AIDS Drug Treatment

While no cure has been found for AIDS, progress is being made in developing antiviral, immune-modulating, and biological agents to treat AIDS.

The Food and Drug Administration (FDA) designates all anti-AIDS investigational new drugs (INDs) and new drug applications (NDAs) "AA," giving them top priority review to ensure evaluation of the application within 180 days of FDA review time.

Zidovudine

Zidovudine (formerly known as azidothymidine or AZT) is the first drug therapy approved for the treatment of patients with AIDS. FDA's review and approval of this product took less than four months—one of the shortest approval actions on record. The Agency is giving it top priority and working closely with the manufacturer from the early IND phase made this speedy review possible.

A thymidine analog, zidovudine is an inhibitor of the in vitro replication of some retroviruses, including HIV.

Marketed as Retrovir by Burroughs Wellcome, the drug is approved for the management of certain adult patients with symptomatic HIV infection (AIDS and advanced ARC) who have a history of cytologically confirmed Pneumocystis carinii pneumonia (PCP) or an absolute \( CD_4 \) count of less than 200/\( \text{mm}^3 \) in the peripheral blood before therapy is begun.

Specifically, this indication includes HIV-infected patients with one or more of the following disease manifestations:

1. history of cytologically confirmed PCP regardless of \( CD_4 \) count;
2. history of another AIDS-defining opportunistic infection and a \( CD_4 \) count less than 200/\( \text{mm}^3 \);
3. advanced ARC characterized by multiple signs and symptoms of HIV infection including otherwise unexplained weight loss (greater than 15 lbs or greater than 10% of prior body weight) and/or recurrent oral candidiasis and a \( CD_4 \) count of less than 200/\( \text{mm}^3 \). The efficacy and safety of zidovudine have not been adequately studied in patients with AIDS-related malignancies such as KS and lymphomas, in patients with AIDS-dementia complex and/or other neurologic manifestations, or in patients with earlier manifestations of HIV-infection. However, controlled studies of zidovudine are currently under way in all these categories.

Warning

The labeling of the drug begins with a boxed warning stating that therapy with zidovudine is often associated with hematologic toxicity, including granulocytopenia and severe anemia requiring transfusions. The boxed warning further points out that patients treated with zidovudine may continue to develop OIs and other complications of AIDS or ARC and thus should be under close clinical observation by physicians experienced in diseases associated with HIV.

The Adverse Reactions of the labeling discusses the occurrence of significant anemia, which in the clinical trial most commonly occurred after four to six weeks of therapy and which in many cases required dose adjustment, discontinuation of therapy, and/or blood transfusions.

In the placebo-controlled trial, although severe headaches were reported more commonly in patients receiving zidovudine than in those on placebo, frank adverse neurologic events were rare. However, in one published report, a patient with advanced AIDS (extensive KS plus multiple opportunistic infections, including PCP, MZV, retinitis, disseminated MAI, and esophageal candidiasis) developed severe headache, unresponsiveness, and focal seizures 48 hours after beginning zidovudine therapy. No structural or metabolic abnormalities were found to explain his condition. Following discontinuation of therapy, he recovered neurologically. Because of the possibility that multiple drug interactions at the initiation of therapy contributed to the presumed zidovudine toxicity, the drug was reinstated. Seventy-two hours after rechallenge, the patient developed headache and confusion leading to focal status epilepticus unresponsive to anticonvulsants, and he died(3).

Although two double-blind, placebo-controlled trials are generally required for the approval of a drug, the approval of zidovudine was based primarily on the results of one randomized, double-blind, placebo-controlled trial conducted at 12 U.S. medical centers. The study involved 281 patients with AIDS or advanced ARC who were treated for an average of 4-1/2 months. A second study was not required because AIDS is a fatal illness with no
other therapy and the results of the first study made it unethical to withhold treatment.

Designed for a treatment period of 24 weeks, the trial was stopped early at the advice of a data safety monitoring board due to a significant reduction in mortality in the zidovudine-treated group. Additional data were collected on about 80% of these patients who received zidovudine in an open-label extension of the trial for an average of five more months. Opportunistic infections and deaths continued to occur in both groups; however, the efficacy of zidovudine in prolonging survival for most patients continued during the additional five months of treatment.

In addition to reducing mortality, results of the controlled trial showed that zidovudine also significantly reduced the risk of acquiring an AIDS-defining opportunistic infection (OI), such as PCP, after the first four to six weeks of treatment. Zidovudine-treated patients generally did better than the placebo group in terms of Kanofsky performance level (ability to perform tasks of daily living), neuropsychiatric function, maintenance of body weight, and the number and severity of symptoms associated with HIV infection. A summary of the data upon which the approval was based has been published recently(1,2).

Drug Interactions

Co-administration of zidovudine with other drugs metabolized by glucuronidation should be avoided because the combination may potentiate toxicity of either drug. During the controlled clinical trial, zidovudine recipients who also took acetaminophen had an increased incidence of granulocytopenia that appeared to be related to the duration of acetaminophen use.

The interaction of other drugs with zidovudine has not been studied in a systematic manner. Co-administration of zidovudine with drugs that are nephrotoxic, cytotoxic, or that interfere with the red blood cell/white blood cell (RBC/WBC) number or function may increase the risk of toxicity. Some experimental nucleoside analogs being evaluated in AIDS and ARC patients may affect RBC/WBC number or function and may increase the potential for hematologic toxicity of zidovudine.

In addition, in vitro experiments indicate that ribavirin decreases the activity of zidovudine in inhibiting replication of the AIDS virus when infected cells are exposed to the two drugs simultaneously(4). Also, there is a published report of neurotoxicity associated with concomitant use of zidovudine and acyclovir(5).

Patient Information

The labeling contains a section of information that should be communicated to patients. This includes the importance of taking zidovudine exactly as prescribed—every four hours, round-the-clock—even though it may interrupt normal sleep. Physicians are also advised to tell patients that the long-term effects of zidovudine are unknown at this time, and that zidovudine therapy has not been shown to reduce the risk of transmission of HIV to others.

FDA is cooperating with the manufacturer in monitoring a special post-marketing program to compile and analyze extensive data on patients receiving zidovudine on a chronic basis.

Investigational Agents

Several potential AIDS therapies are in clinical research. It is important to note that these treatments have not been approved by FDA. However, sponsors have shown that they are sufficiently safe for use in clinical studies.

Information about therapies currently under consideration at FDA is regarded as a trade secret and is therefore confidential and not releasable without consent of the drug sponsor. However, because information about the following therapies has previously been released by the sponsors themselves, FDA can pass this information on to practitioners. Requests for additional information about any of these therapies should be directed to the appropriate sponsor.

References