concerns about using the drug in patients at increased risk of bleeding.

No pattern of abnormal coagulation parameters has been identified in patients receiving Aptivus in general or preceding the development of intracranial hemorrhage. For this reason, routine measurement of coagulation parameters is not currently indicated for the management of patients taking the drug.

Aptivus/ritonavir therapy should be used cautiously in patients who may be at risk for increased bleeding from trauma, surgery, or other medical conditions, or who are taking other medications known to increase the risk of bleeding.

Of note, patients with advanced HIV-1 disease/AIDS have been observed to have an increased risk of intracranial hemorrhage. Investigations are ongoing to determine the role of Aptivus in the development of intracranial hemorrhage.

For more information or to report adverse reactions, contact Boehringer Ingelheim Pharmaceuticals by calling 800-542-6257 (option 4). Adverse reactions can also be reported to the Food and Drug Administration's MedWatch program by calling 800-332-1088. ■

Primary Care Physicians Are Urged To Watch for Acute HIV

BY TIMOTHY F. KIRN
Sacramento Bureau

ASPEN, COLO. — A rash in a teenager with an apparent viral syndrome should raise the diagnostic possibility of acute retroviral syndrome because of a recently acquired HIV infection, Dr. Elizabeth McFarland said at a conference on pediatric infectious disease sponsored by Children's Hospital, Denver.

HIV infection "is not necessarily a rare disease," said Dr. McFarland, director of the Children's Hospital (Denver) HIV program.

About 40,000 new cases of HIV infection occur annually in the United States, and half of them may affect teenagers. Moreover, those patients do come for medical attention.

In one urgent-care center in Boston, 1% of adults who presented with any viral symptoms had acute HIV, she noted. In a university hospital in the same city, almost 1% of persons tested for mononucleosis had acute HIV infection.

Similarly, in an emergency department in North Carolina, 0.3% of all people presenting with fever had acute HIV infection.

The most distinctive symptoms seen with acute HIV infections are rash, thrush, and neurologic symptoms, Dr. McFarland said. Around 2 weeks after exposure, 40%-90% of those newly infected with HIV will have symptoms; 96% of them will have fever, 74% will have lymphadenopathy, 70% will have pharyngitis, and 70% will have rash.

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DR. McFARLAND

As the fourth most common symptom and the only relatively uncommon one in a patient with an apparent viral illness, rash should trigger suspicion of HIV.

The appearance of the skin rash is not notable, but mouth ulcers often are also present or may occur alone.

The thrush and neurologic symptoms are not common, but like the rash, they are unusual for a viral illness. Both are seen in 12% of newly infected patients.

Other symptoms include myalgia or arthralgia (54%), diarrhea (32%), headache (32%), and nausea and vomiting (27%).

"If they have compatible symptoms, it really is reasonable to test" patients for human immunodeficiency virus, Dr. McFarland urged. ■

HAART Response Improving While Mortality Flatlines

BY DEEANNA FRANKLIN
Associate Editor

The virologic response in HIV-positive patients to highly active antiretroviral therapy has improved over the past 10 years; however, there has been no corresponding decrease in mortality, reported Dr. Margaret T. May of the University of Bristol (England) and her colleagues.

The researchers analyzed data from the Antiretroviral Treatment Cohort Collaboration, and examined 12 cohort studies.

The studies focused on characteristics of antiretroviral-naive patients at the start of highly active antiretroviral therapy (HAART) as well as their response to therapy and disease progression.

The trend toward lower CD4-lymphocyte count at the start of HAART 'might have increased the risk of immune restoration syndrome.'

The cohort studies were conducted in Europe, the United States, and Canada, and they enrolled at least 100 patients aged 16 years or older with HIV-1 infection (median age was 36 years). The participants had started antiretroviral therapy with a combination of at least three drugs, and the median duration of follow-up was 1 year.

The medications included nucleoside reverse transcriptase inhibitors, protease inhibitors, and nonnucleoside reverse transcriptase inhibitors (NNRTIs). The severity of immunodeficiency at baseline ranged from severe to nonexistent, and viral replication ranged from undetectable to extremely high, the investigators wrote (Lancet 2006;368:451-8).

Starting with data from 1995-1996 and ending in 2002-2003, the researchers evaluated the clinical prognosis of 22,217 patients based on two primary end points: AIDS events and death from all causes.

The percentage of women infected rose from 16% in 1995-1996 to 32% in 2002-2003. In 1995-1996, 56% of patients starting HAART were presumed to have been infected via male homosexual contact, but this figure dropped to 34% by 2002-2003, while the percentage of patients infected via heterosexual contact rose from 20% in 1995-1996 to 47% in 2002-2003.

"The percentage of patients infected via injection drug use declined from 20% in 1997 to 9% in 2002-2003," wrote Dr. May and colleagues. Fewer than 1% of patients were infected by contaminated blood, and about 9% had an unspecified mode of transmission.

The median CD4 cell count at the initiation of HAART rose from 170 cells per μL in 1995-1996 to 269 cells per μL in 1998, and decreased to about 200 cells per μL in 2002-2003. According to the researchers, most patients started on a protease inhibitor-based HAART regimen in 1995-1998, whereas from 1999 onwards, at least 40% started HAART with NNRTI-based regimens. The percentage of patients starting HAART with four or more drugs rose from 1% in 1995-1996 to 11% in 2002-2003.

In 1995-1996, 58% of patients achieved an HIV-1 RNA of 500 copies per mL or less by 6 months of treatment. By 1997, this figure increased to 73% of patients, and by 2002-2003, it was 83% of patients.

"The estimated probability of death up to 1 year after starting HAART did not differ greatly by calendar period. Compared with 1998, the adjusted hazard ratio for AIDS was 1.30 in 1997 and 1.35 in 2002-03," Dr. May noted.

The researchers evaluated whether the rise in AIDS events (including AIDS-related deaths) in the most recent years could be attributed to an increase in the rate of tuberculosis. Their analysis demonstrated that, compared with 1998, the rise in AIDS events in 2002-2003 "is largely attributable to an increase in tuberculosis."

"The discrepancy between the clear improvement we recorded for virological response and the apparently worsening rates of clinical progression might be related to the change in the demographic characteristics of study participants with an increasing number of patients from areas with a high incidence of tuberculosis," the investigators wrote.

The lower CD4 cell count at the initiation of HAART in recent years was of great concern, and research showed many missed opportunities for earlier diagnosis. Expansion of screenings for AIDS would be beneficial, they concluded.

In a commentary by Dr. Gregory J. Dore and Dr. David A. Cooper of the University of New South Wales in Australia, they called for more widespread tuberculosis screenings and prophylaxis initiatives, particularly for individuals from high-prevalence regions (Lancet 2006;368:427-8). The trend toward lower CD4-lymphocyte count at the start of HAART was also a point of concern, and "might have increased the risk of immune restoration syndrome," they said. "Undiagnosed active opportunistic infections at the start of HAART might be a further contributing factor." ■