Imminent Marketing of AZT Raises Problems

AZT can keep some AIDS patients alive and even reverse their dementias, but it is so toxic that a majority of patients may not be able to take it

On 4 March, the Secretary of State for Health in the United Kingdom announced that the anti-AIDS drug azidothymidine is approved for marketing. The next week, the governments of France and Norway approved the drug. The Food and Drug Administration of the United States is expected to announce its approval of AZT within weeks. For the first time, a drug that is effective against AIDS is on the market.

However, although AIDS patients are clamoring for the drug, a number of investigators have serious concerns about its safety and efficacy. Toxicity is so serious in some cases that patients cannot tolerate AZT. Moreover, Burroughs Wellcome, which manufactures AZT, is still trying to work out a system for allocating the drug only to patients for whom it is thought to prolong life. Ordinarily, any drug approved for marketing is available to anyone with a prescription for it.

AZT is the only drug demonstrated to help AIDS patients in a randomized, controlled clinical trial, and it has been rushed through the FDA with unusual speed. The expected FDA approval, "does not mean the drug has been comprehensively studied," says Dannie King, Wellcome's AZT project director. "It also does not mean we know which patient populations will benefit from it. We are going forward very quickly with minimal data to answer one of the critical medical needs of the decade."

The drug was "developed under emergency conditions," says Samuel Broder of the National Cancer Institute. "It was first found to be active against HIV [the AIDS virus] in February of 1985. We gave it to the first patient in July of 1985."

In September of 1986, a placebo-controlled study of the drug was prematurely terminated when it became clear that significantly more AIDS patients taking placebo were dying than patients taking AZT.

On 16 January, an FDA advisory committee recommended that AZT be approved for use by AIDS patients. AZT went from in vitro observations to a recommendation for market approval in less than 2 years.

But, at the same time, some FDA officials voiced uneasiness with the limited amount of information on AZT. Ellen Cooper, an FDA medical officer, said at the January advisory committee meeting that there are no good data from in vitro studies that would explain how the drug stems AIDS infections in patients. "This absence of convincing virologic data may be primarily methodological and certainly is not for lack of effort. But the fact remains that for the approval of an anti-infective agent we normally require in vitro evidence of specific anti-infective activity," she declared.

The AZT clinical trial did clearly show that the drug extends the lives of some patients. The question that is troubling investigators now is whether patients outside these narrowly defined groups will benefit from the drug. The clinical trial patients "were highly selected," says Jerome Groopman of the New England Deaconess Hospital in Boston. "They had either just recovered from a first bout with *Pneumocystis carinii* and were newly diagnosed with AIDS or they had ARC [AIDS-related complex]. Clearly, they represent a very small component of the spectrum of AIDS." Burroughs Wellcome and the National Institutes of Health are now conducting studies of AZT in AIDS patients with Kaposi's sarcoma, in children with AIDS, and in persons who have antibodies to the AIDS virus but who have not yet shown symptoms of the disease. These studies should provide some answers, but the drug is expected to be on the market before those answers are in.

Burroughs Wellcome wants to "err on the side of a very cautious approach," says King. "We will try to target the drug so it is given to patients that are very close if not identical to the patient population that was already evaluated. At least philosophically, that's the approach we're taking."

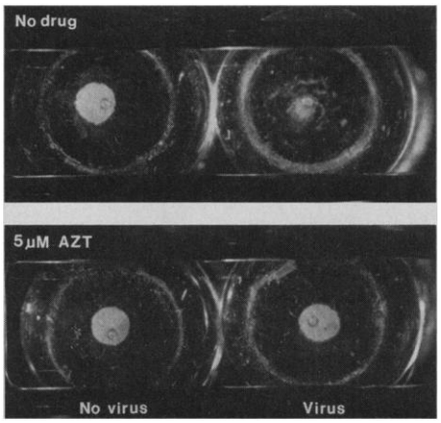
Yet, King continues, "One of our major concerns is, Will there be a black market for the drug? We feel very strongly that we don't want that to happen. But wishing is not enough. We are building a system of allocating the drug. Our idea is that physicians will write prescriptions and that they would have to write on the prescription certain key information, such as that the patient has a T4 count [the white blood cells killed by the AIDS virus] below 200. This information would have to be present before the prescription could be honored." Would such a system work? "It's never been tried before," says King. "No one knows precisely the best way to go, but an allotment procedure is one of the most reasonable to attempt." King says that Burroughs Wellcome will be able to supply enough AZT for the narrowly defined population it thinks should get the drug, but will not have enough drug on hand to treat all AIDS and ARC patients.

Martin Sherwood, a spokesperson for Burroughs Wellcome in London, says that the company hopes to limit distribution of the drug in the United Kingdom by requiring that only physicians who have experience in treating AIDS be allowed to prescribe it. "Although it is a clinical decision, we are encouraging physicians only to prescribe it for patients who fit into the categories [defined by the U.S. clinical trial]," he says. The company expects that in the U.K., such a system will restrict AZT's availability. In Norway and in France, according to Sherwood, Burroughs Wellcome is making a "similar effort" to limit the distribution of AZT.

A number of investigators who are treating patients with AZT are concerned that the drug is more toxic than is generally recognized. This is not to cast doubt on the clinical trial results, notes Martin Hirsch of Harvard Medical School. "I don't think anything has developed since the initial trial to even suggest that AZT doesn't work or doesn't prolong life," he says. But more than half of all AIDS patients may not benefit from the drug because it is more toxic for them than their AIDS infection.

The most serious side effect of AZT is to suppress the bone marrow, leaving patients highly vulnerable to bacterial infections (see box). Once this occurs, they either have to stop taking AZT altogether or take a reduced dose. But there is no information on whether a reduced dose is effective, because there is no way of measuring the effects of AZT except to look for increased survival and lessening of opportunistic infections. There is no simple way to see if the drug is working.

Researchers have tried looking at AIDS antibodies, reasoning that if the drug were preventing the virus from replicating, AZT patients would have fewer antibodies. According to that measure, Groopman says, preliminary data indicate that reduced doses of AZT seem to be less effective. Burroughs Wellcome has trials under way to determine if lower doses of the drug are effective. But



AZT protects against AIDS in vitro. *T cells are destroyed by the AIDS virus, as occurs in the top panel. The photo on the left is a clump of T cells before the AIDS virus is added and the photo on the right is the same cells after virus infection. In the bottom panel, the drug AZT is added before the viral infection. The photo on the right illustrates that the cells survive.*

for now, Groopman says, "no one knows the correct dose."

The issue is pressing because at least half of all AIDS patients that should be eligible to take the drug either cannot take it at all or must take a lower dose to prevent toxicity. Toxicity may be even worse among AIDS patients in general. When Groopman gave it to 14 patients on a compassionate basis, only 2 were still able to take it after 3 months. "We found it nearly impossible to keep patients on the drug," Groopman says.

On the other hand, says Broder of NCI, those who do tolerate AZT may go on for very long periods with no apparent ill effects. For example, Broder began studying AZT by giving the drug to 19 AIDS patients in an uncontrolled study meant to detect toxic effects at different dose levels. Of those 19, 13 are still alive and are still taking AZT after 18 months. In addition, Broder reports that AZT may ameliorate the effects of the AIDS virus on the brain, a totally unexpected finding that "means we have to take a fresh look at what is going on in the brain," Broder says.

AIDS patients develop neurological problems, including memory loss, lowering of their scores on intelligence tests, and even dementia. Researchers suspected that the virus irreversibly damages the brain and that there was no hope of making the brain whole again.

What was worse, says Broder, is that the AIDS patients knew they were losing their ability to think. "They were aware that their minds were not working. Many had been extremely bright and they noticed differences in their mental functions. It was as though they were trapped in a prison of darkness," Broder says. But he reports that seven AZT patients regained some of their lost mental functions. "Some patients could return to work and interact with friends. One patient told me that he had returned from the dead," Broder says.

Yet no one thinks that AZT is anywhere near the answer to AIDS. Broder is looking forward to the second generation of AZT-like drugs, which he hopes will be less toxic. Also, there are indications that if acyclovir is given along with AZT, the two drugs may work together to control the infection and patients may get by with lower doses of AZT. This drug combination is now being tested in clinical trials. Other new approaches include that of Groopman who hopes to boost the bone marrow's functioning by giving hormones that stimulate blood cell production at the same time as he gives AZT.

"Within broad limits, the most important lesson of AZT is that *something* can be done for AIDS patients, even if they have advanced disease," Broder says. "Before the advent of AZT, there was a significant question of whether anti-retroviral therapy was even possible. I believe as a first step that any time you can start realistic discussions of long-term toxicity of a drug, you've got a partial victory."

AZT, says Hirsch, "is by no means a cure for AIDS, but it's the only show in town right now." ■ GINA KOLATA

Marrow Suppression Hampers AZT Use in AIDS Victims

A group of researchers at New England Deaconess Hospital in Boston has discovered why the AIDS virus suppresses bone marrow. The finding is important, says Jerome Groopman, who heads the group, because patients with poorly functioning bone marrow are unable to take AZT, which is the only anti-AIDS drug that has been proven useful in a randomized controlled clinical trial.

Groopman's evidence leads him to propose that the AIDS virus infects certain bone marrow cells. Then antibodies to the AIDS virus bind to those cells and prevent them from growing. It is the patient's own immune response to the AIDS virus that suppresses the bone marrow. But there is at least some hope that this suppression can be overcome by a newly available class of hormones that stimulate the bone marrow. Groopman and his colleagues reported their findings in the 12 March issue of *Nature*.

The investigators studied about 20 patients with AIDS or with ARC, the AIDS-related complex. All of these patients had anemia, indicating they had too few red blood cells, and leukopenia, indicating they had too few white blood cells. Both red and white blood cells originate in the bone marrow. Because the patients "were not on antibiotics or chemotherapy, there was nothing other than HIV [the AIDS virus] that could be impairing their bone marrow," Groopman says.

Groopman first established that these patients had normal numbers of bone marrow stem cells and that the cells could grow and develop normally in vitro. This left him with the question of why, if the stem cells are normal in number and in their growth, patients have so few circulating white and red blood cells?

The next step was to study serum from the patients. This serum, Groopman found, markedly suppressed the development of the patients' bone marrow cells in vitro. It did not suppress bone marrow cells from normal volunteers, however. So there was something in the serum of AIDS patients that interacted with something that is present only in the bone marrow of AIDS patients to stop the bone marrow cells from growing and developing.

The substance in the serum, Groopman suggests, is antibody to the envelope protein of the AIDS virus. Rabbit serum containing this antibody suppresses the patients' bone marrow in the same way their own serum does. Groopman and colleagues have preliminary data that the AIDS virus itself is lurking in some of the bone marrow cells. AIDS virus can be recovered from bone marrow of the patients, but it is not yet known whether the virus has infected stem cells or whether it infects primitive blood cells that are derived from stem cells. In any event, the hypothesis is that the antibodies bind to bone marrow cells containing the AIDS virus and prevent those cells from growing.

Groopman is now conducting a study to determine whether hormones that stimulate the bone marrow can overcome the bone marrow suppression that occurs with AIDS. If they can, more AIDS patients may be able to take AZT. ■ G.K.