Antiretrovirals May Increase Cardiovascular Risk

BY SHERRY BOSCHERT

SAN FRANCISCO — Antiretroviral medications may protect against heart attacks or increase cardiovascular risk, depending on the drug and the duration of use, recent studies suggest.

"This is an extremely complicated issue," Dr. Priscilla Hsue said at a meeting on HIV management that was sponsored by the University of California, San Francisco.

In general, the risk of MI appears to decrease in patients with HIV after starting most antiretroviral therapies, probably resulting from control of HIV-related inflammation, said Dr. Hsue, a cardiologist at the university. Two drugs, however, may increase the risk of MI with short-term use—abacavir and didanosine. Six studies (some not yet published) now have shown increased risk of MI with short-term abacavir, while three studies found no association between short-term abacavir and MI risk.

Six studies, some of which are still unpublished, have shown increased risk of MI with short-term abacavir.

DR. HSUE

Other data show increased cardiovascular risk with long-term use of protease inhibitors, she added.

In the six studies showing increased risk of MI with short-term abacavir, patients tended to be older (in their mid-40s) than the patients in the three negative studies (mid- to late 30s), she noted. Patients in the six positive studies were highly treatment experienced, and most had an undetectable viral load. In the three negative studies, patients had no previous antiretroviral use and so had higher viral loads.

Some investigators have hypothesized that the negative cardiovascular effects of abacavir appear only in patients who are virally suppressed. "That's most of the patients we see," Dr. Hsue noted.

Prior to viral suppression, any increased cardiovascular risk from abacavir may be outweighed by abacavir's beneficial effects in reducing HIV-relate inflammation. "That's speculative. We need a lot more studies to look at that," she continued.

The heart benefits of short-term control of HIV first became apparent with the Strategies for Management of Antiretroviral Therapy (SMART) study, which compared strategies of viral suppression with drug conservation (repeatedly starting and stopping therapy) in 5,472 patients. Patients in the drug conservation group were 57% more likely to have an MI, coronary intervention, or cardiovascular death, compared with the viral suppression group (N. Engl. J. Med. 2006;355:2283-96).

A separate study found improvements in endothelial function in 82 antiretroviral-naive patients after starting treatment for HIV in all three randomized treatment regimens. The vascular function improvements appeared as early as 4 weeks after starting therapy and were sustained through the 64-week study (J. Am. Coll. Cardiol. 2008; 52:569-76).

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"That was another important bit of evidence that antiretroviral therapy in the short term improves cardiovascular risk," though risk levels were not reduced to normal levels, Dr. Hsue said.

Protease inhibitors were associated with a 16% relative increase in MI risk per drug exposure per year in the 23,437-patient Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study (N. Engl. J. Med. 2007;356:1723-35). The study adjusted for the effects of dyslipidemia.

"The increased risk with protease inhibitors is not just associated with lipid abnormalities," she noted.

A separate analysis of DAD study data launched the controversy regarding MI risk with abacavir and didanosine. Data on 517 MIs in 33,347 patients who were followed for 5 years suggested a 90% higher relative risk of MI with recent use of abacavir and a 49% higher risk with recent use of didanosine, compared with patients who did not recently use those drugs (Lancet 2008;371:1417-26).

"The study was highly controversial, and a surprise to everyone. It has since been confirmed in other studies," Dr. Hsue said.

An unpublished analysis of SMART study data showed increased risk of cardiovascular disease with continuous use of abacavir, but not with didanosine. And an unpublished study done using the French Hospital Database found a doubling of MI risk in patients with exposure to abacavir in the past 6 months and cumulative exposure of less than 1 year. Another unpublished analysis of DAD study data reported increased MI risk with the use of protease inhibitors, recent use of didanosine, and both recent and cumulative exposure to abacavir, but no increased MI risk with several other antiretrovirals.

Physicians should keep these findings in perspective. More traditional cardiovascular risk factors play a much larger role in MI risk than do antiretrovirals in people with HIV, Dr. Hsue added.

"We spend millions of dollars talking about which antiretroviral medications increase cardiovascular risk, but smoking cessation is much more important" for reducing the risk of MI in patients with HIV, she said. ■

Disclosures: *Dr. Hsue reported having no conflicts of interest.*

Antiretrovirals May Contribute to Bone Loss in HIV Patients

BY SHERRY BOSCHERT

SAN FRANCISCO — People with HIV infection tend to have more risk factors for bone loss than do those without, and antiretroviral medications may be adding to that risk.

The specific role of antiretroviral therapy in bone loss has been controversial: Some studies say there is no association, but others suggest that the drugs do contribute to bone loss.

The results of two small but well-conducted studies recently tipped the emphasis toward concern about the differential effects of antiretrovirals on bone mineral density, Dr. Dolores Shoback said.

"I think it's very provocative. We certainly need more data, and this needs to be confirmed," she said at a meeting on HIV management sponsored by the University of California, San Francisco.

One randomized, controlled trial of 71 HIV-infected patients suggested that antiretroviral regimens that contain a protease inhibitor booster have a greater negative impact on spinal bone density than do regimens without a boosted protease inhibitor, said Dr. Shoback, who is professor of medicine at the university.

At baseline, 31% of the patients were osteopenic and 3% were osteoporotic.

Bone densities were retested after 48 weeks of combination HIV therapy with a nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTIs), or an NNRTI and a boosted protease inhibitor, or two NRTIs and a boosted protease inhibitor.

On average, the cohort as a whole lost 4% of lumbar spine bone mineral density and 3% of hip bone density over the course of 48 weeks (AIDS 2009;23:817-24).

"To put that in perspective, in early menopause, 1%-5% per year is about the rate of change we see at the spine, so this is a significant change in bone mineral density," she said.

In one study, patients on combination HIV therapy lost 4% of lumbar spine bone mineral density.

DR. SHOBACK

The groups that were treated with boosted protease inhibitors lost significantly more spinal density—4.4% when combined with an NNRTI and 5.8% when combined with NRTIs—compared with the NNRTI-plus-NRTI arm (1.5%).

The changes in hip bone density did not differ significantly by treatment group, Dr. Shoback reported.

The second study randomized 50 HIV-infected patients to treatment with lopinavir/ritonavir plus zidovudine/lamivudine or lopinavir/ritonavir plus nevirapine, with bone densities compared at baseline and 2 years.

The zidovudine/lamivudine group lost 6.3% of bone mineral density in the hip and 5.1% in the spine, compared with smaller losses of 2.3% in the hip and 2.6% in the spine in the nevirapine group.

Spinal density decreased mainly in the first year and then stabilized, but hip density continued to fall in the second year (AIDS 2009;23:1367-76).

The investigators speculated that zidovudine/lamivudine increased osteoclastic activity. "I think there probably is, in fact, a signal here," Dr. Shoback said.

There are not enough data yet to support changing antiretroviral regimens if bone mineral density is low, she added, but physicians should pay attention to nutrition (especially calcium and vitamin D), lifestyle factors, and weight-bearing exercise in patients with HIV.

Ongoing immune activation in HIV infection leads to high levels of cytokines.

"There pretty much isn't a cytokine that doesn't have a negative effect on bone," she said.

Many other risk factors for bone loss and fractures are more common in the setting of HIV. Five of six cross-sectional studies found low levels of hydroxyvitamin D in patients with HIV.

Compared with the HIV-negative population, people with HIV have higher rates of smoking and alcohol use, are more likely to be treated with steroids, and are more likely to have periods of immobilization and illness, bouts of weight loss, hypogonadism (in men), and amenorrhea (in women). ■

Disclosures: *Dr. Shoback has been a speaker for Novartis.*