Baraclude Induces HIV Drug Resistance

March 5, 2007 By Tim Horn

New research concludes that hepatitis B virus (HBV) treatment Baraclude® (entecavir) is active against HIV, suggesting that that the drug will need to be used with caution in people coinfected with both viruses. The data, reported at the 14th Conference on Retroviruses and Opportunistic Infections, follows recent warnings from the U.S. Food and Drug Administration (FDA) and Bristol-Myers Squibb (BMS) involving Baraclude's potential to cause HIV drug resistance if used as monotherapy to treatment hepatitis B.

For HIV-positive people with chronic hepatitis B, it is notable that some of the medications used to treat HIV infection can also be used to treat HBV disease. For example, Viread® (tenofovir), Emtriva® (emtricitabine), and Epivir® (lamivudine) are believed to be highly effective against HBV, although Epivir is the only one of the three approved for the treatment of both infections.

People infected with both viruses may benefit from treatment regimens that contain Viread and Emtriva or Epivir. In fact, experts generally recommend holding off on the use of these drugs in people coinfected with HIV and HBV until combination antiretroviral therapy is to be started, such as when the CD4 cell count falls below 350.

But what about patients who do not require combination antiretroviral therapy – due to a high CD4 count, for example – but do require therapy for their hepatitis B? One possibility is to use an approved hepatitis B treatment, as monotherapy, that is active against HBV but not HIV.

When Baraclude was approved for hepatitis B in 2005, the package insert for the drug claimed that it did not have any activity against HIV. This was heralded as good news, as it meant that Baraclude could be used as monotherapy in coinfected patients to treat HBV without the risk of HIV becoming resistant to the drug and cross-resistant to other nucleoside reverse transcriptase inhibitors.

In recent months, however, there have been case reports of coinfected patients who were taking Baraclude monotherapy and saw their HIV viral loads drop significantly, suggesting that the drug is active against HIV and associated with HIV drug resistance. For example, BMS has reported the experience of a 31-year-old HIV/HBV-coinfected man who began Baraclude monotherapy in early 2006. Prior to starting the drug, his HIV viral load was 35,000, with no evidence of HIV drug resistance. Within two months, not only did his HBV viral load drop, but so did his HIV viral load.

Six months after initiating treatment with Baraclude, his HIV had developed the M184V mutation in its reverse transcriptase gene, known to cause high-level cross resistance to Epivir and Emtriva.

At CROI, researchers at Johns Hopkins University School of Medicine reported the results of test tube experiments in which HIV-infected CD4 cells were exposed to increasing concentrations of Baraclude. They found that the drug was active against HIV's reverse transcriptase gene and that it was a potent inhibitor of HIV replication. Ongoing exposure to the drug also demonstrated the emergence and proliferation of the M184V mutation.

The conclusion of the Johns Hopkins study, along with the three case reports, indicate that the drug is effective against HIV and, if used as monotherapy, can rapidly select for a key mutation that confers high-level resistance to two vital HIV medications.

The Johns Hopkins researchers suggested that Baraclude should not be used as monotherapy in coinfected patients. The U.S. Food and Drug Administration, along with BMS, seem to agree and are notifying healthcare provider that the Baraclude package insert is being revised to reflect this new information.

Source:

McMahon M, Jilek B, Brennan T, et al. **The anti-hepatitis B drug entecavir inhibits HIV-1 replication and selects HIV-1 variants resistant to ARV drugs** [Abstract 136LB]. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles, 2007.
