



# Perispinal etanercept for neuroinflammatory disorders

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**Excess TNF is centrally involved in the pathogenesis of a variety of neuroinflammatory disorders, including Alzheimer's disease, other forms of dementia, intervertebral disc-related pain, and related disorders. TNF causes neuronal dysfunction, regulates synaptic mechanisms, and mediates amyloid-induced disruption of molecular mechanisms involved in memory. Perispinal administration of etanercept, a potent anti-TNF fusion protein, is a treatment modality whose rapid clinical effects may be related to modulation of these TNF-related mechanisms, particularly the role of TNF as a gliotransmitter capable of regulating synaptic transmission. This approach utilizes therapeutic delivery of etanercept across the dura via the cerebrospinal venous system, a confluence of the venous plexuses of the spine and the brain, in which flow is bi-directional owing to the absence of venous valves.**

Recent advances in the basic scientific understanding of the role of the immune system in the regulation of neuronal function have provided new insight into the central role played by an excess of the cytokine, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), in neuroinflammatory disorders [1–3]. The pro-inflammatory effects of TNF are widely recognized to contribute to the pathogenesis of a variety of diseases [4]. It is now recognized that, in addition to its role as a pro-inflammatory cytokine, TNF is one of a handful of identified gliotransmitters [5,6]. As a gliotransmitter, TNF functions to modulate synaptic transmission [7,8]. TNF plays a central role in the glial–neuronal interactions that influence both memory mechanisms and neuropathic pain [1,9–12]. These insights now help to explain, in selected neuroinflammatory disorders, the rapid positive clinical effects of etanercept, a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two human p75 TNF- $\alpha$  receptors linked to the Fc fragment of human IgG1 [13]. By binding to TNF and blocking its interaction with cell surface TNF receptors, etanercept reduces the biologic effect of excess TNF [14]. Optimal therapeutic efficacy, however, requires that etanercept be able to reach the therapeutic target in adequate concentration [15]. For neuroinflammatory disorders involving the central nervous system this requires novel

methods of anatomically targeted delivery because large molecules, such as etanercept, cannot cross the blood–brain barrier when delivered systemically [16]. The anatomic and functional continuity of the spinal and cerebral venous systems, such that their combination may be referred to as the cerebrospinal venous system, provides an anatomic route whereby perispinal etanercept may cross the dura and reach the neuraxis [17–20]. An understanding of the use of perispinal etanercept for the treatment of neuroinflammatory disorders, such as Alzheimer's disease (AD), sciatica, and related disorders, requires a more detailed knowledge of the cerebrospinal venous system and the effects of TNF on glial–neuronal interactions.

## **TNF and glial–neuronal interactions**

*TNF, a gliotransmitter, regulates synaptic communication between neurons*

Neuroinflammation involves activation of both microglia and astrocytes [1,2,11,20,21]. Activated microglia may produce a variety of signaling molecules, including TNF [1,11,20,22–27]. Glial activation is operative in disorders of both the brain and spinal cord, including Alzheimer's disease, neuropathic pain, and spinal radiculopathy [1,2,11,20–27]. In Alzheimer's disease neuroinflammation may accelerate amyloid deposition, and amyloid deposition may activate microglia, producing a deleterious positive feedback loop [2,25–30]. Modulation of glial activation has been

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# Perispinal TNF-alpha inhibition for discogenic pain

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## Summary

**Objective:** To examine the potential of etanercept, a biological inhibitor of tumour necrosis factor-alpha (TNF), delivered by perispinal administration, for the treatment of pain associated with intervertebral disc disease.

**Methods:** Charts from 20 selected patients treated at our private clinic by perispinal delivery of etanercept 25 mg for severe, chronic, treatment-resistant discogenic pain were reviewed. Therapeutic benefit was assessed clinically and was documented by changes in a validated pain instrument, the Oswestry Disability Index. The patients were treated off-label with etanercept as part of our usual practice of medicine. Five detailed case reports are presented, including three additional patients.

**Results:** Rapid, substantial and sustained clinical pain reduction was documented in this selected group of patients. The cohort of 20 patients had a mean age of 56.5 and mean duration of pain of 116

months. Nine of the patients had undergone previous spinal surgery; 17 had received an epidural steroid injection or injections (mean 3.2). This group of patients received a mean of 1.8 doses (range 1-5, median 1.0) of etanercept during the observation period. The mean length of follow-up was 230 days. Clinical improvement was confirmed by a decrease in the calculated Oswestry Disability Index from a mean of  $54.85 \pm 12.5$  at baseline, improving to  $17.2 \pm 15.3$  ( $p < 0.003$ ) at 24 days and ending at  $9.8 \pm 13$  ( $p < 0.003$ ) at 230 days.

**Conclusions:** TNF inhibition by etanercept delivered by perispinal administration may offer clinical benefit for patients with chronic, treatment-resistant discogenic pain. Further study of this new treatment modality is warranted.

**Key words:** tumour necrosis factor; TNF; etanercept; discogenic pain; cervical radiculopathy; lumbar radiculopathy; failed back syndrome

## Introduction

The biological TNF inhibitors, consisting of etanercept, infliximab, adalimumab, CDP 870, oncept and other molecules in clinical development, constitute a new class of therapeutic agents which have proved remarkably effective for a variety of treatment-refractory chronic inflammatory disorders [1-6]. Etanercept, an anti-TNF fusion protein, was the first recombinant TNF inhibitor to be available for subcutaneous use. It functions as a selective and potent inhibitor of the biological action of TNF. Etanercept is currently approved for the treatment of rheumatoid arthritis in children [7] and adults [8] and psoriatic arthritis [9]. It has also been shown to be effective in relieving refractory back and neck pain associated with ankylosing spondylitis [10]. Because of the fundamental involvement of TNF in generating the inflammatory response, etanercept has potential for treating a diverse group of systemic and localised clinical disorders. It is currently being studied with a view to treating Wegener's granulomatosis, dermatomyositis, histiocytosis, psoriasis, cancer

cachexia, temporomandibular disorders, pain and swelling after molar extraction, and a number of other inflammatory disorders with documented involvement of TNF.

A central role of TNF in one localised inflammatory disorder, pain associated with intervertebral disc disease, has been suggested by an elegant series of experiments conducted over two decades. It is known that disc herniation can lead to pain by mechanical compression of adjacent nerve roots. However, a subset of patients have pain without demonstrable compression, or continue to have pain despite seemingly successful surgical removal of the offending protruding disc [11]. A chemical component of the pain, independent of structural deformation, was suspected [12, 13]. Subsequent research showed that a component of the intervertebral disc, the nucleus pulposus, was inherently inflammatory and could cause nerve damage without compression [14, 15]. Investigation has confirmed that TNF duplicates nucleus pulposus-induced inflammation and neuropathy [16]. TNF

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ORIGINAL ARTICLE

# Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients

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*Key words:* Back pain – Chronic pain – Disc – Etanercept – Radiculopathy – Sciatica – TNF

## SUMMARY

*Objective:* Documentation of the clinical results obtained utilizing perispinal etanercept off-label for treatment-refractory back and neck pain in a clinical practice setting.

*Research design and methods:* The medical charts of all patients who were treated with etanercept for back or neck pain at a single private medical clinic in 2003 were reviewed retrospectively. Patients were treated if they had disc-related pain which was chronic, treatment-refractory, present every day for at least 8 h, and of moderate or severe intensity. Patients with active infection, demyelinating disease, uncontrolled diabetes, lymphoma or immunosuppression were excluded from treatment with etanercept. Etanercept 25 mg was administered by subcutaneous injection directly overlying the spine. Visual Analogue Scales (VAS, 0–10 cm) for intensity of pain, sensory disturbance, and weakness prior to and 20 min, 1 day, 1 week, 2 weeks, and 1 month after treatment were completed. Inclusion criteria for analysis required baseline and treatment VAS data.

*Main outcome measures:* Before and after treatment VAS comparisons for intensity of pain, sensory disturbance, and weakness.

*Results:* 143 charts out of 204 met the inclusion VAS criteria. The 143 patients had a mean age of  $55.8 \pm 14$ , duration of pain of

$9.8 \pm 11$  years, and an initial Oswestry Disability Index of  $42.8 \pm 18$ , with 83% having back pain, 61% sciatica, and 33% neck pain. 30% had previous spinal surgery, and 69% had previously received epidural steroid injections (mean  $3.0 \pm 3$ ). The patients received a mean of  $2.3 \pm 0.7$  doses of perispinal etanercept separated by a mean interval of  $13.6 \pm 16.3$  days. The mean VAS intensity of pain, sensory disturbance, and weakness were significantly reduced after perispinal etanercept at 20 min, 1 day, 1 week, 2 weeks, and 1 month with a  $p < 0.0001$  at each time interval for the first dose in this patient population.

*Conclusions:* Perispinal etanercept is a new treatment modality which can lead to significant clinical improvement in selected patients with chronic, treatment-refractory disc-related pain. Generalizability of the present study results is limited by the open-label, uncontrolled methodology employed. Based on this and other accumulating recent studies, etanercept may be useful for both acute and chronic disc-related pain. Further study of this new treatment modality utilizing double-blind placebo controlled methodology is indicated.

*Note:* This treatment method is protected by multiple patents awarded to Edward Tobinick MD, including U.S. patents 6015557; 6177077; 6419944; 6537549 and Australian patent 758523.

# Perispinal Etanercept for Treatment of Alzheimer's Disease

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**Abstract:** Background: Increasing basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of Alzheimer's Disease. Excess TNF-alpha, a cytokine with pleotropic effects in the CNS, has been suggested to be involved in the pathogenesis of AD. In addition to its pro-inflammatory effects, TNF-alpha affects synaptic transmission; and glutamate, NMDA, and amyloid pathways. More specifically, TNF-alpha, produced by glia, has been shown to affect both synaptic strength and to mediate synaptic scaling, a homeostatic mechanism important to the control of neural networks. A recently published small, open-label pilot study suggested that inhibition of the inflammatory cytokine TNF-alpha utilizing the perispinal administration of etanercept may lead to sustained cognitive improvement for six months in patients with mild, moderate, and severe Alzheimer's disease. Results: Continued open-label clinical experience with this new treatment modality, now for more than two years, suggests that weekly maintenance treatment with perispinal etanercept may have a sustained positive effect. In addition, rapid clinical improvement, within minutes of dosing, has been observed on a repeated basis in multiple patients. Discussion: It is hypothesized that perispinal administration of etanercept may enable rapid delivery to the CNS via the cerebrospinal venous system, resulting in improvement in synaptic mechanisms which have been dysregulated by excess TNF-alpha. TNF-alpha modulation in Alzheimer's disease may also act by influencing glutamate, NMDA, amyloid and other inflammatory pathways. Methods of perispinal administration, as described in the pilot study, may prove useful for delivering other therapeutics, particularly large molecules, to the CNS. Further study in randomized, placebo-controlled clinical trials and in basic science studies is merited.

**Keywords:** TNF, etanercept, Alzheimer's, synaptic scaling, dementia, cytokines.

Increasing basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of Alzheimer's Disease (AD) [1, 2]. Recognizing that brain inflammation is a hallmark of AD, clinical trials for AD utilizing pharmacologic anti-inflammatory agents, including prednisone and non-steroidal anti-inflammatory drugs were attempted. Despite the fact that these initial trials were unsuccessful, it was still surmised that more successful methods to intervene in the inflammatory pathways of AD could be developed [3, 4]. The scientific community was aware that tumor necrosis factor-alpha (TNF) had been identified as the "master regulator" of the inflammatory response across multiple organ systems[5]. TNF, a pro-inflammatory cytokine, both initiates and amplifies the immune response. Using recombinant DNA technology selective and potent biologic antagonists of TNF were developed for human use. The biologic anti-TNF agents currently available for human use in the U.S. are etanercept, an anti-TNF fusion protein; infliximab, a chimeric anti-TNF monoclonal antibody; and adalimumab, an anti-TNF monoclonal antibody. Both etanercept and adalimumab are approved for subcutaneous use; infliximab is approved for intravenous dosing. Each of these anti-TNF biologics has been demonstrated to slow disease progression for their approved indications, which include rheumatoid arthritis. TNF had been implicated in the pathogenesis of RA.

Increasing scientific evidence suggests that TNF is also centrally involved in the pathogenesis of AD. Excess TNF has been demonstrated in the cerebrospinal fluid, the serum, and the plasma in patients with AD [6-8]. There is substantial scientific evidence that amyloid, glutamate, and NMDA pathways are involved in AD pathogenesis. Increasing evidence suggests that TNF may interact with each of these pathways to increase neurotoxicity and neuronal damage in AD [9-19].

Recently an additional mechanism through which TNF may contribute to the pathogenesis of AD has been identified: interference with synaptic mechanisms. Synaptic dysfunction in AD is well-recognized, and it has previously been suggested that alterations in synaptic homeostatic mechanisms might contribute to memory impairment in AD [20]. TNF has been demonstrated to have synaptic effects, controlling synaptic strength and directly affecting glutamate transmission [21, 22]. In addition TNF has been demonstrated to mediate synaptic scaling, a homeostatic mechanism for regulating synaptic connectivity that may have important implications for the maintenance and efficiency of neural networks [20, 23].

Excess TNF therefore represents a target for therapeutic intervention in AD, but there remained issues regarding the delivery of an anti-TNF biologic to the brain. Each of the three approved biologic TNF inhibitors is a large molecule, with a molecular weight in excess of 100,000 daltons. The blood-brain barrier characteristically prevents passage of molecules larger than approximately 500 MW [24].

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Research article

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## Rapid improvement in verbal fluency and aphasia following perispinal etanercept in Alzheimer's disease

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### Abstract

**Background:** Recent clinical studies point to rapid and sustained clinical, cognitive, and behavioral improvement in both Alzheimer's disease and primary progressive aphasia following weekly perispinal administration of etanercept, a TNF-alpha inhibitor that acts by blocking the binding of this cytokine to its receptors. This outcome is concordant with recent basic science studies suggesting that TNF-alpha functions *in vivo* as a gliotransmitter that regulates synaptic function in the brain. We hypothesized that perispinal etanercept had the potential to improve verbal function in Alzheimer's disease, so we included several standardized measures of verbal ability to evaluate language skills in a clinical trial of perispinal etanercept for Alzheimer's disease.

**Methods:** This was a prospective, single-center, open-label, pilot study, in which 12 patients with mild-to-severe Alzheimer's disease were administered etanercept, 25–50 mg, weekly by perispinal administration for six months. Two additional case studies are presented.

**Results:** Two-tailed, paired t-tests were conducted comparing baseline performance to 6-month performance on all neuropsychological measures. Test batteries included the California Verbal Learning Test-Second Edition, Adult Version; Logical Memory I and II(WMS-LM-II) from the Wechsler Memory Scale-Abbreviated; the Comprehensive Trail Making Test (TMT); Boston Naming Test; and letter(FAS) and category verbal fluency. All measures revealed a significant effect except for the Boston Naming Test and the TMT-4, with WMS-LM-II being marginally significant at  $p = .05$ . The FAS test for letter fluency was most highly significant with a  $p < 0.0007$ . In addition, rapid improvement in verbal fluency and aphasia in two patients with dementia, beginning minutes after perispinal etanercept administration, is documented.

**Conclusion:** In combination with the previously reported results of perispinal etanercept in Alzheimer's disease and primary progressive aphasia, these results further argue that larger scale studies of this therapeutic intervention, including Phase 3 trials, are warranted in dementias. In addition, these results may provide insight into the basic pathophysiologic mechanisms underlying Alzheimer's disease and related forms of dementia, and suggest the existence of novel, rapidly reversible, TNF-mediated pathophysiologic mechanisms in Alzheimer's disease which are worthy of further investigation.

Case report

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## Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration

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### Abstract

Substantial basic science and clinical evidence suggests that excess tumor necrosis factor-alpha (TNF-alpha) is centrally involved in the pathogenesis of Alzheimer's disease. In addition to its pro-inflammatory functions, TNF-alpha has recently been recognized to be a gliotransmitter that regulates synaptic function in neural networks. TNF-alpha has also recently been shown to mediate the disruption in synaptic memory mechanisms, which is caused by beta-amyloid and beta-amyloid oligomers. The efficacy of etanercept, a biologic antagonist of TNF-alpha, delivered by perispinal administration, for treatment of Alzheimer's disease over a period of six months has been previously reported in a pilot study. This report details rapid cognitive improvement, beginning within minutes, using this same anti-TNF treatment modality, in a patient with late-onset Alzheimer's disease. Rapid cognitive improvement following perispinal etanercept may be related to amelioration of the effects of excess TNF-alpha on synaptic mechanisms in Alzheimer's disease and provides a promising area for additional investigation and therapeutic intervention.

### Background

Neuroinflammation with overexpression of cytokines is a standard characteristic of the brain pathology present in Alzheimer's disease [1-4]. Involvement of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) in the pathogenesis of Alzheimer's disease has long been suspected [5-9]. Increasing basic science, genetic, and clinical evidence now supports the concept that excess TNF-alpha plays a central role in Alzheimer's disease [5-25].

In 1998 etanercept, a potent anti-TNF therapeutic, was approved for human use, with rheumatoid arthritis as the initial indication. Etanercept is a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two human p75 TNF-alpha receptors linked to the Fc fragment of human IgG1. Etanercept

binds to TNF-alpha and blocks its interaction with cell surface TNF-alpha receptors, thereby reducing the biologic effect of excess TNF-alpha. The medical community now has more than 1 million patient-years of experience using etanercept for treatment of a variety of inflammatory disorders in which TNF-alpha has been postulated to play a role [26].

In 2006 the present authors published a pilot study which provided proof-of-concept that a novel method of administration of etanercept was efficacious for the treatment of Alzheimer's disease [20]. This novel method, perispinal extrathecal administration in the posterior neck, was hypothesized to improve delivery of etanercept to the brain via the cerebrospinal venous system [21,27]. In an open-label study of 15 patients treated weekly for a period

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## Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration.

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### Comments

**If confirmed by additional cases, this report of almost immediate and significant cognitive improvement triggered by perispinal administration of a TNF antagonist in one patient with the clinical signs of Alzheimer's disease will be considered a landmark in the treatment of this increasingly devastating disease.** Although a single case study is reported, it is part of a larger clinical trial underway to treat AD patients by weekly administration of etanercept, and thus replication of the reported observation should become available soon. On the basis of extensive work related to the role of pro-inflammatory cytokines such as TNF in neuroinflammation and AD, the authors propose working hypotheses on the role of TNF in regulation of synaptic transmission to explain their observations. This should trigger, in the short term, validation studies aimed at testing these provocative and stimulating hypotheses.

**Competing interests:** None declared

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Short Report

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## Rapid intracerebroventricular delivery of Cu-DOTA-etanercept after peripheral administration demonstrated by PET imaging

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### Abstract

**Background:** The cytokines interleukin-1 and tumor necrosis factor (TNF), and the cytokine blocker interleukin-1 receptor antagonist, all have been demonstrated to enter the cerebrospinal fluid (CSF) following peripheral administration. Recent reports of rapid clinical improvement in patients with Alzheimer's disease and related forms of dementia following perispinal administration of etanercept, a TNF antagonist, suggest that etanercept also has the ability to reach the brain CSF. To investigate, etanercept was labeled with a positron emitter to enable visualization of its intracranial distribution following peripheral administration by PET in an animal model.

**Findings:** Radiolabeling of etanercept with the PET emitter <sup>64</sup>Cu was performed by DOTA (1,4,7,10-tetraazadodecane-N,N',N'',N'''-tetraacetic acid) conjugation of etanercept, followed by column purification and <sup>64</sup>Cu labeling. MicroPET imaging revealed accumulation of <sup>64</sup>Cu-DOTA-etanercept within the lateral and third cerebral ventricles within minutes of peripheral perispinal administration in a normal rat anesthetized with isoflurane anesthesia, with concentration within the choroid plexus and into the CSF.

**Conclusion:** Synthesis of <sup>64</sup>Cu-DOTA-etanercept enabled visualization of its intracranial distribution by microPET imaging. MicroPET imaging documented rapid accumulation of <sup>64</sup>Cu-DOTA-etanercept within the choroid plexus and the cerebrospinal fluid within the cerebral ventricles of a living rat after peripheral administration. Further study of the effects of etanercept and TNF at the level of the choroid plexus may yield valuable insights into the pathogenesis of Alzheimer's disease.

### Background

Excess tumor necrosis factor-alpha (TNF) has been identified as a therapeutic target in Alzheimer's disease (AD)[1]. Excess TNF in the cerebrospinal fluid (CSF), at concentrations 25 times higher than in controls, has been demonstrated in AD, and may predict disease progression[2]. Etanercept is a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two

human p75 TNF receptors linked to the Fc fragment of human IgG1, which functions *in vivo* as a potent anti-TNF therapeutic. Recent reports of rapid clinical improvement in patients with AD and related disorders following the perispinal administration of etanercept (MW = 150,000) suggested that etanercept had the ability to penetrate into the CSF in the brain in a therapeutically effective concentration[3,4], an ability which recently had been demon-

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## Neurology & Neurosurgery Clinical Cases

# Perispinal Etanercept Produces Rapid Improvement in Primary Progressive Aphasia: Identification of a Novel, Rapidly Reversible TNF-Mediated Pathophysiologic Mechanism

**Edward Tobinick, MD**

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## Abstract

Primary progressive aphasia (PPA) is an uncommon form of progressive dementia for which there exists no established treatment. The underlying pathology may be that of either frontotemporal dementia or Alzheimer's disease. Increasing evidence suggests that excess tumor necrosis factor (TNF) may play a central role in Alzheimer's disease. Additionally, excess TNF has been documented in patients with frontotemporal dementia. Excess TNF may therefore represent a therapeutic target in PPA. Etanercept, an anti-TNF fusion protein, binds to TNF, thereby reducing its biologic effect. Emerging evidence suggests that perispinal administration of etanercept may have therapeutic efficacy for Alzheimer's disease. This evidence, in combination, supports a rationale for the use of perispinal etanercept for the treatment of PPA. This report documents rapid improvement in verbal abilities, beginning within 20 minutes of perispinal etanercept, in a patient with severe PPA. With repeated weekly dosing, sustained improvement at 1 month is documented, with a more than 10-point improvement in the patient's abilities to perform activities of daily living as measured by a standardized instrument, the Alzheimer's Disease Cooperative Study-Activities of Daily Living inventory. Rapid clinical improvement in PPA following perispinal etanercept administration may be related to TNF's role as a gliotransmitter and modulator of synaptic communication in the brain. These results may provide insight into the basic pathophysiologic mechanisms underlying PPA and related forms of dementia and suggest the existence of novel, rapidly reversible, TNF-mediated pathophysiologic mechanisms in both PPA and Alzheimer's disease. Further study of this therapeutic method is indicated.

## Introduction

Primary progressive aphasia (PPA) is an uncommon form of progressive dementia without established treatment. One third of these patients have underlying Alzheimer's disease pathology, and two thirds have pathology characteristic of frontotemporal dementia.<sup>[1]</sup> These patients characteristically present with progressive difficulty with language as the most prominent initial manifestation of the disease, which advances in an unrelenting fashion until all language abilities are lost.<sup>[2]</sup> No effective treatment has been established.<sup>[1,2]</sup>

Basic science and genetic, epidemiologic, and clinical evidence suggest that excess tumor necrosis factor-alpha (TNF-alpha) may play a central role in the pathogenesis of Alzheimer's disease.<sup>[3-23]</sup> In addition, excess TNF has been documented in the cerebrospinal fluid of patients with frontotemporal dementia.<sup>[24]</sup> Excess TNF may, therefore, represent a therapeutic target in PPA. Etanercept, a recombinant dimeric anti-TNF fusion protein, binds to TNF and blocks its interaction with cell-surface TNF receptors, thereby reducing the biologic effect of excess TNF. Emerging evidence suggests that perispinal administration of etanercept may have therapeutic efficacy in Alzheimer's

Commentary

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## Perispinal etanercept: Potential as an Alzheimer therapeutic

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### Abstract

Tumor necrosis factor-alpha (TNF) is one of a number of systemic and immunomodulating cytokines that generally act to promote acute-phase reactions but can drive degenerative changes when chronically elevated. Traditional focus on TNF has been directed at these inflammation-related functions. Of particular relevance to intersections between neuroinflammation and neurodegeneration is the ability of TNF to increase expression of interleukin-1 (IL-1), which in turn increases production of the precursors necessary for formation of amyloid plaques, neurofibrillary tangles, and Lewy bodies. More recent data have revealed that TNF, one of the few gliotransmitters, has strikingly acute effects on synaptic physiology. These complex influences on neural health suggest that manipulation of this cytokine might have important impacts on diseases characterized by glial activation, cytokine-mediated neuroinflammation, and synaptic dysfunction. Toward such manipulation in Alzheimer's disease, a six-month study was conducted with 15 probable-Alzheimer patients who were treated weekly with perispinal injection of Etanercept, an FDA-approved TNF inhibitor that is now widely used for treatment of rheumatoid arthritis and other systemic diseases associated with inflammation. The results demonstrated that perispinal administration of etanercept could provide sustained improvement in cognitive function for Alzheimer patients. Additionally, the authors were impressed by the striking rapidity with which these improvements occurred in the study patients. An example of this rapid improvement is presented in this issue as a case report by Tobinick and Gross. Such rapid gain of function inspires speculation about the role of gliotransmission or other equally rapid synaptic events in the relationship of TNF to Alzheimer-impacted neurophysiology. Because of the inability of large molecules such as etanercept to cross the blood brain barrier following conventional systemic administration, it is likely that the more direct drug delivery system pioneered by Tobinick also contributed to the effectiveness of the treatment. If so, this system could be useful in drug delivery to the brain in other neural disorders, as well as in animal research studies, many of which currently employ delivery strategies that inflict damage to neural cells and thus engender neuroinflammatory responses.

### Introduction

The Tobinick and Gross case report in this issue of the *Journal of Neuroinflammation* [1] is hopefully the first of many articles attesting to the benefit of direct-to-the-brain

delivery of anti-cytokine therapies, which may result in rapid and sustained improvement in cognition, behavior, and attentiveness. In view of the discouraging results to date of trials testing the efficacy of anti-inflammatory

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## TNF-alpha Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study

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Posted

### Abstract and Introduction

#### Abstract

**Context:** Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD.

**Objective:** To investigate the use of a biologic TNF-alpha inhibitor, etanercept was given by perispinal extrathecal administration for the treatment of AD.

**Methods:** This was a prospective, single-center, open-label, pilot (proof-of-concept) study, in which 15 patients with mild-to-severe AD were treated for 6 months. We administered etanercept, 25-50 mg, once weekly by perispinal administration. Main outcome measures included the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Severe Impairment Battery (SIB).

**Results:** The average age of our patient population was 76.7. The mean baseline MMSE was 18.2 (n = 15); the mean baseline ADAS-Cog was 20.8 (n = 11); and the mean baseline SIB was 62.5 (n = 5). There was significant improvement with treatment, as measured by all of the primary efficacy variables, through 6 months: MMSE increased by  $2.13 \pm 2.23$ , ADAS-Cog improved (decreased) by  $5.48 \pm 5.08$ , and SIB increased by  $16.6 \pm 14.52$ .

**Conclusion:** Increasing amounts of basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of AD. This small, open-label pilot study suggests that inhibition of the inflammatory cytokine TNF-alpha may hold promise as a potential approach to AD treatment. Further study in randomized, placebo-controlled clinical trials is merited.

#### Introduction

Inflammatory immune mechanisms play a central role in the causation of Alzheimer's disease (AD).<sup>[1-5]</sup> Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, the "master regulator" of the immune response, is the key initiator of immune-mediated inflammation in multiple organ systems, including the brain.<sup>[6]</sup> Scientific evidence identifying TNF-alpha involvement in the pathogenesis of AD began accumulating a decade ago in experimental models. In vitro, with use of a human monocytic cell line, beta amyloid was found to stimulate secretion of TNF-alpha.<sup>[7]</sup> TNF-alpha plus gamma-interferon was found to induce beta-amyloid production.<sup>[8]</sup> Beta amyloid was shown to stimulate microglial inflammatory pathways, resulting in neurotoxicity mediated by TNF-alpha generated by reactive microglia and monocytes.<sup>[9]</sup> Clinical evidence followed, with a central place for TNF-alpha in AD pathogenesis suggested by demonstration of 25-fold elevated levels of TNF-alpha in the cerebrospinal fluid of patients with AD,<sup>[10]</sup> and the finding that increased cerebrospinal fluid TNF-alpha levels correlated with clinical deterioration.<sup>[11]</sup> In 2005, the evidence supporting TNF-alpha involvement in AD accelerated, including identification of a greater risk for AD in an Australian population associated with a polymorphism in the promoter region of the TNF gene.<sup>[12]</sup>

Increasing amounts of laboratory evidence implicate TNF-alpha in inflammatory molecular mechanisms producing neurotoxicity, neuronal death, or neuronal dysfunction involving both TNF-glutamate<sup>[13-17]</sup> or TNF-amyloid