New AIDS Drug Passes First Clinical Test

The drug DDI appears to be safe and may be active against the AIDS virus in patients. Efficacy studies may begin this fall

THE RESULTS of the first clinical trials of the new AIDS drug known as DDI are coming out—and they look promising. On page 412 of this issue of *Science*, Robert Yarchoan, Samuel Broder, and their colleagues at the National Cancer Institute report that the drug appears to be safe. In contrast to AZT, the only drug currently approved by the U.S. Food and Drug Administration for combating AIDS virus infections, DDI has so far shown few toxic side effects in AIDS patients.

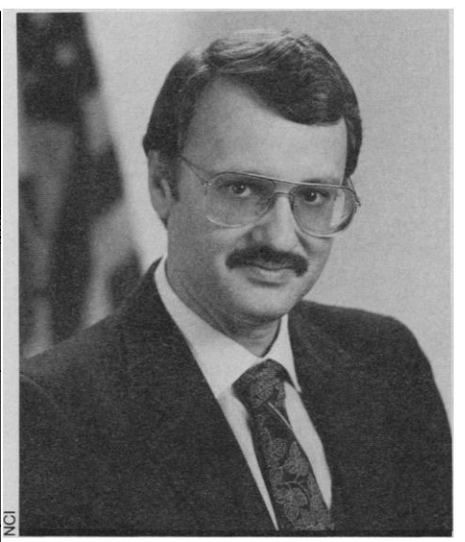
In addition, there are indications that the drug suppresses AIDS virus reproduction in the patients, although it is still too early to know whether this will translate into actual clinical benefits, such as a longer or better life for the people who take DDI.

Other studies are yielding similarly positive results. "I would say that [DDI] is much more impressive than AZT at a comparable level of development," says Jerome Groopman of New England Deaconess Hospital in Boston, who is also beginning to test DDI in AIDS patients.

The need for new AIDS therapies is still great because AZT is hardly ideal. Its toxicity, especially to the bone marrow, which produces the red and white blood cells, prevents some patients from taking it all. And there is another problem. The drug usually loses its effectiveness after patients have taken it for a year to 18 months, possibly because the AIDS virus can become resistant to it (*Science*, 24 March, p. 1551, and 31 March, p. 1731).

With the early (phase I) trials of DDI now winding down successfully, researchers hope that they can begin more extensive studies to assess the drug's effectiveness as early as September, provided that the FDA gives the go-ahead. Meanwhile, the Bristol-Myers Co., which makes DDI, has taken a step that should help to make the drug available to AIDS patients faster than it normally would be.

A drug cannot be sold before it completes its clinical testing and receives FDA approval. But the company has announced that once the planned phase II and III trials of DDI begin, it will make the drug available at no cost to patients who have a critical need for it—they may have become resistant to AZT, for example—and are unable to take part in the formal clinical testing of DDI. The company and the FDA have not yet agreed on a system for distributing the free DDI, however.



NCI

"You have to crawl before you can walk, but this study shows that we can crawl pretty fast."

—Samuel Broder

Bristol-Myers could not have taken its unusual action if the phase I DDI trials had not been producing encouraging results. In the NCI study, 26 individuals with either full-blown AIDS or advanced AIDS-related syndrome were treated for up to 40 weeks with one of eight different DDI dose regimens. The drug did not produce serious side effects at any dose level, Broder says, although he cautions, "There's always the possibility that we will get toxicities in long-term studies that were not seen in these studies."

A particularly hopeful sign was the apparent absence of the bone marrow toxicity that so often limits the doses of AZT that patients can take. This may mean that DDI will be tolerated by people who cannot handle AZT, or that the two drugs can be given together to give better suppression of the AIDS virus. Many clinicians think that combination therapies will be needed to control AIDS.

Although phase I studies traditionally do not assess clinical efficacy, the preliminary news on this front is also good, Broder says. DDI, like AZT, interferes with the reproduction of the AIDS virus by inhibiting the synthesis of the viral genetic material. An indication that DDI can inhibit the virus reproduction in living patients is the NCI workers' finding that several of the individuals on the four higher dose regimens showed greater than 80% reductions in the serum concentrations of an AIDS virus protein.

But more than that, they also had highly significant increases in the counts of the T cells that the AIDS virus destroys. "To have a lot of activity jump out at you is unusual," notes Broder, who was also instrumental in developing AZT for AIDS therapy. The finding may mean that DDI can restore the patients' immune functions. Patients also gained weight on the higher DDI doses, another indication of improved clinical status.

As yet unpublished work from other groups supports the NIH findings. Two of these groups, one including John Lambert and Raphael Dolin of the University of Rochester and Fred Valentine of New York University Medical Center and the other including Timothy Cooley, Howard Liebman, and their colleagues at Boston University School of Medicine, presented their results last month at the International AIDS Congress in Montreal.

In all the studies to date, however, a total of only 90 people have received DDI. The next step then is to perform the more extensive trials needed to determine whether DDI actually helps AIDS patients. But even if it does prove to be as good as everyone hopes, it will not mean that AIDS can be cured. "There's no drug we have now, or is even on the drawing board, that will handle all the problems of AIDS patients without toxicity," Broder says.

Nevertheless, the DDI results are contributing to a new optimism about treating AIDS that was notably absent just 4 or 5 years ago. Back then, Groopman points out, because of the nature of the AIDS virus, people were skeptical that there would ever be any drugs for combating the infection. Now, AZT is in clinical use, and DDI is moving expeditiously along the regulatory track. "You have to crawl before you can walk, but this [DDI] study shows that we can crawl pretty fast," Broder says.

■ JEAN L. MARX