Scientists Still Seeking Clues to Abacavir Heart Attack Mystery

February 18, 2009 By David Evans

Seeking to unravel the mystery surrounding possible heart problems in people taking abacavir (found in Ziagen, Epzicom and Trizivir), researchers have found that HIV-positive men and women on the drug don't have higher levels of blood vessel inflammation, as was previously suggested, but may have overly reactive blood clotting factors that potentially lead to heart attacks. The presentations were given Wednesday, February 11, at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal.

At last year's CROI, researchers first reported that people taking abacavir may have an increased risk for a heart attack. Paradoxically, the increased risk only exists while a person is taking the drug, and it does not increase over time. Since that report, a number of studies on the topic have been published or presented at conferences, with some echoing the earlier findings and others showing no increased heart attack risk.

In an effort to explain the mechanism behind the potential increased risk, researchers first turned to blood proteins associated with blood vessel inflammation, which have been linked to heart attacks in HIV-negative people with heart disease. These proteins include D-dimer, high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6). Some studies found increases in these proteins in people on abacavir, while others showed no increases.

Not Inflammation After All?

Researchers from two large HIV natural history studies—which follow HIV-positive people over long periods of time—sought to determine whether people in their cohorts had elevated inflammatory proteins when taking abacavir. The cohorts included were the Multicenter AIDS Cohort Study (MACS), which has been following HIV-positive men since the 1980s, and the Women's Interagency HIV Study (WIHS), which has been following HIV-positive women since the early 1990s. Frank Palella, MD, from the Feinberg School of Medicine at Northwestern University in Chicago, presented the findings from the MACS and WIHS studies.

Palella's team measured hsCRP and D-dimer levels in 326 men and women, and IL-6 levels in 290. In each group, roughly half were on a regimen containing abacavir and half were on a regimen without it. The abacavir and non-abacavir groups were matched in terms of age and heart disease risk factors. The levels of the inflammatory proteins were measured before a person started his or

her antiretroviral (ARV) regimen and a minimum of several months after starting treatment.

Palella and his colleagues found no significant differences in the inflammatory protein levels of people on an abacavir-containing regimen compared with people on a regimen without abacavir. Overall, D-dimer levels fell and hsCRP levels rose in both the groups after starting treatment, but there was no difference in levels between the groups.

Data from another study—a clinical trial comparing Epzicom to Truvada—reported similar findings. Grace McComsey, MD, of Case Western Reserve University School of Medicine in Cleveland and her colleagues reported on an analysis from the GlaxoSmithKline-sponsored HEAT study. They found that both Epzicom and Truvada recipients saw reductions in their hsCRP, IL-6 and sVCAM-1 (another inflammatory protein) levels during the 96-week follow-up period.

Blood Clotting Factors Could Be the Link

On a different track, Claudette Satchell, a PhD candidate from the University College of Dublin in Ireland, and her colleagues followed up on hints that abacavir could increase the likelihood of blood clot formation by affecting platelet function. When platelets are activated, they change their shape and their surface structure and are more likely to join with collagen and other platelets to form blood clots. Studies in HIV-negative patients have found that blood clots, resulting from higher platelet reactivity levels, correspond to a higher risk for heart attacks and strokes.

Satchell and her colleagues compared the degree of platelet reactivity in 30 people taking abacavir with platelet reactivity in 28 people on an ARV regimen that did not include abacavir. Platelet reactivity was assessed by exposing a person’s blood to increasing concentrations of several different compounds known to affect platelet function.

Satchell reported that the degree of reactivity to the different compounds varied in both groups, but that overall people taking abacavir had significantly higher levels of platelet reactivity than people not taking abacavir. This difference remained consistent when Satchell’s group controlled for factors such as smoking history, diabetes, blood pressure and family history of cardiovascular disease.

Satchell confirmed that all the individuals in the study received an HLA-B*5701 test before starting treatment to confirm whether they were allergic to abacavir. This is an important point, since not all studies looking at the potential increase in heart attack risk with abacavir have controlled for this factor. Some researchers have theorized that the increased risk could be due to inflammation from abacavir allergic reactions. However, the fact that Satchell found increased platelet reactivity in people with no abacavir allergy suggests that the influence of HLA-B*5701 does not explain the increased risk for heart attacks seen in some studies.
