Hope is rising

AIDS research and treatment conference points to encouraging advances, and much yet to be learned

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by Bob Roehr

The wave of optimism in AIDS research and treatment that exploded in these halls last year continued to spread and deepen at the Third Conference on Retroviruses and Opportunistic Infections. The premier research gathering drew 2,000 top scientists and clinicians from around the world for five days of meetings in Washington, D.C., in February.

The big news last year was a quantum leap in therapy. It included exciting but limited initial clinical data on combination therapies of 3TC with AZT, and the new family of drugs known as protease inhibitors, which attack the virus at a different stage in its life cycle than do nucleoside analogs such as AZT. 3TC and Saquinavir, the first protease drug, were approved for general use in December. The Food and Drug Administration has since approved the second protease inhibitor, Ritonavir, and approval seems imminent for a third, Crixivan.

Findings last year were often based on clinical trials involving a mere handful of patients over a dozen weeks. Data on ongoing trials this year involve significantly larger groups of patients tracked for more than a year.

Most encouraging is that the expanded data continues to show that protease inhibitors are powerful antiviral medications, and they appear to remain effective during extended periods of use.

"There is no question that these drugs are at least tenfold, and in some cases more multiples, more potent than drugs we have been using for the last eight to nine years," said Robert T. Schooley, M.D.

Schooley chaired the scientific program committee of the conference and heads up the Health Sciences Center at the University of Colorado in Denver.

Protease Inhibitors

The pharmaceutical giant Merck led the bandwagon of those touting protease inhibitors at the conference with data on its product Indinavir (trade name Crixivan) used in combination with AZT and 3TC in patients with a range of 50 to 400 CD4 cells. Scientists have long theorized that a triple drug combination would offer greater clinical benefits than single or double treatment therapy.

Merck's data appear to bear this out. Four months into the trial the amount of HIV circulating in the blood was reduced by 99 percent, falling below levels detectable by current tests in 85 percent of the patients.

"It is the best result seen to date," said Dr. Emilio Emini, chief AIDS researcher with the company.

Emini and others caution that the data are only preliminary, involving 26 patients in the triple combination arm of the trial, only eight of whom have gone beyond week 16. The results are encouraging enough, however, that an FDA advisory panel recommended at the end of February that Crixivan be approved for general use.

Abbott Laboratories won FDA approval Feb. 23 to market its protease inhibitor, Ritonavir, which will be sold under the brand name Norvir. The company will continue to test the drug. Abbott's is a larger trial, involving a thousand more advanced patients (CD4 count of 100 or less) on the drug for 16 weeks. Patients were allowed to continue taking other medications except another protease inhibitor.

The Ritonavir arms showed a 40 to 50 count median rise in CD4 cells, and an increase in CD8 from a median baseline of 500 to 800. The incidence of opportunistic infections was less than half that of the control groups.

"The slope seems to be going back up at the end," noted Anthony S. Fauci, M.D., director of the National Institute of Allergies and Infectious Diseases at the National Institutes of Health. He asked if there were any "resistance data," and was told those studies have not been completed.

That is a key unanswered question with all of the protease inhibitor and combination therapies. It appears that viral resistance to drugs emerges sooner or later depending on how they are used.

"If we use them improperly, we are going to mess up the benefits," warns Douglas D. Richman, M.D. He is a leading researcher at the University of California at San Diego and vice-chair of the conference.

Further clinical trials seem likely to indicate the most promising treatment regimes.

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PHOTO BY BOB ROEHR

Kaposi's Sarcoma

Research published little more than a year ago first indicated that Kaposi's sarcoma is caused by a virus, KSHV, in the herpes family. Data presented at the conference reinforced that view: 93 percent of the KS lesions examined showed evidence of KSHV.

"Detection of KSHV predicts development of KS and correlates with immune system suppression," said Dr. Patrick S. Moore of the Columbia University School of Public Health.

KSHV appears to be closely related to the Epstein-Barr virus, but much remains unknown. It may in fact be part of a family of up to three separate, closely related viruses, Moore explained. KSHV is difficult to maintain in a cell line and, therefore, to study.

There is no direct evidence that KSHV is sexually transmitted. Though it is present in semen, the levels are so low that transmission is thought to be extremely difficult. It has appeared primarily in gay men, in geographic clusters, and seems to be less prevalent than it was years ago.

KSHV has been detected in 91 percent of the semen of HIV-positive gay men, but also in 23 percent of healthy sperm donors. That has led to "speculation the virus might be ubiquitous and needs something to activate it," says Moore.

He believes KSHV is an infection that occurs after infection with HIV.

"There is strong evidence [that] we are seeing seroconversion of individuals," he says.

He is not sure of the incubation period but suggests it could be as short as six months, with a mean time of one and a half years before progression to a KS diagnosis.

The difficulty in maintaining cell lines contributes to limited lab work on therapy. Some researchers have speculated that medications used against other herpes viruses might have an effect on KSHV, but no data have been presented.

Wasting Syndrome

AIDS-associated wasting isn't as simple as reduced levels of eating or absorption of food by the body. Research is also pointing to dysfunctions at the cellular level.

Dr. Carl Grunfeld at the University of California at San Francisco proposes "a theory of compounding factors: HIV infection and secondary infection," which lead to weight loss.

He found that 82 percent of those who lost more than 4 kilograms in four months also had a secondary infection. Most common were gastrointestinal problems and diarrhea. Eighty-three percent gained weight during recovery periods but never restored the loss, and so ratcheted down in weight with each bout of infection.

"Failure to recover is the major problem.... If you can treat the infection, things are going to get at least somewhat better," Grunfeld advised.

Dr. Donald P. Kotler at St. Luke's-Roosevelt Hospital Center in New York said, "Reduced food intake does not explain it all. There are also metabolic changes."

He pointed to appetite stimulants, which increase food intake but show little impact on body cell mass. Most of the increase goes to fat, not to lean body mass.

Dr. Morris Schambelan, also at U.C. San Francisco, discussed data on how growth hormones "increase both weight and lean body mass," even turning fat into lean body mass. He has been able to sustain these results for two years. He pressed for studies to determine what is the appropriate patient population, when to start therapy, and what is the optimum dosage and regime.

Viral Load

The "viral load," the amount of HIV virus RNA gene package in the bloodstream, "is a better predictor than CD4 T-cell counts of how quickly people with HIV infection will progress to AIDS," said John W. Mellors, M.D., of the University of Pittsburgh Medical Center. "The quantity of circulating virus is the most significant determinate of progression to AIDS. Having a high RNA is bad news, having a low RNA is good news."

He called it "a one- to three-year lead time over CD4 as a predictor."

The average of two tests taken six months apart is more accurate than a single baseline test.

The test that measures viral load is called branched DNA, or bDNA. It is experimental technology, approved only for limited use in clinical trials. Chiron Diagnostics is trying to develop a commercially viable product that will be easier to handle and less expensive. Indications are that it is at least six months away from approval and marketing.

Mellors' work was a retrospective study that tested blood gathered since 1984 and matched it against the natural history of its donors. He was able to track individuals over several years, both prior to and throughout various therapies, and measure the effect of treatments on their viral load.

He found that 19 percent of those studied were rapid progressors, proceeding to an AIDS diagnosis within five years, and 12 percent were slow or perhaps even nonprogressors, likely to remain AIDS-free at the end of 20 years.

Douglas D. Richman, M.D., a leading researcher at the University of California at San Diego and vice chair of the conference, put it in stark perspective: "If someone comes in with 200,000 copies of RNA, I don't care what their CD4 count is, that is telling you their chances of having AIDS within two years is approaching 50 percent. That CD4 count is a false reassurance."

He sees viral load measurement as an important surrogate marker for staging therapy and believes that it will become useful in monitoring treatment as the knowledge base grows.

Clyde S. Crumpacker of Harvard University provided some of the first components toward that base. He used viral load tests to show that high resistance to AZT predicts accelerated progression to an AIDS diagnosis and death. Conversely, 16 weeks of AZT therapy is enough to disrupt the predictive value of a baseline RNA test. Therapy that brings a 15 percent drop in RNA levels correlates with a 27 percent decline in clinical events.

The study seems to solidify use of the viral load surrogate marker as the new gold standard by which drug efficacy and treatment will be monitored. By pointing out inadequacies in the previous lead surrogate—CD4 counts—however, it raises some questions on the utility of earlier research based on that marker. Furthermore, lack of a commercially available viral load test will make it difficult to translate research advances into broad clinical practice. The transition from one measurement to another seems likely to be rocky.