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Anti-TNF-alpha Therapy Produces Rapid Improvement in Alzheimer's Disease

Caroline Cassels

January 15, 2008 — Perispinal etanercept (*Enbrel*, Amgen), an anticytokine therapy that targets excess tumor necrosis factor–alpha (TNF-α) in the brain, has been shown to produce almost immediate cognitive and behavioral improvement in a patient with moderate Alzheimer's disease (AD).

If confirmed in larger studies, researchers say these findings may herald a major breakthrough in the treatment of the condition, which currently affects about 5 million Americans and 27 million individuals worldwide.

"This rapid response within minutes and the more prolonged response that we've seen [in other patients], is largely, or entirely, unprecedented in Alzheimer's disease," principal investigator Edward Tobinick, MD, director of the Institute for Neurological Research, a private medical group in Los Angeles, told *Medscape Neurology & Neurosurgery.*

Etanercept, which was approved for human use in 1998 for the initial indication of rheumatoid arthritis, is currently used to treat a wide variety of inflammatory disorders in which TNF-α is thought to play a role.

Using a unique, patented method that may enable direct-to-the-central-nervous-system delivery of etanercept via injection with a fine-gauge needle into the cerebrospinal venous system, investigators administered the drug in an 81-year-old male who had moderate AD, with "remarkable" results.

"Prior to treatment this patient was unable to tell us which state he lived in or what year it was and was unable to identify 9 out of 10 common everyday objects that are included in the Boston Naming Test," said Dr. Tobinick.

However, the authors report that within 10 minutes of drug administration, there was a marked improvement and the patient was able to name the state he was in and was 1 year off in identifying the correct year. Furthermore, he was calmer and less agitated, and his responses to questions were less effortful and more rapid, with less latency.

Two hours after treatment the patient's status continued to improve, and he could correctly name 9 of the first 10 pictures on the Boston Naming Test.

The study is published online January 9 in the *Journal of Neuroinflammation.*

In addition to this single case study, Dr. Tobinick and colleagues previously published the results of a 6-month proof-of-concept study in 2006 demonstrating the efficacy of perispinal etanercept in an open-label trial of 15 patients.

Although the investigators noted a similar, immediate improvement in several of the subjects, who received once-per-week therapy, the study protocol allowed only for monthly evaluation, prompting the investigators to document the treatment's rapid response in the current, single case study.

"When we initially designed the study we didn't expect such a rapid response, but once we started treatment we noticed that many patients responded very quickly, often within a few minutes. This was quite a surprise, but it has since been repeated and confirmed, and now we have seen positive clinical responses with maintenance therapy that, in some cases, has exceeded 3 years," said Dr. Tobinick.

Not a Cure

Despite these encouraging results, Dr. Tobinick was quick to point out that this therapy should not be considered curative.

"This is not a cure. It doesn't bring patients back to normal, but all indications lead us to believe that it produces a significant effect that is noticeable and important to family members and to the patients themselves," he said.

Neuroinflammation accompanied by overexpression of cytokines is a standard characteristic of brain pathology in AD, and scientists have long suspected the involvement of the proinflammatory TNF-α in AD pathogenesis — a hypothesis that is supported by a rapidly growing body of basic science and genetic evidence.

More relevant than the proinflammatory effects associated with overexpression of TNF-α that ultimately may give rise to the development of amyloid plaques are recent findings by Irish researchers that beta amyloid, and specifically beta amyloid oligomer interference with memory mechanisms in AD, are mediated by TNF-α.

"The current thinking among the Alzheimer's research community is that it is probably the small groups of dissolved amyloid plaques, known as amyloid oligomers, that circulate in the brain and the cerebrospinal fluid, rather than the plaques deposited in the brain, that are responsible for memory problems [in AD].

"The fact that the amyloid interference with memory seems to be mediated by TNF-α suggests that an anti–TNF-α approach might have the potential to ameliorate these memory deficits, and that is one of the things I think we're seeing in these patients," said Dr. Tobinick.

Tremendous Promise

Before beginning perispinal etanercept for the treatment of AD, Dr. Tobinick's facility had more than 5 years of clinical experience using it in thousands of patients with severe disk-related back and neck pain. In the course of this experience, he observed that some of these patients seemed to experience improved cognitive function as a "side effect" of treatment.

This observation, coupled with increasing evidence that TNF may play a role in synaptic dysfunction, led him to test the therapy in suspected AD patients.

Currently, he said, his team is available to partner with academic medical institutions to help design controlled clinical trials to test the therapy in larger numbers of AD patients.

"We have enough information now to indicate that these larger trials really should go forward as quickly as possible," said Dr. Tobinick.

In addition to AD, he believes this therapy holds "tremendous promise" for patients with other types of brain disorders, including frontotemporal dementia, primary progressive aphasia, and chronic traumatic brain injury.

Other areas of possible future research for the therapy could also include treatment of spinal cord injury, brain tumors, and a variety of other neurodegenerative diseases.

No Time to Waste

In an accompanying editorial, Sue Griffin, PhD, director of research at the Donald W. Reynolds Institute on Aging at the University of Arkansas for Medical Sciences, in Little Rock, said the findings by Dr. Tobinick and colleagues are unprecedented and warrant immediate further investigation.

Considered a pioneer in the field of neuroinflammation, Dr. Griffin was the first to describe the link between cytokine overexpression in the brain and AD in a landmark study published in 1989.

"I hope the scientific community will look at this work and respond very quickly to investigate it. With 5 million Americans with Alzheimer's, we have no time to waste," Dr. Griffin told *Medscape Neurology & Neurosurgery*.

Dr. Griffin said she personally witnessed perispinal etanercept therapy in several of Dr. Tobinick's patients and was "amazed."

"I must admit I was skeptical at first. So I went down to watch the procedure and to speak with both the patients and their families before and after treatment. It was truly one of the most remarkable things I've ever seen," said Dr. Griffin.

She is currently working to set up a research collaboration with Dr. Tobinick to bring the procedure to her institution for the purposes of clinical as well as basic scientific research.

One potential downside of the therapy, said Dr. Griffin, may be its cost, which comes in at approximately $30,000 annually for once-weekly treatment. However, she said, if proven viable, the cost of therapy needs to be weighed against the cost of caring for millions of severely disabled patients.

More information is available on the Institute for Neurological Research Web site. Dr. Tobinick can be reached at etmd@ucla.edu.

Study coauthor Dr. Hyman Gross declares no competing interest related to the study. Dr. Tobinick owns stock in Amgen, the manufacturer of etanercept, and has multiple issued and pending patents, including US patents 6,982,089 and 7,214,658, which describe the parenteral and perispinal use of etanercept for the treatment of Alzheimer's disease and other neurological disorders.

J Neuroinflammation. Published online January 9, 2008. Abstract

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