Drug Monitor

Balancing Antiretroviral Benefit and MI Risk

Combination antiretroviral therapy has revolutionized HIV treatment, but it also may contribute to factors that increase the risk of myocardial infarction (MI). After analyzing data from their large, prospective, observational study, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group found that the risk of MI rose with each year of antiretroviral therapy.

The median known duration of HIV-1 infection among the 23,468 study participants (from 188 clinics in Europe, Australia, and the United States) was 3.5 years. At baseline, 26% of the participants already had been diagnosed with AIDS, 81% had received at least one antiretroviral drug, and 74% had received combination antiretroviral therapy.

Since the patients were relatively young (median age, 39 years), the prevalence of previous cardiovascular disease was low (1.5%). Many patients, however, had such cardiovascular risk factors as current or previous smoking, diabetes, hypertension, or dyslipidemia.

Between December 1999 and February 2002, 126 patients had MIs—a rate of 3.5 per 1,000 person-years. When the researchers factored in duration of antiretroviral therapy, they found a 26% relative increase in the rate of MI per year of therapy during the first four to six years. Other factors that independently predicted MI were smoking, previous cardiovascular disease, and male sex.

The researchers say a link between antiretroviral therapy and MI is plausible, since combination antiretroviral therapy can cause metabolic changes (such as dyslipidemia, insulin resistance, and overt diabetes mellitus) that are known risk factors for cardiovascular disease. In their study, total cholesterol and triglyceride levels appeared to contribute to the association between antiretroviral therapy and MI—but diabetes, hypertension, and lipodystrophy did not. The researchers call for randomized trials to clarify whether there is a true causal relationship.

Regardless, they stress that the absolute risk of MI in their study remained low, and that it "must be balanced against the marked benefits from antiretroviral treatment." Before the advent of combination antiretroviral therapy, the annual mortality rate among patients with HIV-1 infection exceeded 20%, compared with less than 2% in this study. Moreover, progression of HIV-related disease was the leading cause of death in this study—MI was the cause of only 6.4% of deaths. Even patients who had been taking antiretroviral treatment for four to six years had an annual MI rate of less than 0.6%. Finally, only a portion of the apparent excess risk could be attributed to combination antiretroviral therapy.

Source: *N Engl J Med.* 2003; 349:1993–2003.

Anticancer Drug Aces Phase III Trial

In May 2003, bortezomib received an accelerated FDA approval due to promising rates of tumor response in patients with refractory multiple myeloma. Now, preliminary results from a phase III trial—involving 670 patients with relapsed or refractory multiple myeloma who received one to three previous therapies—indicate such a clear advantage for the drug that the manufacturer, on the recommendation of an independent data monitoring committee, has halted the control arm of the study to give patients the opportunity to switch to bortezomib.

The drug, which is the first in a new class called proteasome inhibitors, was significantly more effective at reducing time to disease progression (the trial's primary endpoint) when compared with high dose dexamethasone, the current standard of care. Data on secondary endpoints (including measurements of safety and survival) were found to support the primary endpoint and the decision to halt the dexamethasone arm. ●

Sources: Millennium Pharmaceuticals News Release. December 15, 2003.

FDA News Release. May 13, 2003.