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Drug may help some AIDS patients

AZT studies confirm that, while apparently not a cure, there is a lower mortality rate among those administered the drug.

At a Sept. 19 press conference in Washington, D.C., officials of the U.S. Department of Health and Human Services and representatives of the Burroughs Wellcome pharmaceutical firm announced the first drug that may help some AIDS patients. The drug, 3'-azido-3'-deoxythymidine (AZT), is an analog of thymidine, one of the nucleotide bases of the genetic material DNA, and binds to the reverse transcriptase enzyme which the AIDS virus uses to reproduce its genetic material. As a result of this binding, the enzyme is inhibited and hampers the ability of the Human Immunodeficiency Virus (HIV) to produce new particles.

AZT was one of a group of chemicals, known as pyrimidine analogs, synthesized in the 1960s as potential anti-cancer agents. The mode of action of these agents is to combine with the DNA of rapidly dividing cells, such as cancer cells, and produce a defective DNA which results in the inability of the cells to reproduce. It did not show significant anti-cancer activity and languished on the shelf until November 1984, when Burroughs Wellcome researchers found that it inhibited certain viruses in test-tube cultures.

Based on these preliminary results, the company sent the compound to three other laboratories to test its activity against HIV. Duke University, the National Cancer Institute, and the Food and Drug Administration conducted tests from November 1984 to January 1985. After subsequent toxicologic and pharmacologic studies, an application for an Investigational New Drug exemption was filed and approved in June 1985.

Phase I studies, designed to assess safety and pharmacological behavior of the drug, began in July 1985 at the Clinical Center of the NIH and were expanded to Duke University, the National Cancer Institute, and the University of Miami. The results were reported in the March 15, 1986 issue of *The Lancet*. For six weeks, 19 patients at the participating institutions were treated under four different dosage schedules.

The phase I studies showed that AZT crossed the blood-brain barrier and therefore had the potential to affect virus which had entered the nervous system. Side effects were relatively mild, and a number of patients showed evidence of partial restoration of immune function. A small number, on the highest dose, became virus negative.

On the basis of these results, the first Phase II trial began in February 1986 with 12 centers in the United States participating. The first patient was enrolled on Feb. 18, 1986 and by the end of June, 282 patients had been enrolled.

The purpose of Phase II trials is to determine if the drug is actually effective in treating the disease. This is done by a double-blind study, in which half the patients receive the investigational drug and the other half receive either a standard treatment or a placebo. In this case, since there is presently no effective treatment for AIDS, the control patients received a placebo.

Because of the potential problems of drug toxicity to the patients receiving the drug, and the possibility that the placebo treated patients were being denied a life-saving treatment, the data were monitored on a regular basis by a board of experts independent of the drug company and the researchers conducting the study. An interim analysis presented to this Data and Safety Monitoring Board showed a significant difference in death rate between patients receiving AZT and those receiving a placebo. So far 16 of 137 patients receiving the placebo have died, as compared to 1 of 145 patients receiving AZT. In addition, AZT treated patients gained weight, showed improved immune function, and have had fewer AIDS-related complications than the placebo group.

This dramatic difference in mortality prompted the Data and Safety Monitoring Board to recommend that the study be stopped and that AZT be given to all patients in the study.

Burroughs Wellcome will make the drug available, free of charge, through the NIH, to "a certain narrow category of patients with AIDS who have been shown in this clinical trial to have received some benefit from AZT."

While these studies indicate that AZT can decrease mortality in some AIDS and ARC patients, it does not yet represent a cure, in the sense of permanently eliminating the virus. The drug does show bone marrow depressing effects, and it is not yet known how long patients can tolerate it, or if the effects will last. Indeed, patients under treatment with AZT may still be infectious to others and hence AZT would do little if anything to stop the spread of the virus. The promise of AZT is that it may extend the life of AIDS victims till more definitive treatments can be developed.