AZT Still on Trial

Two committees looking at one set of data have come to radically different conclusions about the anti-AIDS drug AZT. In the United States, a committee of the National Institute of Allergy and Infectious Diseases decided that AZT was too good to withhold and stopped a trial involving HIV-infected individuals so that some of those receiving a placebo could be offered AZT. But after reviewing the same data, a group of European researchers decided that the U.S. evidence was not strong enough to warrant terminating Concorde I, a similar study being conducted jointly in France and England. Meanwhile, a third trial of asymptomatic, HIV-infected patients being conducted by the Veterans Administration will also proceed and may, in fact, provide a bridge between the two studies.

The AIDS Clinical Trials Group at NIAID captured headlines when it stopped part of its trial—dubbed 019—in mid-August because AZT appeared to delay the onset of symptoms. At the time, NIAID estimated that as many as 40,000 patients in the United States could benefit from the drug: the only ethical thing to do was to offer them AZT (*Science*, 25 August, p. 811).

The Concorde I trial, which began 6 months ago, has also been comparing AZT with a placebo and was designed with the 019 protocol very much in mind. So when NIAID stopped 019, Concorde I officials were anxious to know why. But they had to wait until last month for a briefing by U.S. health officials. Before that, because of the embargo prior to full publication, they were given little more than the data made available to the general public.

The explanation they finally received left them puzzled. Jean-Pierre Aboulker, the trial physician responsible for the French side of Concorde, said, "The results we have seen do not allow us to give a strict recommendation to give AZT." Under the terms of the prepublication briefing, Aboulker cannot justify this statement with details. Nevertheless, Concorde I has now been modified to allow physicians to prescribe AZT openly if they choose to, with a request that they continue to monitor patients for long-term effects.

Aboulker says it is "very difficult to know if it is a good thing to do," but concedes that some patients and some physicians may want to switch to AZT on the basis of the limited information available from 019.

The different attitudes of the U.S. researchers and their British and French counterparts to the same set of results reflect the different perceptions surrounding AIDS on either side of the Atlantic. Ian Weller, Aboulker's British counterpart, thinks the sheer numbers in the United States have created greater pressure for results.

Anthony S. Fauci, director of NIAID, said when NIAID's trial stopped that "this study has clearly demonstrated that early treatment with zidovudine [AZT] can slow disease progression." But Ian Weller told *Science* that because the average duration of treatment in 019 was just a year, there are no data on long-term effects. The decision to stop 019, Weller believes, will make such data difficult to obtain in the United States.

Weller is also worried that treating asymptomatic patients "may be squandering the benefits of zidovudine [AZT] and perhaps even doing long-term harm." Although Weller is privy to the full data from 019—the results have not yet been published—he is forced to use numbers gleaned from the press release announcing the end of 019 to support his argument: without AZT, almost 9% progressed to AIDS or AIDS-related complex (ARC) within a year. With AZT, the numbers halved. But even without AZT, Weller stresses, 90% are still well a year later.

"The Americans see a significant short-term benefit," Weller admits, but he thinks it may prove more useful to limit AZT to patients who have developed the infections that characterize ARC. "It's not as if these events are unmanageable," he says, and treatment with AZT seems to produce resistant virus, two factors that may make AZT more valuable in the later stages of HIV infection.

"The worry is that when [the patient] really needs the drug, it is not going to be of benefit," said Weller.

But Dan Hoth, director of the division of AIDS at NIAID, says the priority in the United States is to make a drug of proven benefit available now and take the chance that it might not work in the future. "It's all a question of how you assess the fact that you have information now that the therapy is useful."

An important difficulty that Weller and Aboulker have with the results from 019 is that they do not square well with the natural history of AIDS, as it is currently understood. Progression from HIV infection to ARC to AIDS is associated with a decrease in the number of CD4 cells in the patient's immune system. Physicians expected AZT to be of most benefit in patients with especially low CD4 cell counts, say below 200, but 019 offers no evidence that this is so.

Aboulker says it is "rather surprising that there is no observable benefit" for patients with very low CD4 counts. Weller feels it "isn't right." It is, according to Weller, "the big mystery." If patients with lower CD4 counts had benefited most, Weller says, "that would have fitted so well with the natural history data, you would have seen clinical practice change overnight."

The answer may lie with Protocol 298 of the Veterans Administration. Initially, it compares AZT with a placebo in patients who have CD4 cell counts between 200 and 500 CD4 cells per cubic millimeter of blood. The potentially illuminating aspect of VA 298 is that patients on placebo are switched to AZT when their CD4 counts drop below 200. "It might be considered a trial of early versus late AZT," said Mitchell Gail, a statistician at the National Cancer Institute who is on the data monitoring board of VA 298. Weller is "delighted" that VA 298 is continuing: "It's nice not to be out on our own," he said. ■ **JEREMY CHERFAS**

Young's Sudden Move

On 18 December, Frank E. Young, presently commissioner of the Food and Drug Administration, will move to the Department of Health and Human Services headquarters as deputy assistant secretary for health/science and the environment. Young held the FDA post for 5 years.

Federal officials were hard pressed to put a positive spin on Young's impending job change. "It's not a demotion," said PHS spokesman Jim Brown. No replacement has been named.

Although the recent scandal at FDA over the generic drug approval brought noisy criticism for FDA, Young himself received a chorus of praise when news of his departure was announced on Monday, 13 November. Congressman John D. Dingell (D–MI), who has chaired hearings investigating the generic drug affair, said Young "acted honorably, and I consider him a friend and hold him in high regard." The Pharmaceutical Manufacturers Association called Young's achievements as FDA commissioner "numerous and sweeping."

Young's new position has not existed within HHS. He will be a senior adviser to Public Health Service head James O. Mason. His duties will include coordinating PHS activities in physical sciences, biotechnology, nutrition, and food safety. He is also charged with "identifying and analyzing technological developments that can be expected to impact on the nation's health care system." ■ **JOSEPH PALCA**