Abacavir and Cardiovascular Risk: Is There or Isn't There?

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New data from the SMART trial indicate that abacavir—found in Ziagen, Epzicom and Trizivir—is associated with an increased risk of cardiovascular disease, echoing the findings of a recent analysis of the D:A:D study. The study results, reported at the XVII International AIDS Conference (IAC) in Mexico City, also point to a possible reason for the elevated risk—higher levels of two inflammatory proteins that may be associated with disease of the arteries. However, as was also reported at IAC, an analysis of 54 clinical trials in which abacavir was used failed to find any such risk.

Abacavir was initially associated with an increased risk of heart attacks in the 33,000-patient Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. According to a report at the Conference on Retroviruses and Opportunistic Infections in February in Boston, abacavir increased the relative risk of a heart attack by 90 percent and didanosine (Videx) increased the risk by 49 percent, despite the fact that neither drug has ever been known to contribute in any way to cardiovascular disease.

According to the D:A:D report, the risk of a heart attack only persisted while patients were on either drug. If they stopped taking them, the risk decreased.

Quadrupled Heart Attack Risk in SMART Study

The SMART study enrolled HIV-positive individuals with CD4 counts above 350, who were either on antiretroviral (ARV) treatment or who had not yet started. They were randomized to one of two groups: a continuous treatment (CT) group that did not stop HIV treatment, or an deferred treatment (DT) group that started treatment only once the CD4 count fell below 250; treatment was discontinued once the CD4 count rose to 350. If the count dropped below 250 again, treatment was restarted..

Various findings from SMART have been published in medical journals and reported at scientific conferences. In the most recent analysis, Jens Lundgren, MD, of the Copenhagen HIV Programme and his colleagues looked for associations between nucleoside reverse transcriptase inhibitor (NRTI) use among the 2,750 patients in SMART's CT group and the risk of various cardiovascular diseases, such as heart attacks, strokes and coronary artery disease.

Patients using abacavir were 4.3 times more likely to have a heart attack than those not using the drug. Another analysis included the risk of a major cardiovascular event, including a heart attack, stroke, coronary artery disease or the need for cardiovascular surgery. Here the risk was 1.8 times

higher. And using an expanded definition of a cardiovascular event—including a diagnosis of congestive heart failure, peripheral artery disease or the need for cardiovascular treatment—the risk was 1.9 times higher among those taking abacavir compared with those who weren't using the NRTI.

Didanosine was not found to increase the risk of cardiovascular events in the SMART study, which was the only major difference in findings compared with the D:A:D study.

Dr. Lundgren emphasized that the increased risk associated with abacavir is relative to patients' other cardiovascular risk factors. The cardiovascular risk of abacavir, he and his SMART colleagues found, was only significant among those with five or more other risk factors, including being male, smoking cigarettes and having high blood pressure, increased cholesterol or diabetes. The increased risk was not significant in those with fewer than five other cardiovascular risk factors.

The SMART researchers also examined why patients on abacavir experienced elevated cardiovascular risks. Focusing on six key blood tests, or "biomarkers," believed to be associated with inflammation and damage of the cardiovascular system, the SMART investigators found two that were significantly increased in those taking abacavir compared with those taking other NRTIs: high sensitivity C-reactive protein (hsCRP; 27 percent higher in those taking abacavir) and interleukin-6 (IL-6; 16 percent higher in those taking abacavir).

Lundgren explained that both proteins are associated with inflammation and hardening of the blood vessels (artherosclerosis). In turn, he concluded, abacavir treatment may cause some degree of inflammation that can increase the chance of a cardiovascular event in patients with other important risk factors for heart disease.

No Confirmation in GSK Analysis of 54 Abacavir Studies

To make sense of the abacavir-cardiovascular link initially found in D:A:D, researchers associated with GlaxoSmithKline (GSK)—under the direction of John Pottage, MD, vice president for global clinical development at GSK—analyzed 54 studies in which patients took either abacavir or a competitor NRTI.

Taken together, the studies included roughly 14,000 HIV-positive patients—including 500 children—more than 9,500 of whom took abacavir. While the average age of the patients entering SMART was 44, the average age of those in the pooled abacavir studies reflected a slightly younger patient population. The average age among those entering studies for patients starting treatment for the first time was about 36, whereas it was 40 among those entering studies intended for treatment-experienced patients.

Using an analysis similar to the one employed in SMART, Dr. Pottage and his colleagues reported that the frequency of cardiovascular events for both groups—those using ARV regimens with and without abacavir—was low and similar to the general population. Among those taking abacavir, there were 2.5 cardiovascular events per 1,000 patients, compared with 4.1 cardiovascular events per 1,000 patients taking non-abacavir regimens. Rates of documented heart attacks were even lower—1.1 heart attacks per 1,000 patients taking abacavir, vs. 1.4 heart attacks per 1,000 patients receiving an HIV treatment regimen not containing abacavir.

One study conducted by GSK, the HEAT study comparing Epzicom (abacavir plus lamivudine) to Truvada (tenofovir plus emtricitabine), has collected biomarker data to compare with SMART's hsCRP and IL-6 findings. And in stark contrast with the SMART findings, compared with pre-treatment levels, hsCRP and IL-6 levels decreased in both groups after 48 and 96 weeks of treatment. Additionally, GSK reported, there were no significant differences between the two groups with respect to any biomarker levels at any time point during the study.

Whether the differences between the studies—such as the age difference between those in SMART and those in the GSK studies—might explain the different results has not been determined. It is also important to stress that studies showing an association, or link, between a medication and an adverse outcome do not prove that one causes the other—additional studies designed specifically to look at causation are required.

Moving forward, both Pottage and Lundgren argue that much more comprehensive cardiovascular data from a large and long-term clinical trial will ultimately be necessary to determine whether abacavir truly is linked with, and a cause of, increased cardiovascular risk.

Until then, however, Lundgren stresses that, based on the results of D:A:D and SMART, the risk of a heart attack or another cardiovascular event is only relevant for those with other well-established risk factors.
