"On the Shelf" AIDS Drug in Clinical Trial

Fusidic acid, an antibacterial drug used in Europe, is effective against the AIDS virus in vitro, shows promise in vivo, and is being tested in two clinical trials

A new study indicates that fusidic acid, an antibiotic described in the early 1960s, may become a useful treatment for AIDS. Angus Dalgleish of the Clinical Research Center in Harrow, England, and Vigo Faber of the University Hospital of Copenhagen, Denmark, and their colleagues state in the 10 October issue of *Lancet* that fusidic acid is effective against the AIDS virus in vitro and is also associated with "striking clinical improvement" in a 58-year-old Danish man with AIDS. Fusidic acid is now the subject of two clinical trials in AIDS patients in Europe.

Until the recent report, the potential of fusidic acid as an AIDS drug was a well-kept secret. "I had never heard of it," says Anthony Fauci of the National Insititute of Allergy and Infectious Diseases. "But in vitro activity of a drug is certainly not the same as in vivo activity. Nevertheless, it's worth a try." Samuel Broder of the National Cancer Institute is also cautious. "It's an exciting in vitro observation, but it is quite literally impossible to draw any conclusions about the in vivo effects of fusidic acid based on one patient."

"Here is a drug that has been sitting on the shelf, so to speak," says Dalgleish. "Fusidic acid has been used for other conditions for a long period of time, it is relatively free of side effects, and it can be given orally. Fusidic acid is very effective against the AIDS virus in vitro at concentrations that can easily be attained in vivo." He also stresses that clinical trials are necessary to determine if the drug works as well in vivo as it does in vitro and thinks it is likely that fusidic acid will be most effective if it is given in combination with other drugs.

If fusidic acid does prove to be generally effective, the inexpensive antibiotic should quite literally give Burroughs Welcome, the company that makes AZT (3′-azido-3′-thymidine), a run for its AIDS money. AZT or Zidovudine is the only drug so far approved by the Food and Drug Administration as a treatment for AIDS. It is not a cure, it can cause severe bone marrow toxicity, and many patients are unable to take it. Burroughs Welcome charges about $10,000 per year for AZT. Dalgleish estimates that even if fusidic acid were taken on a daily basis—which would probably not be necessary—it would only cost about $1000 per year.

The route that led to the discovery of fusidic acid as a possible AIDS drug is unusual. Instead of first testing it in vitro and then in patients—the typical approach for screening most potential AIDS treatments—Faber found it to be effective in patients before it was tested in vitro. This was possible because the drug had already been approved as an antibiotic.

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According to the *Lancet* report, the Danish patient treated with fusidic acid has been infected with HIV, the human immunodeficiency virus that causes AIDS, at least since 1984. By 1986, he had very severe symptoms of AIDS, including fever, diarrhea, and marked weight loss, and was not responding to a combination of other drugs. Faber, his physician, started fusidic acid treatment for a *Mycobacterium tuberculosis* infection of the lungs and noted that the patient's fever disappeared and that he began to gain weight. He has remained well since then.

"Faber asked me if I thought the drug could have any effect on the AIDS virus," says Dalgleish. "I said no, but it's worth trying." Dalgleish tested the drug—a steroid derived from a fungus—and found that, like AZT, it prevents HIV production in vitro. But unlike AZT, fusidic acid does not work by inhibiting the activity of reverse transcriptase, the viral enzyme that allows HIV to make DNA copies of its RNA genome.

Dalgleish and his colleagues have not yet identified the mechanism by which fusidic acid inhibits HIV replication in vitro. It blocks bacterial protein synthesis by interfering with the interaction between ribosomes and transfer RNA. A different mechanism might account for its activity against the AIDS virus, however. "Fusidic acid may be a protease inhibitor, but whether it works against viral proteases or cellular enzymes is still unclear," says Dalgleish.

An important property of the drug is its ability to penetrate many types of cells and tissues, including monocytes, macrophages, bone, and fatty tissue. "I think that any cell that could take up the AIDS virus could also take in the drug," says Dalgleish. He speculates that macrophages that have incorporated both fusidic acid and HIV might be unable to spread infection because the drug prevents production of infectious virus particles. If this were to occur in vivo, it might reduce the likelihood that infected macrophages entering the brain will produce HIV there and cause brain disease.

The reported side effects of fusidic acid in humans include transient jaundice—possibly because the drug is excreted by the liver into the bile, rather than in the urine—and itchy skin. In mice, fusidic acid dampens the immune reponse—cell-mediated immunity in particular—but whether similar effects will occur in AIDS patients has yet to be determined.

Fusidic acid or fusidate sodium, its water-soluble salt, is made by the Leo Foundation in Copenhagen. Leo has taken out an additional patent on the drug as a possible treatment for AIDS. But in the United States, fusidic acid was not found to be worth pursuing as an antibiotic. "It's not our compound," says Sal Lucania of Squibb in Princeton, New Jersey. "We considered it for licensing about 20 years ago, but we haven't touched it in many years. It's not available from Squibb, of course."

Dalgleish and Faber will oversee clinical trials of fusidic acid in England and Denmark, respectively. In England, the drug will be tested initially on AIDS patients who do not respond to AZT or who were not eligible to receive AZT, says Dalgleish. He also hopes to gain approval for testing fusidic acid in combination with other drugs, such as AZT and ribavirin.

"Fusidic acid should go through the same kind of rigorous trial process as AZT," says Dalgleish. Because of the effectiveness of AZT, however, few AIDS patients are willing to participate in a clinical trial unless they are assured that they will be treated with an experimental drug. Understandably, they do not want to be part of a control group that receives an inactive placebo compound. This makes it more difficult for researchers to show that a change in their clinical condition is due to an experimental compound such as fusidic acid. ■

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