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UPDATE

EMBARGOED FOR RELEASE
6:00 p.m. EDT
Wednesday, October 14, 1987

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New Drug Therapy Developed for Pneumonia in AIDS Patients

Scientists have developed a new drug treatment for the life-threatening pneumonia caused by the organism Pneumocystis carinii which afflicts AIDS patients. The findings are reported in the October 15 New England Journal of Medicine by scientists from the National Cancer Institute, the National Institutes of Health (NIH) Clinical Center in Bethesda, Md., and the George Washington University Medical Center in Washington, D.C.

The new treatment uses the anticancer drug trimetrexate in combination with an antidote, leucovorin, that rescues noncancerous cells from the effects of the anticancer drug. Trimetrexate is presently under development by the NIH's National Cancer Institute (NCI) as a cancer treatment. The drug was first synthesized by Dr. Edward Elslager of the Warner-Lambert Company in Morris Plains, N.J., in 1969. The firm provided the drug for this study.

The study was headed by Dr. Carmen J. Allegra and Dr. Bruce A. Chabner of the NCI, Dr. Henry Masur of the NIH, and Dr. Carmelita U. Tuazon of the George Washington University Medical Center.*

*Other authors of the paper are: Barbara Baird, James C. Drake, Dr. Ernest E. Lack, and Dr. Frank Balis of NCI; Dr. J. Thayer Simmons, Debra Ogata-Arakaki, and Dr. James H. Shelhamer of the NIH Clinical Center; Dr. Robert Walker, Dr. Joseph A. Kovacs, and Dr. H. Clifford Lane of the National Institute of Allergy and Infectious Diseases, NIH. The paper is titled "Trimetrexate for the Treatment of Pneumocystis Carinii Pneumonia in Patients with the Acquired Immunodeficiency Syndrome."

The study showed that two weeks following treatment with trimetrexate, 38 out of 49 (77 percent) patients with Pneumocystis carinii pneumonia (PCP) were alive. This included patients with advanced disease who could not tolerate or were resistant to standard drug treatments. "The study suggests that trimetrexate is a safe and effective therapy for PCP and is comparable to today's standard treatments," Dr. Allegra said.

While PCP is a major cause of death in AIDS patients, surviving this infection does not mean that AIDS is cured.

The promising new treatment will now be compared with trimethoprim-sulfamethoxazole in a large multicenter trial that will begin soon. This trial has been organized by the National Institute of Allergy and Infectious Diseases (NIAID) in cooperation with Warner-Lambert and will be carried out in the AIDS Treatment Evaluation Units around the country. This 370-patient trial is a high priority for NIAID.

PCP is the most commonly recognized life-threatening infection in AIDS patients, ultimately occurring in 80 percent of patients. The current standard treatments for PCP are trimethoprim-sulfamethoxazole (a sulfa drug and frequently used antibiotic for respiratory and urinary tract infections) or pentamidine (an antiparasitic drug). While these drugs are useful, 25 percent of PCP episodes result in death. A more effective drug is clearly needed and could have a major impact on the quality and duration of survival for AIDS patients.

Furthermore, both trimethoprim-sulfamethoxazole and pentamidine are very poorly tolerated by AIDS patients. According to various studies, from 40 to 100 percent of AIDS patients will develop a toxic reaction to trimethoprim-sulfamethoxazole, and a similar number will develop a toxic reaction to pentamidine. In 25 percent of AIDS patients, the initial antipneumocystic

drug must be stopped because of the severity of the toxic reaction. Thus, safer, better-tolerated drugs are needed. There are currently no approved alternatives for patients with PCP who fail the two standard drugs or who cannot tolerate them because of severe toxic reactions.

In the currently reported study, 49 AIDS patients with PCP were given daily doses of trimetrexate and leucovorin for 21 days. The patients consisted of three groups, all receiving trimetrexate and leucovorin. The first group consisted of 16 patients who were not able to tolerate or had failed standard therapy, and were switched to trimetrexate. The second group consisted of 16 patients who had a history of sulfa drug or pentamidine intolerance, and received trimetrexate as initial therapy for PCP. The third group of 17 patients did not have a history of sulfa drug intolerance and received the antibiotic sulfadiazine in addition to trimetrexate and leucovorin.

Two weeks following treatment, the percentages of patients alive in each group were 69 percent (11 patients) for the first group, 88 percent (14 patients) for the second group, and 77 percent (13 patients) for the third group.

Dr. Allegra pointed out that these results are impressive because a relatively high percent of very poor risk patients survived. Furthermore, 69 percent of patients who had failed or been unable to tolerate standard therapies recovered due to trimetrexate therapy.

Dr. Allegra also said that, unlike the standard therapies, the new treatment caused minimal toxicity which was easily managed by changing the dosage of the drugs. Four patients developed mild liver abnormalities, and 12 patients had transient low neutrophil counts (neutropenia) or low platelet counts (thrombocytopenia). One patient was discharged from the study because of a rash.

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The patients were treated at the NIH Clinical Center and the George Washington University Medical Center. The study began in May 1985.

Trimetrexate's effectiveness against PCP was discovered in NCI laboratories. In the Spring of 1985 when Dr. Allegra was studying the drug's anticancer properties, he tested trimetrexate in the laboratory for its ability to inhibit enzymes isolated from the PCP organism and found it extremely potent. The NCI scientists further found that leucovorin reversed the toxic effects of trimetrexate on normal cells but not on the PCP organisms, thus providing the scientific rationale for using the drug combination to treat patients with PCP.

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