Neutrexin® New Life from an Old Drug: A Case Study

Patients with impaired immune systems often suffer "opportunistic infections"(mild to severe infectious diseases) [i]. People who are at the greatest risk of contracting this serious type of infection are those who have weakened immune systems such as AIDS, cancer, and transplant patients. *Pneumocystis carinii* pneumonia (PCP) is the most common opportunistic infection in people with HIV and had been the major cause of death for HIV/AIDS patients.

It is estimated that without treatment over 85% of people with HIV would eventually develop PCP. However, due to dedicated physicians and scientists such as those at the National Institutes of Health (NIH), PCP is now almost entirely preventable and treatable in people with HIV.

PCP results when the microscopic fungus, *Pneumocystis carinii*, infects the lungs. While a healthy immune system retains the T cells necessary to control the fungus, serious disease develops in patients whose immune systems are compromised. Signs of this condition are an unexplained fever, shortness of breath, dry cough, recurring fungal infections in mouth and throat, previous episodes of PCP, and other AIDS defining illnesses. The successful treatment and prevention of PCP is essential for improving the quality of life and life expectancy of these immuno-compromised patients.

Neutrexin® (trimetrexate glucuronate for injection) is an intravenous treatment for PCP in immuno-compromised patients, including those with AIDS. Neutrexin® inhibits the enzymes that interrupt DNA, RNA, and protein synthesis that in turn results in cell death. Neutrexin® selectively destroys the *Pneumocystis carinii* organism that causes PCP by the inhibition of these enzymes.

Epidemiological Features of PCP

On June 4, 1981, the Morbidity and Mortality Weekly Report (MMWR) published by the Center for Disease Control (CDC) reported PCP in 5 homosexual men in Los Angeles [ii]. This was the first published report of what, one year later, became known as AIDS. This report in MMWR alerted the medical and public health communities to other unusual cases of PCP. The observation of an increased number of cases of PCP resulted in the CDC forming a task force that established that this was a new syndrome whose incidence was increasing rapidly. Subsequent epidemiological studies performed over the next eighteen months strongly suggested that a sexually transmitted agent caused this syndrome. Transmission was also observed among intravenous drug users and recipients of blood or blood products.

To prevent further transmission, in 1983 the Public Health Service used this epidemiologic information about PCP to recommend that sexual contact be avoided with persons known or suspected to have AIDS and that persons at increased risk for AIDS refrain from donating plasma or blood. These recommendations were developed and published only 21 months after the first cases of PCP were reported. Earlier diagnoses of HIV, anti-retroviral therapy (HAART) and effective prophylaxis have all contributed to a 75% decline in PCP cases, although PCP remains the most common AIDS defining illness[iii].

Success in preventing and treating PCP (USA)

Pre HAART	Post HAART	
63%	**32%**	Incidence (In AIDS patients)
32%	**14%**	PCP mortality

Pneumocystis carinii Pneumonia Management

Anti-HIV therapies that strengthen the immune system and maintain the number of CD4+ T cells are the best way to prevent opportunistic infections in HIV patients. Prior to the advent of HIV specific therapies, antibiotics were routinely used to control PCP in HIV patients. However, a substantial number of PCP patients continually fail to respond to, or are intolerant to, first line antibiotics, including trimethoprim/sulfametho-xazole (TMP/SMX). For example, adverse effects with TMP/SMX are reported in more than one half of patients treated and treatment-limiting toxicities may occur in up to one third of patients. Those infected with HIV have higher rates of TMP/SMX side effects. Additionally, even in patients who present positive clinical responses, lung biopsies have found *Pneumocystis carinii* cysts in 75% of patients two weeks after the initiation of TMP/SMX therapy[iv].

Another antibiotic therapy employing pentamidine requires a monthly clinic visit to use a nebulizer (a machine that produces a very fine mist of the antibiotic for inhalation). However, patients using aerosol pentamidine relapse more often than people taking oral TMP/SMX. When patients continue to deteriorate or fail to improve after 7 to 10 day TMP/SMX treatment or pentamidine treatment, doctors are faced with the dilemma of finding a more successful regimen.

Although these antibiotics are consistently used for the treatment of PCP, scientists were also interested in exploring the usefulness of the compound trimetrexate in treating PCP because of the possibility that, when used in combination with leucovorin, it may be both less toxic and more effective than antibiotic therapies.

R & D TIMELINE

Synthesis of trimetrexate – 1969

NCI screens trimetrexate for medicinal purposes – 1980

Pneumocystis Pneumonia - Los Angeles - 1981

NIH treats PCP infected patients - 1982

Trimetrexate for PCP infected mice - 1984

NIAID files protocol for human testing - 1985

Patent application - 1986

Patent 4,694,007 issued - 1987

Neutrexin® available for HIV infected patients intolerant of TMP/SMX - Feb 1988

US Bioscience license to market Neutrexin® - 1990

FDA Approval - Dec 1993

First Commercial Sale - Jan 1994

Development of Neutrexin®

Interest in the application of trimetrexate, experimentation using animal model systems and clinical testing led to the development of Neutrexin® as an alternative therapy for the treatment of moderate-to-severe PCP in patients with weakened immune systems. The development of Neutrexin® exemplifies how the NIH carries out its public

health mission because the development of this new therapeutic drug came in response to an emerging public health need. The resources provided to the NIH by the American taxpayer permitted the necessary collaborations between academic research scientists and practicing clinicians that resulted in the creation of this new treatment option for PCP.

Role of NIH

In 1982, Dr. Henry Masur arrived at NIH and was one of the pioneers who first documented unusual cases of PCP in homosexual men. Dr. Masur brought both medical and research expertise to the table when he also conducted scientific research on the *Pneumocystis carinii* organism. The NIH provided him with the resources necessary to follow these rare presentations of PCP including access to nationwide patient populations, a cohort of expert clinical and scientific collaborators, and the academic freedom to address interesting scientific observations. The identification of a PCP epidemic was essential to the creation of a new therapy for the thousands of individuals afflicted with PCP at that time.

In pursuing new therapeutic approaches to the treatment of PCP, Dr. Masur collaborated with Drs. Allegra and Chabner at the National Cancer Institute (NCI), who were using trimetrexate to treat head and neck cancers. These three along with Dr. Joseph Kovacs from the Clinical Center hypothesized that it might be possible to destroy *Pneumocystis carinii* by interfering with folate metabolism in ways similar to those observed using trimetrexate for the treatment of head and neck cancers. This hypothesis was tested in animal studies that provided evidence that trimetrexate was also able to disrupt folate metabolism in the *Pneumocystis carinii* and result in death of these microorganisms. This observation permitted Drs. Kovacs and Masur to begin Phase II clinical trials of trimetrexate in AIDS patients afflicted with PCP. The response rate for patients with PCP disease was 70% - 90% in small preliminary clinical studies in which trimetrexate and leucovorin were used,[v] even though relapses appeared to occur more frequently than after conventional therapy. The critical funding by the taxpayer allowed the NIH to invest in basic and clinical research that enabled the collaboration that generated the initial treatment hypothesis as well as the actual therapy that improved the health for patients.

Role of Technology Transfer

As scientists working for the NIH, the collaborators disclosed their discovery in 1985. The resulting intellectual property covering the inventive finding that trimetrexate can be used as an antiparasitic agent was licensed to a private partner for further research and commercialization.

An exclusive license was negotiated with US Bioscience, which also held a license to methods to manufacture trimetrexate. This license provided the protection and incentive necessary for industry to make the expensive investment in clinical trials. The transfer of the NIH invention ultimately resulted in the creation of a product to treat PCP within four years of identifying the PCP epidemic.

Role of Industrial Partners

US Bioscience was a suitable industry partner because the company produced stable formulations of trimetrexate that could be used in humans. The scope of the license agreement allowed US Bioscience to increase patient participation in clinical trials, complete regulatory evaluations, and achieve marketing approval for Neutrexin®. The company funded the conclusion of an essential clinical trial necessary for this approval[vi]. In November 1999, MedImmune Inc. acquired US Bioscience and its portfolio and continues to market Neutrexin®.

Public Health Benefits

Neutrexin® was the first AIDS related drug to receive investigational new drug approval by the Food and Drug Administration in 1988[vii]. This drug indication provides a mechanism for pharmaceutical manufacturers to provide promising experimental drugs to patients with immediately life-threatening conditions before complete data on the drug's efficacy or toxicity are available that would enable approval for full commercial distribution. As a result, the overwhelming need for physicians and scientists to respond to the growing cases of PCP was met through the use of this therapy. Neutrexin® assists thousands of patients affected by PCP who are nonresponsive to conventional first line anti-parasitic treatments.

The discovery of trimetrexate's use as an antiparasitic agent is an example of how NIH carries out its mission to improve the public health by investing in basic and biomedical research. Once NIH physicians and scientists identified an emerging health epidemic, resources were invested to expedite the research that enabled the development of an alternative therapy for PCP that at the time afflicted 85% of HIV-infected patients.

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[i] Illnesses caused by various organisms, some of which usually do not cause disease in persons with normal immune systems.

[ii] Gottlieb MS, et al. Pneumocystis Pneumonia—Los Angeles. MMWR (1981) 37(12): 181

[iii] Palella FJ Jr, Delaney KM, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus. N Engl J Med (1998) 338: 853-60

[iv] Fisch, MA "Treatment and prophylaxis of Pneumocystis carinii pneumonia" (1988) 2(Suppl):S143-S150

[v] Allegra, CJ, et al. Trimetrexate for the treatment of Pneumocystis carinii pneumonia in patients with the acquired immunodeficiency syndrome. N Engl J Med (1987) 317: 978-985

[vi] Sattler, FR, et al. Trimetrexate with Leucovorin versus Trimethoprim-Sulfamethoxazole for Moderate to Severe Episodes of Pneumocystis carinii Pneumonia in Patients with AIDS: A Prospective, Controlled Multicenter Investigation of the AIDS Clinical Trials Group Protocol 029/031. J Infect Dis (1994) 170:165-172

[vii] Trimetrexate Treatment IND. News 2/16/1988 (http://www.fda.gov/bbs/topics/NEWS/NEW00180.html) Accessed 8/3/2004

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