Protease Inhibitors Linked to Increased Heart Attack Risk

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COPENHAGEN, April 26 -- The use of protease inhibitors to treat HIV is associated with an increased risk of heart attack, according to a large observational study.

The risk increase is 16% a year, which amounts to about a doubling of the risk of myocardial infarction over five years, reported Nina Friis-Mller, M.D., Ph.D., of the University of Copenhagen, and colleagues, in the April 26 issue of the New England Journal of Medicine.

The magnitude of the increase, found in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study, is similar to that seen for diabetes or cigarette smoking, Dr. Friis-Mller and colleagues added.

On the other hand, they found no association between heart attack and the use of non-nucleoside reverse transcriptase inhibitors.

The DAD study is an international collaboration of 11 research groups following 23,437 HIV-infected patients at 188 clinics in 21 countries in Europe, the United States, and Australia.

In 2003, the researchers reported that they had been able to show that anti-retroviral therapy led to an increased risk of an MI. With an additional three years of follow-up, they said, the current analysis sought to see which drugs were responsible for the rise.

The protease inhibitors, which have been shown to cause lipid abnormalities, were the prime suspect, Dr. Friis-Mller and colleagues said, and indeed analysis showed:

- During 94,469 person-years of observation, 345 patients had an MI.
- The incidence of MI was 1.53 per 1,000 person-years in those not exposed to protease inhibitors and 6.01 in those using protease inhibitors for more than six years.
- After adjustment for use of non-nucleoside reverse transcriptase inhibitors and established cardiovascular risk factors (but not lipid levels), the relative rate of MI per year of protease-inhibitor exposure was 1.16, with a 95% confidence interval from 1.10 to 1.23. The risk increase was significant at P<0.001.
- After adjustment for the use protease inhibitors and other risk factors, the relative rate per year of non-nucleoside reverse transcriptase inhibitor use was 1.05, with a 95% confidence interval from 0.98 to 1.13.
- Including lipid levels in the model reduced the effect of exposure to each drug class to 1.10 for protease inhibitors and 1.00 for non-nucleoside reverse transcriptase inhibitors (with 95% confidence intervals from 1.04 to 1.18 and from 0.93 to 1.09, respectively). The risk increase for protease inhibitors remained significant at P=0.002.

Dr. Friis-Mller and colleagues noted that the increased risk of MI associated with protease inhibitors wasn't completely explained by the changes in lipids produced by the drugs.

"The full mechanism by which protease inhibitors may lead to increased rates of myocardial infarction remains to be elucidated," they said.

While the association may seem alarming, doctors should recall that it is not in the scheme of things, said James Stein, M.D., of the University of Wisconsin in Madison in an accompanying editorial.
Dr. Stein noted that the 1.16 relative risk increase per year is "considerably smaller" than those of increasing age (1.39), male sex (1.91), and history of cardiovascular disease (1.39, 1.91, and 4.3, respectively).

Clinicians should also bear in mind that the incidence of MI among patients using protease inhibitors for more than six years was only 0.6% a year, which would be considered "low or at most moderate, depending on a patient's risk-factor burden."

"Thus, there does not appear to be an epidemic on the horizon -- simply a risk that needs to be managed" -- perhaps by targeting the modifiable risk factors associated with heart disease, rather than the lipid or other effects on anti-retroviral therapy, he said.

In an accompanying Perspective article, two Boston researchers cautioned that the design of the DAD study leaves it open to possible confounding by unknown factors.

Unlike randomized controlled trials, observational studies "raise complex questions concerning both the potential confounding of risk associations and the mechanisms by which treatment might cause an adverse effect," said Michael Hughes, Ph.D., and Paige Williams, Ph.D., both of the Harvard School of Public Health.

They commended the DAD researchers for finding ways of standardizing the risk of adverse events from treatment and said the study "should thus serve as a model for other studies."

However, they said, the analytical issues are sufficiently complex that "replication of findings in different studies, ideally using a variety of analytic methods, is important."

The DAD study is supported by the Oversight Committee for the Evaluation of Metabolic Complications of HAART, a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the FDA, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the U.S. market. The study also has support from the Netherlands Health Insurance Fund Council, the Agence Nationale de Recherches sur le SIDA, the Commonwealth Department of Health and Ageing, the Australian National Council on AIDS, Hepatitis C and Related Diseases' Clinical Trials and Research Committee, the Fondo de Investigacin Sanitaria, the Fundacin para la Investigacin y la Prevencin del SIDA en Espa, the National Institute of Allergy and Infectious Diseases, the European Commission, and the Swiss National Science Foundation.

Dr. Friis-Mller reported receiving lecture fees from Bristol-Myers Squibb and other members of the study writing group report financial associations with Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Hoffmann-La Roche, Theratechnologies, Tibotec, Merck, Abbott, Pfizer, TRB Chemedica, Johnson & Johnson, and Janssen-Cilag.

Dr. Stein reported receiving consulting fees from Abbott and Bristol-Myers Squibb and grant support from Bristol-Myers Squibb. Dr. Hughes reports being a paid member of the data and safety monitoring committee for Boehringer Ingelheim, Tibotec, and Virionyx.

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