Alzheimer's Study Will Target Plaque Formation

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A new treatment in the works for Alzheimer's disease is designed to act at the cellular level to reverse plaque formation and prevent development of further disease.

Prana Biotechnology Ltd. has received approval from the Medicines and Healthcare Products Regulatory Agency in the United Kingdom to begin a phase II/phase III study of clioquinol, also known as PBT-1. The investigators maintain that clioquinol will target the formation of amyloid plaques in the brain and thereby slow the progression of Alzheimer's disease (AD).

Ideally, clioquinol will both break up existing plaques and stop new ones from forming by redistributing the buildup of excess metals that are thought to cause plaques. "We believe that this is potentially a disease-modifying agent," Jonas Alsenas, D.V.M., Prana's chief executive officer told this newspaper in an interview. Currently approved and available AD medications treat the symptoms; Prana is going after the source.

Vaccines to prevent AD have fallen short because they target amyloid beta indiscriminately, whereas clioquinol goes after the toxic, aggregated form of the protein, Dr. Alsenas noted.

Known as the Progression Limitation in Alzheimer's: Clioquinol's Efficacy (PLACQUE) trial, the 1-year, randomized, double-blind, placebo-controlled study will include 435 adults with moderate AD, defined as baseline scores between 12 and 20 on the Mini-Mental State Examination (MMSE). Patients will take one pill in the morning and a second in the evening. One-third of them will take two 125-mg pills daily, one-third will take two 250-mg pills daily, and a third group will take a placebo. The researchers are targeting patients at a moderate stage of illness because these patients normally decline most rapidly, allowing the investigators to show an effect within the limits of a 1-year study.

Researchers will enroll both patients who have taken no other AD medications and those who have taken memantine or similar medications for at least 4 months prior to the study.

In a pilot study of 36 patients, clioquinol effectively slowed cognitive loss in patients who scored greater than 25 on the AD assessment scale cognitive instrument. It was also significantly associated with an increased concentration of zinc in the patients' plasma (Arch. Neurol. 2003;60:1685-91).

The drug was generally well tolerated by the patients. Both folate and vitamin B_{12} were administered to all patients to counteract an observed association between oral clioquinol and myelo-opticoneuropathy that led to the drug's withdrawal from sale in 1970. A vitamin B_{12} deficiency was posited to be the cause of the neuropathy and levels of the vitamin were monitored throughout the trial, the researchers noted.

Many AD patients have slightly lower levels of zinc than would normally be expected. Craig Ritchie, M.B., of the department of psychiatry, University College London, explained that when clioquinol breaks up plaques, it has the added effect of returning zinc levels to normal. "One explanation is that some of the body's zinc is being sequestered into plaques in AD," said Dr. Ritchie, the lead investigator on both the pilot study and the upcoming clinical trial.

However, the role of metals in maintaining the body's homeostatic functions is not fully understood, and a buildup of zinc has not been associated with dietary or environmental factors. "We are not saying that people should cut copper and zinc out of their diets," Dr. Ritchie emphasized.

Brains of patients with AD are known to contain higher than expected levels of some metals, an observation that provided some of the inspiration for clioquinol treatment. Postmortem research by Ashley Bush, Ph.D., a senior scientist at Prana and coauthor of the pilot study, involved the use of strong chelators such as edetic acid to break up the plaques and access the amyloid beta proteins. The chelation idea is part of the science behind the study, although clioquinol works by combining with metals only long enough to break up the aggregates.

The study will be done at sites in the United Kingdom, Australia, and South Africa. The company's goal is to have results from the study by the end of 2006, Dr. Alsenas said. ■