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抗TNF-alpha治疗阿兹海默氏症产生迅速改善

作者：Caroline Cassels
出处：WebMD医学新闻

January 15, 2008 — 经脊椎注射etanercept (Enbrel, Amgen)进行抗细胞激素治疗，目标是脑中过量的肿瘤坏死因子 α (TNF- α)，显示可以对中度阿兹海默氏症(Alzheimer's disease, AD)病患产生立即的认知与行为改善。

研究者表示，如果经大型研究确认之后，这些发现代表此病症治疗的新时代来临，此病目前在美国约有5百万病患、全球有2700万病患。

主要研究者、洛杉矶的一间私人医疗团队、神经科学研究中心主任Edward Tobinick向Medscape神经学&神经外科学表示，在其它疾病我们见过几分钟内出现治疗反应且持续的情形，但是在阿兹海默氏症则是完全出乎意料之外。

Etanercept于1998年获得核准治疗人类的类风湿性关节炎，目前用于各种与TNF- α 有关之发炎异常治疗。

使用一种独特的专利方式，可以将etanercept直接注射到中樞神经系统，方法是使用一种细针注射到脑脊随神经系统，研究者以这种方法治疗一位81岁中度AD男性病患，获得了明显的结果。

Tobinick医师表示，治疗前，这位病患无法告诉我们他居住在哪里一州、今年是哪一年，也无法辨识波士顿名称测验(Boston naming test)中的日常物件图卡(10种有9种无法辨识)。

不过，作者报告指出，给药之后10分钟，出现了明显的改善，病患可以说出居住在哪里一州，说出的年份只和实际相差一年；再者，他比较镇定且较少焦虑，对于问题的反应比较不费力且比较迅速，不用等太久。

治疗后2小时，病患的状态持续改善，他可以正确的说出波士顿名称测验中的10张图卡中的9件物品名称。

此研究发表于1月9日的Journal of Neuroinflammation期刊。

除了这个单一研究案例，Tobinick医师和同事之前在2006年发表了一个为期6个月的观念验证研究(proof-of-concept study)，介绍了15位病患的经脊椎etanercept开放卷标试验的效果。

这些案例接受每周一次的治疗，研究者指出其中有多位有类似的立即改善，但是研究当时为每月进行评估，因此促使他们以

目前这个单一研究案例探讨治疗的反应有多迅速。

Tobinick医师表示，当我们开始设计研究时，我们并不预期会有迅速反应，但是当我们开始治疗之后，许多病患有着迅速的反应，通常仅需几分钟，这是相当大的惊喜，不过需要反覆确认，现在我们已经从维持治疗中获得正面的临床反应，有些案例已经维持超过3年。

【非治愈】

尽管有令人鼓舞的结果，但Tobinick医师表示，这种治疗方式仍无法被视为可以治愈的方法。

他表示，这不是可以治愈的方法，无法让病患完全恢复正常，但是我们相信可以产生明显的效果，对病患本身和家人而言，显然是相当重要的。

AD的脑部病理典型特征是神经发炎合并细胞激素过度表现，科学家一直怀疑发炎前TNF- α 与AD病理有关联——这种假设是基于基础科学和基因证据之研究成果。

比发炎前效果更有关的，是TNF- α 的过度表现，会造成类淀粉斑 (amyloid plaques) 增加，而最近已有爱尔兰的研究者发现是乙型-淀粉样蛋白 (beta amyloid)，特定的乙型-淀粉样蛋白寡聚物 (beta amyloid oligomer) 干扰AD病患的记忆机制，而由TNF- α 调节。

目前的阿兹海默氏症研究中，认为可能是一些类淀粉斑(如淀粉样蛋白寡聚物)在脑和脑脊髓液悬环，而不是沉积在脑部，与AD病患的记忆问题有关。

Tobinick医师表示，干扰了记忆的种类淀粉似乎是由TNF- α 调控，因此认为利用抗TNF- α 方式可能可以改善这些缺损，而这也是我们在这些病患所发现的。

【惊人的诺言】

开始使用经脊椎etanercept治疗AD之前，Tobinick医师任职的机构已经有超过5年、数千位严重椎间盘相关背痛和颈痛病患的临床经验，从这些经验中，他观察到有些病患因而发生认知改善这种「副作用」；这种观察发现加上越来越多有关TNF对突触失能的证据，让他决定对AD病患开始试验治疗。

目前，他的团队与学校的医疗机构合作帮助设计控制临床试验，对更多的AD病患进行试验；Tobinick医师表示，我们有足够的信息指出这些大型试验将可迅速获得成果。

除了AD，他相信这种治疗对于各类脑部异常，如额颞叶痴呆 (frontotemporal dementia)、本态性进行性失语症 (primary progressive aphasia) 以及慢性创伤性脑损伤 (chronic traumatic brain injury) 的病患都有惊人的成果。

未来的可能研究方向包括治疗脊索损伤、脑肿瘤、以及各种神经退化疾病。

【不能浪费时间】

一篇编辑评论中，阿肯色大学医学中心Donald W. Reynolds老化研究中心研究主任Sue Griffin博士表示，Tobinick 医师等人的发现是空前的，需要立即进行后续研究。

Griffin博士是神经发炎领域的先驱，在1989年时，第一个描述脑中细胞激素过度反应与AD之间的关联。

Griffin博士向Medscape神经学&神经外科学表示，我希望科学界重视并立即开始后续研究，美国有5百万阿兹海默氏症患者，我们不可以浪费时间。

Griffin博士表示，她个人见证了Tobinick博士的病患经脊椎etanercept治疗后的惊人成果。

Griffin博士表示，我必须承认我一开始有所怀疑，所以我继续观察过程且在治疗前后和病患与家属交谈；这是我见过最令人经验的发现之一。

她目前正着手与Tobinick博士建立合作研究计划，未来将在她的研究机构对此方式进行临床与基础科学研究。

Griffin博士表示，这种治疗方式的不利之处在于它的费用，如果以每周一次治疗计算，一年需美金3万元；不过，她表示，如果证明可行，治疗费用需与照顾数百万名失能病患的照护费用相权衡。

在神经科学研究中心（Neurological Research）的网页有进一步的信息，Tobinick医师的电子信箱是etmd@ucla.edu。

研究的共同作者，Hyman Gross医师宣称没有与此研究相关的利益冲突；Tobinick医师拥有etanercept制造商Amgen的股权，且有许多专利权，包括美国专利编号 6,982,089 与 7,214,658，描述肠道外与经脊椎使用 etanercept治疗阿兹海默氏症与其它神经异常。

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TOP

Anti-TNF-alpha Therapy Produce

By Caroline Cassels
Medscape Medical News

January 15, 2008 — Perispinal etanercept (*Enbrel*, Amgen), an anticytokine therapy that targets excess tumor necrosis factor- α (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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