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# Perispinal etanercept for neuroinflammatory disorders

**Edward Tobinick**

Institute for Neurological Research, a private medical group, inc. 100 UCLA Medical Plaza, Suites 205-210, Los Angeles, CA 90095, United States

**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-α), 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.

*Corresponding author:* Tobinick, E. (etmd@ucla.edu)

## 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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proposed as a potential intervention in neurodegenerative diseases, which may interrupt the amyloid-neuroinflammation positive feedback loop [2,3,20,25–30]. TNF inhibition has been proposed as a potential method of modulating glial activation in neuroinflammatory disorders involving both the brain and the spinal cord [1,2,3,11,12,20].

Glial cells, particularly astrocytes, envelope neuronal synapses and release molecules, gliotransmitters, which regulate synaptic transmission in those enveloped synapses [5,7]. In addition, the processes of one astrocyte may make contact with over 100 000 synapses [5]. Stimulation of a single neuron can cause a change in an animal's behavior [31]. This may be possible because of the massively interconnected nature of the brain: a single cortical pyramidal cell connects to several thousand post-synaptic neurons [31]. Processes affecting glial–neuronal interaction may, therefore, have potential for rapid amplification of their cognitive and behavioral effect, or their effect on spinal pain.

TNF is one of only a handful of recognized gliotransmitters [5,7]. In experimental models, TNF alters synaptic transmission in rat hippocampal slices and produces a rapid exocytosis of AMPA receptors in hippocampal pyramidal cells [32,33]. Glial TNF has been shown to control synaptic strength [34]. In addition, TNF has been shown to regulate a more widespread synaptic mechanism known as synaptic scaling [32]. Synaptic scaling is a homeostatic mechanism necessary for the optimal functioning of neural networks [32,35]. In basic science models of Alzheimer's disease, TNF has recently been demonstrated to mediate the disruption of long-term potentiation and related memory mechanisms produced by amyloid and amyloid oligomers [9,10]. Dysregulation of these synaptic processes by excess TNF may contribute to the pathogenesis of Alzheimer's disease; in a similar fashion, this TNF-mediated synaptic dysregulation may also contribute to the deleterious effects of excess TNF in spinal radiculopathy [36–38]. Optimal neuronal function may require that TNF be maintained within a physiologic range [38]. Amelioration of the adverse synaptic effects of excess TNF by perispinal etanercept may therefore help explain its rapid clinical benefit seen in patients with Alzheimer's disease and disc-related pain, as discussed below.

### *TNF, glia-neuronal interactions and microvascular effects*

Increasing evidence supports the concept that glial–neuronal signaling is central to the dynamic control of the brain microcirculation [6,39,40]. Results in an *in vitro* mouse model of Alzheimer's disease have recently provided evidence that abnormal astrocytic activity may contribute to vascular instability in AD [41]. It is, therefore, tempting to speculate that excess TNF in Alzheimer's disease may also interfere with microvascular cerebral blood flow by interfering with these glial-mediated processes. Etanercept has recently been shown to improve clinical microvascular function and to be vasculoprotective in an experimental model of aging [42,43]. In addition, recent evidence suggests that excess TNF may cause endothelial dysfunction in Alzheimer's disease [42,44]. Amelioration of TNF-mediated endothelial dysfunction and/or TNF-mediated dysregulation of glial control of microvascular cerebral blood flow may provide additional mechanisms whereby perispinal etanercept may produce beneficial effects in Alzheimer's disease, both on a short-term and long-term basis [42,44,45]. In addition, reduction of excess TNF may have the potential to interfere with the production of beta-amyloid [28,46].

## Etanercept, the blood–brain barrier, the cerebrospinal venous system, and the choroid plexus

Etanercept, with a molecular weight of 150 000 daltons, does not cross the blood–brain barrier (BBB) when administered systemically [16]. This may account for the failure of etanercept, delivered systemically (not by perispinal injection), to treat Alzheimer's effectively [47]. Conversely, when delivered via perispinal administration into Batson's plexus, large molecules may have the ability to reach the brain via retrograde delivery through the cerebrospinal venous system, a potential anatomic route first demonstrated by Batson in cadavers [17,19,48].

Perispinal administration introduces etanercept into the region posterior but adjacent to the spine that is drained by a component of the cerebrospinal venous system, the external vertebral venous plexus [17,48] [Figures 1 and 2]. The cerebrospinal venous system is composed of the veins, venous sinuses, and venous plexuses of the brain and the spine, which are in anatomic continuity [17,48]. The first of the two main divisions of this system, the intracranial veins, includes the cortical veins, the dural sinuses, the cavernous sinuses, and the ophthalmic veins [17,48]. The second main division, the vertebral venous system (also known as Batson's plexus), includes the vertebral venous plexuses that course along the entire

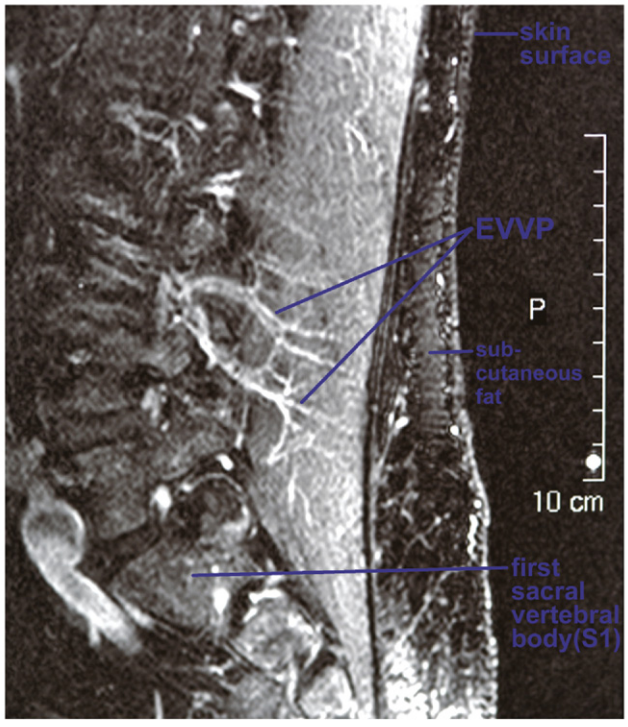


**FIGURE 1**

The external vertebral venous plexus in the lumbar spine. Magnetic resonance venogram without contrast, lateral view of the lumbar spine depicting branches of the external vertebral venous plexus (EVVP) in a human.

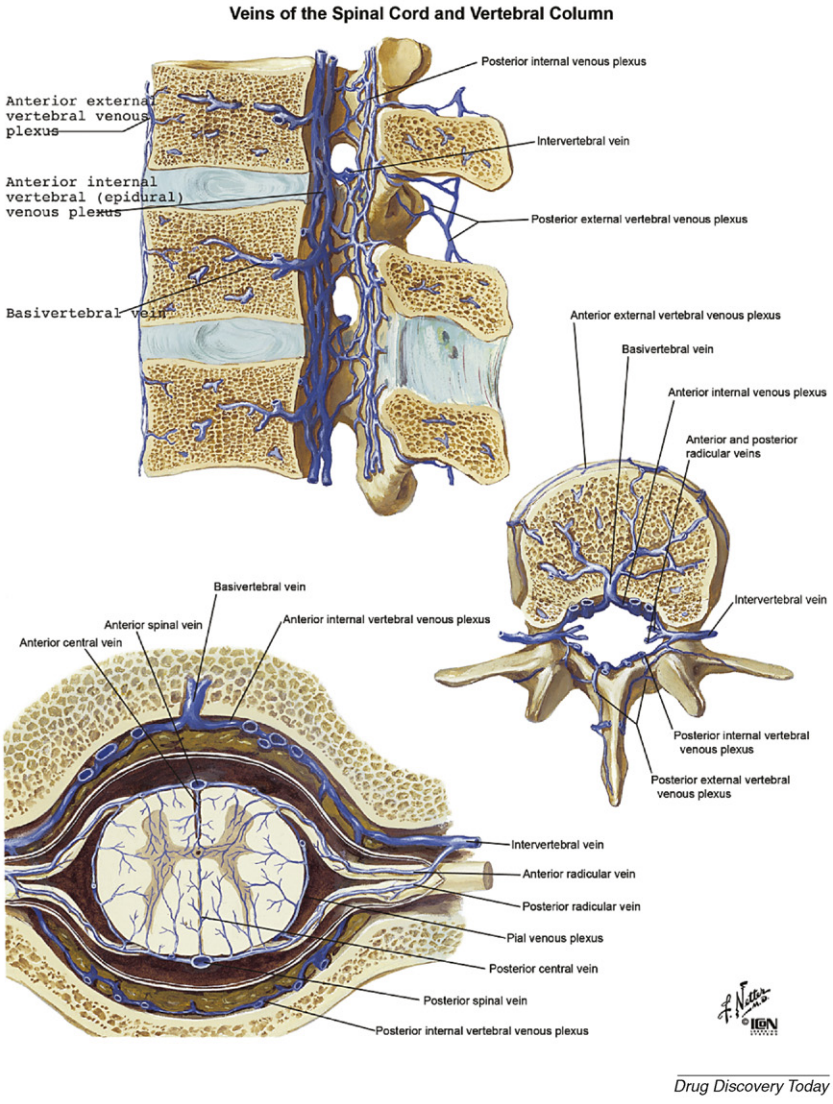


**FIGURE 2**

The spinal division of the cerebrospinal venous system. The veins of the spinal cord, the vertebral column, and the perispinal space are depicted. Note the drainage of the interspinous space by the posterior external vertebral venous plexus as well as the perforation of these veins through both the ligamentum flavum and the dura.

length of the spine [17,48]. Blood flow in the vertebral venous system is bi-directional, facilitated by the lack of valves in this unique venous system [17,48–51]. In the spine, the external vertebral venous plexus is richly connected to the internal vertebral venous plexus, which is in anatomic continuity with the intraspinal veins and the radicular veins [17,48,49] (Figure 2). The intracranial veins richly anastomose with the vertebral venous system in the suboccipital region [17]. Within the brain, the cerebrospinal venous system is richly connected to the veins of the choroid plexus [17,52].

It is hypothesized that delivery of etanercept into the cerebrospinal venous system enables delivery of etanercept into the choroid plexus; in the spine, perispinal delivery allows etanercept to rapidly reach the spine, spinal cord, dorsal root ganglia, and the nerve roots [17,18,49]. It is further hypothesized that Trendelenburg positioning, during which the examination table is tilted head down and the patient is prevented from slipping by shoulder and/or foot supports, as utilized by the author when treating patients with dementia, may assist delivery of etanercept, that has reached the choroid plexus, into the cerebrospinal fluid, particularly within the cerebral ventricles [38,45]. The large surface area of the choroid plexus (which may be as much as one-half of the entire surface area of the cerebral capillaries) and the decreased barrier characteristics of the choroid plexus may facilitate this process [38,45,52,53]. It should be noted that the decreased barrier characteristics of the choroid plexus were first noted by Goldmann in 1913, in his classic study that followed the seminal work of Paul Ehrlich, who had first defined the concept of the blood–brain barrier [54,55]. This hypothesis is supported by animal experiments, at Stanford and UBC, in which radiolabeled etanercept injected into normal rats, which were then held head down for several minutes and scanned, were found to contain radiolabeled

etanercept in the cerebrospinal fluid within their cerebral ventricles (Tobinick, unpublished data)[1] (Figure 3a and b). Delivery into the cerebrospinal fluid and perivascular spaces may also be assisted by increased intraluminal hydrostatic pressure postulated to be present in the post-capillary venules during head-down positioning [19,45,52,57]. The post-capillary venules are known to have less pronounced barrier characteristics than the capillaries themselves [57]. The dorsal tail vein courses longitudinally up the tail and anastomoses with the spinal venous system, which is analogous to the vertebral portion of the cerebrospinal venous system in humans [17,58]. In post-mortem tissue samples from Alzheimer disease patients and age-matched non-demented control individuals, TNF positive cells were found in the surroundings of the third ventricle only in the Alzheimer disease patients [59].

## Perispinal etanercept for Alzheimer's disease and related dementias

Substantial clinical, genetic, epidemiologic, and basic science evidence supports a central role of excess tumor necrosis factor-alpha (TNF-α) in the pathogenesis of Alzheimer's disease, suggesting that excess TNF is a therapeutic target [3,19,20,38,60–65].

Perispinal administration of etanercept had been previously reported to be rapidly effective (within minutes) in providing relief of intervertebral disc-related pain and radiculopathy, including sciatica, chronic low back or neck pain, and cervical radiculopathy [36,37,66]. These findings, which were consistent with the idea that perispinal administration enabled etanercept to cross the blood–dural barrier, led to the expanded concept of the potential of the bi-directional cerebrospinal venous system as a route of delivery of therapeutic molecules to both the spine and the brain [18,19,38]. Specifically, it was conceived that etanercept and potentially other large molecules, could be delivered to the brain by perispinal administration and subsequent retrograde carriage to the brain via the cerebrospinal venous system [18,19,38].

In 2004, the author and his colleagues began an IRB-approved pilot study involving a cohort of 15 patients, which provided proof-of-concept that perispinal delivery of etanercept was effective for the treatment of Alzheimer's disease [65].

This was a prospective, open-label, clinical trial of six months duration involving AD ranging in severity from mild to severe, which utilized perispinal etanercept administered at a dose ranging from 25 to 50 mg per week. The primary efficacy variables were the change from baseline in three standard measures of cognition: the AD Assessment Scale-Cognitive subscale (ADAS-Cog); the Severe Impairment Battery (SIB); and the Mini-Mental State Examination (MMSE) [65]. The study was also registered in the clinical trial database maintained by the National Institute of Health (NCT00203359). During the pilot study, in addition to the standard cognitive measures above, additional neuropsychological test batteries were administered [45]. The additional test batteries administered included the California Verbal Learning Test-Second Edition, Adult Version (CVLT-II), Logical Memory I (LMI), and II (LMII) from the Wechsler Memory Scale—Abbreviated (WMS-a), the Comprehensive Trail Making Test (TMT), Boston Naming Test, and letter (FAS) and category verbal fluency [45,67]. Neurocognitive assessments were conducted monthly. Three of the 15 patients in the pilot study with severe dementia were excluded from these additional test batteries as they could not be reliably assessed with these tools.

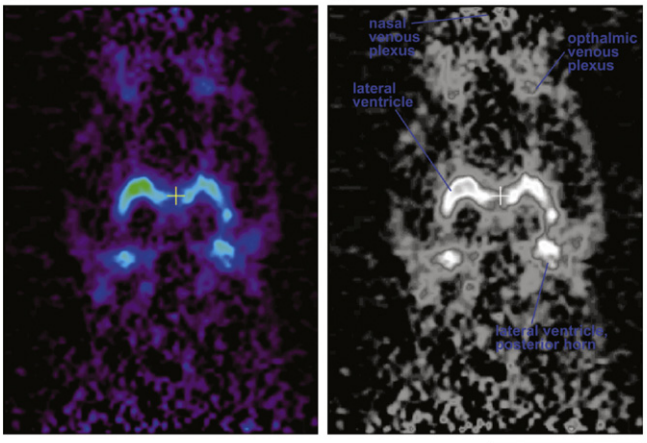


**FIGURE 3**

**(a and b)** Radiolabeled etanercept in the cerebrospinal fluid within the lateral ventricles of a rat following peripheral injection. Positron emission tomographic image, coronal view, depicting delivery of radiolabeled etanercept into the lateral cerebral ventricles of a rat after injection of etanercept into the median dorsal tail vein followed by head-down positioning. (a) is the image as obtained; (b) includes labeling of the anatomic landmarks.

The results for the primary efficacy measures have been previously reported [65]. The average age of the 15 patient study 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 six months: MMSE increased by $2.13 \pm 2.23$, ADAS-Cog improved (decreased) by $5.48 \pm 5.08$, and SIB increased by $16.6 \pm 14.52$ [65].

The secondary efficacy measures revealed significant improvements in verbal learning, memory, and fluency (Figure 4) [45].

In addition to the above results, a more detailed first case study of one of the clinical trial participants was included with the initial pilot results [65]. This was an 82-year-old man with severe Alzheimer's disease, whose clinical improvement over the course of the six months clinical trial was detailed [65]. Now, more than three years later, the patient is continuing to receive perispinal etanercept. With each weekly dose, within minutes, the patient's level of alertness characteristically improves, his affect improves, he walks

[1] Animal studies were conducted following the approval of the applicable protocols by the UBC Animal Care Committee at the University of British Columbia. Preparation of $^{64}$Cu-(1,4,7,10-tetraazadodecane-N,N′,N″,N‴-tetra-acetic acid (DOTA)-etanercept was as previously described [56]. 250 microliters of $^{64}$Cu-DOTA-etanercept solution was infused into the distal median tail vein of a rat anesthetized with inhalation anesthesia, followed by a flush of 1 cc of normal saline. The rat was then placed in the head-down position for three minutes, immediately followed by placement horizontally in the bed of a microPET imaging scanner (Focus 120, Concorde/Siemens, Knoxville, USA), at which time PET imaging was performed, while inhalation anesthesia was maintained. PET images were collected for the next 30 min period.

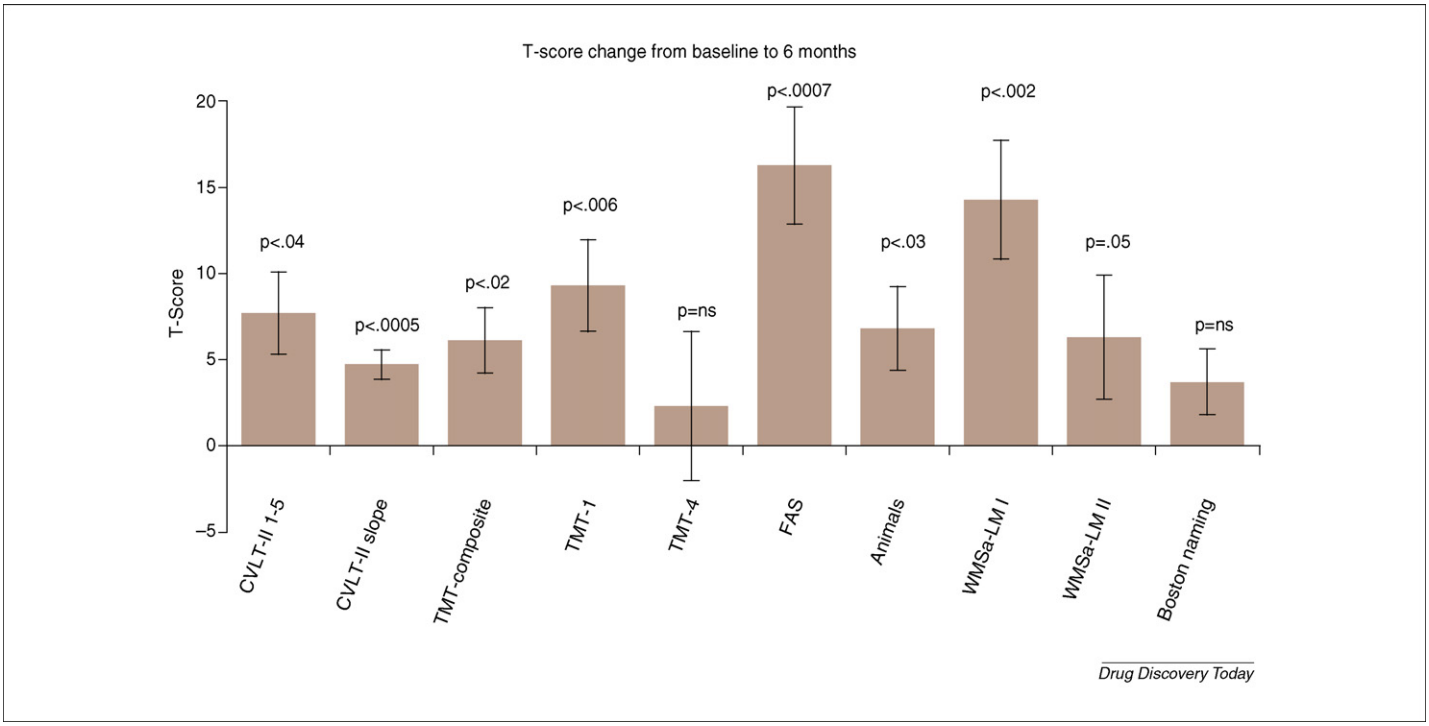


**FIGURE 4**

Changes in verbal fluency, learning, and memory over six months during maintenance treatment with perispinal etanercept in a 15 subject pilot study, as reflected by T-score change from baseline to six months. Two-tailed, paired *t*-tests were conducted comparing baseline performance to 6-month performance on all neuropsychological measures. Abbreviations: California Verbal Learning Test-Second Edition, Adult Version (CVLT-II), including tests 1–5 and slope of change; Logical Memory I (LMI), and II (LMII) from the Wechsler Memory Scale-Abbreviated (WMS-a); the Comprehensive Trail Making Test (TMT), including tests 1 (TMT-1) and 4 (more difficult) (TMT-4); Boston Naming Test; and letter (FAS) and category (animal) verbal fluency. Reproduced with permission from Tobinick and Gross [45].

with greater ease, and his verbal fluency, although very limited, improves.

This rapid clinical improvement, beginning, often subtly, within minutes of administration, is a characteristic response seen following the first dose of perispinal etanercept in the majority of patients with moderate or more advanced Alzheimer's disease, as documented in four additional case studies [20,38,45,68]. Family members, independent neurologists, and other independent observers have confirmed these clinical, cognitive, and behavioral improvements [20,38,45,68].

In the second published case study, the patient was an 81-year old physician with moderate dementia that fulfilled standard criteria for the diagnosis of AD [38]. His Montreal Cognitive Assessment (MOCA) score before etanercept was seven out of 30 possible points, consistent with a moderate to severe cortical dementia [38]. As previously reported, before perispinal etanercept the patient was unable to draw a clock or complete a simple alternating trail making task (Figure 5) and was only able to correctly name one out of the first ten pictures on the Boston Naming Test [38]. Following perispinal etanercept there was noticeable clinical improvement, beginning within minutes [38]. Two hours after his first dose of perispinal etanercept he was able to name correctly nine out of the first ten pictures on the Boston Naming Test, was able to perform correctly the alternating trail-making task, MOCA score improved to 15 and his drawing of a clock was markedly improved (Figure 5) [38].

The third published case study was of a 78-year-old woman with primary progressive aphasia (PPA) [68]. PPA is a progressive dementia without established treatment [69]. Alzheimer disease pathology is underlying in one-third of the patients, with pathology characteristic of frontotemporal dementia in the remainder [69]. Excess TNF in the cerebrospinal fluid has been demonstrated in both Alzheimer's disease and frontotemporal dementia, and has been postulated to contribute to the pathogenesis of both diseases [64,70,71]. As is the characteristic of patients with this disease, this patient had suffered progressive and inexorable decline of her language abilities during the five years of her illness, which had not responded to treatment [68]. Upon presentation for initiation of perispinal etanercept she was nearly mute, had not been able to say her husband's name for more than one year, and was unable to perform the Boston Naming Test [68]. By 20 min after her first dose of perispinal etanercept her language abilities were clearly improved. She was now able to give her husband's name, count to seven, and was more alert. At one month the patient returned for her third dose. Her daughter reported continued improvement in verbal abilities, cognition, and behavior. At one month her activities of daily living were significantly improved [68,72]. The patient regained the ability to take off her own shoes and socks, something she had not been able to do for more than one year [68]. At one month, ten minutes after her third dose of perispinal etanercept, she was able to correctly name seven out of ten objects on the Boston Naming Test, as documented by video [68].

The fourth and fifth published case studies documented rapid clinical improvement, along with improvement in verbal function, following initiation of perispinal etanercept, in both semantic

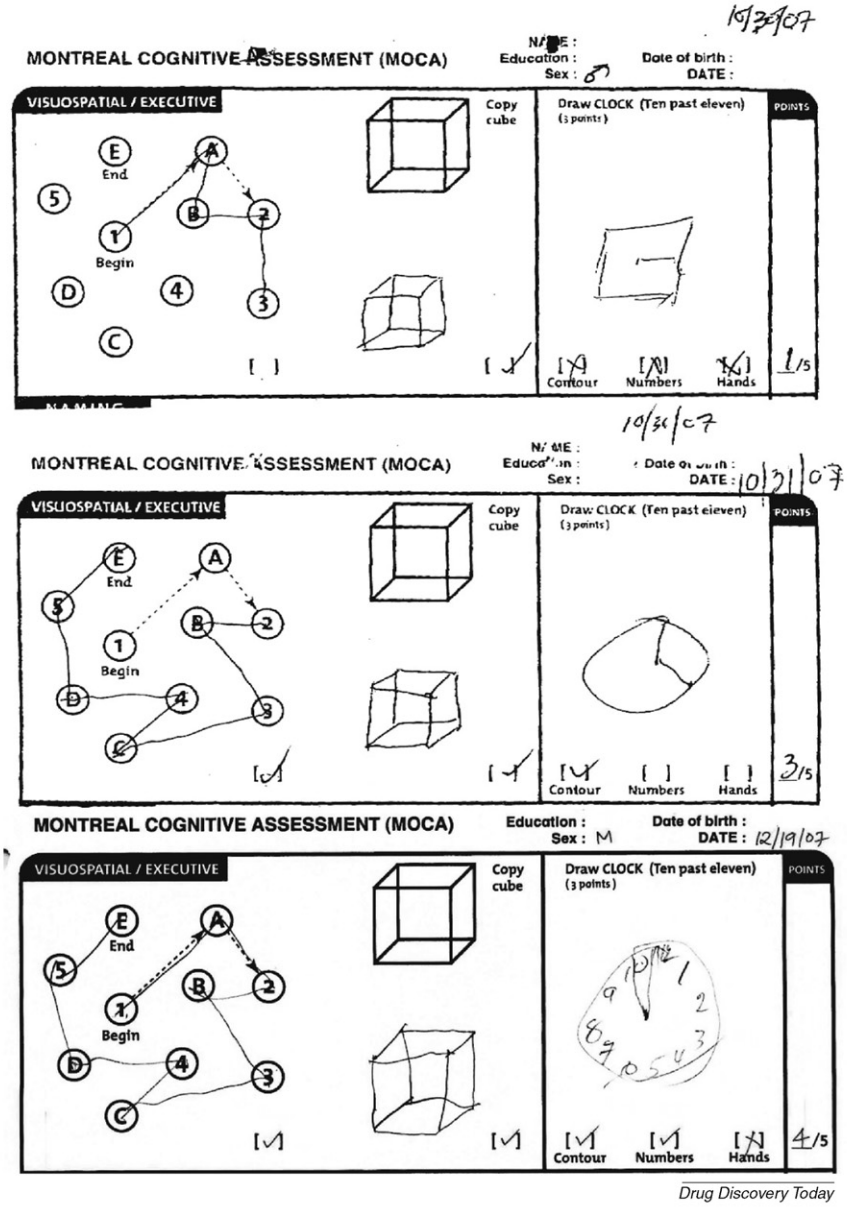


**FIGURE 5**

Rapid and sustained improvement in Visuospatial/Executive function following perispinal etanercept. The top panel depicts the first three tasks from the Montreal Cognitive Assessment completed by the patient one day before perispinal etanercept administration. The middle panel depicts the patient's results two hours after perispinal etanercept administration, showing correct completion of the alternating trail making task documenting improved executive function, and improvement in depiction of a clock face. The bottom panel depicts the patient's results at seven weeks, fourteen days after receiving his previous dose of perispinal etanercept, showing further improvement in his drawing of the clock face, with numerals added, and persistence in improvement in completion of the trail making task (The instruction for completion of the alternating trail making task are as follows: *Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from* 1 *to A then to* 2 *and so on. End here* [point to (E)].). Reproduced with permission from Tobinick and Gross [38].

dementia and in an Alzheimer patient with significant word finding difficulties [45].

Improvements in language function and verbal abilities following the initiation of perispinal etanercept treatment are common [19,38,45,68]. A recent study found that difficulties with language and word finding are commonly seen in advancing Alzheimer's disease and significantly correlate with MMSE and Clinical Dementia Rating scores [73]. This finding is concordant with the parallel improvements in MMSE and verbal fluency documented in the six months perispinal etanercept pilot study [45,67,73]. Clinical experience suggesting continued clinical effectiveness of perispinal etanercept for Alzheimer's disease with maintenance treatment, continuing for more than two years in some patients, was reported in 2007, and now continues to be apparent after more than three and one-half years of weekly treatment [19,38,45].

There exists a 'peripheral sink' hypothesis with regard to administration of therapeutic molecules for Alzheimer's disease. According to this hypothesis, it may be possible to administer therapeutic

agents in the periphery and have these agents affect intracerebral pathology. This indeed may be possible with compounds such as amyloid that have no peripheral regulatory functions. TNF, however, presents a different case. TNF has important and significant physiologic effects in the periphery, particularly with respect to immune defense [4]. In treating Alzheimer's, one would not want to suppress peripheral TNF levels more than necessary. Therefore it would be ideal if one could selectively deliver an anti-TNF therapeutic molecule to the nervous system, rather than delivering it systemically. Thus, an additional rationale for anatomically targeted treatment, utilizing perispinal etanercept administration for neuroinflammatory disorders, is presented.

The 'peripheral sink' hypothesis with regard to etanercept speculates that it might be possible to remove excess TNF from the brain after systemic administration of etanercept. The evidence arguing against the advisablity of this is two-fold. Firstly, since etanercept does not cross the BBB, one would thereby be exposing the treated individual to significant peripheral levels of etanercept and minimal levels in the cerebrospinal fluid, where TNF has been demonstrated to be elevated in AD [16]. Secondly, there is experimental evidence that suggests that TNF does not efficiently traverse the BBB: when actually measured in patients with AD and in controls, the excess TNF found in the cerebrospinal fluid of AD patients did not spill over into their blood:

***"The levels of TNF-alpha in the CSF were on average 25-fold higher in patients with AD compared to the controls. . ..In contrast serum levels of TNF-alpha were neither significantly higher in patients with AD." [70].***

This disparity in TNF levels in the CSF and in the serum probably reflects the local, intracerebral production of TNF in AD [70]. In addition, this disparity probably reflects the normal impermeability of the blood–brain barrier to the passage of large molecules [74]. It has been established that molecules with a molecular weight greater than 600 daltons are normally excluded from the central nervous system by the BBB [74]. While there appears to exist a potential limited ability of TNF [molecular weight 17 000 daltons] to cross the BBB via what is probably a saturable active transport mechanism, the fact that greatly elevated levels of TNF in the CSF in AD are not accompanied by elevated levels of TNF in the serum would suggest that this transport mechanism is inefficient [16,70].

Thus the available scientific evidence would contravene attempts to avoid the inconvenience of perispinal administration of etanercept for AD; systemic administration [not utilizing perispinal delivery] of etanercept may, in fact, expose the patient to the risks of TNF inhibition without a significant possiblity of clinical benefit for AD.

## Perispinal etanercept for sciatica, cervical radiculopathy, and chronic low back and neck pain

A substantial body of evidence suggests that TNF is centrally involved in the pathogenesis of sciatica, cervical radiculopathy, and other forms of disc-related pain [1,11,36,37,66,75]. As in Alzheimer's disease, excess TNF in this setting is associated with glial activation, neuroinflammation, and neuronal dysfunction [1,11,76]. In many cases the source of the pain is thought to be the nucleus pulposus of the spinal intervertebral discs, which is known to be inherently inflammatory and to be a source of excess TNF [75].

In 2003, the first article was published reporting improvement, within minutes, in patients with chronic pain using perispinal etanercept [37]. These clinical results included patients treated as early as June 2001. Results from 20 patients with severe, chronic, disc-related back or neck pain, or sciatica were reviewed [37]. The patients ranged in age from 38 to 79, with a mean age of 56.6 years. Their pain duration ranged from two to 360 months, with a mean duration of 116 months. 13 of the patients had exclusively low back and/or sciatic pain; one had neck pain exclusively; and six had a combination of back and neck pain. 17 of the patients had received epidural steroid injections but the pain had persisted, with a median of 3.2 epidural steroid injections. Nine of the patients had previous spinal surgery. During a mean length of follow-up of 230 days these patients experienced a significant decrease in pain intensity and disability. Their Oswestry Disability index went from a mean of $54.85 \pm 12.5$ at baseline, improving to $17.2 \pm 15.3$ ($p < 0.0003$) at 24 days and ending at $9.8 \pm 13$ ($p < 0.003$) at 230 days after a mean of 1.8 doses (range 1–5, median 1.0) of perispinal etanercept [37].

A second article in 2003 described two patients with chronic, treatment-resistant cervical radiculopathy treated successfully with perispinal etanercept, also documenting pain relief beginning within minutes and persisting for months following treatment [66].

In 2004 the results of 143 patients treated with perispinal etanercept during the previous year were published [36]. All patients had treatment-refractory disc-related pain of moderate or severe intensity. They ranged in age from 16 to 87 years, with a mean age of $55.8 \pm 14.3$. Median pain duration was $9.8 \pm 11.3$ years; median baseline Oswestry Disability Index was $42.8 \pm 17.9$. Approximately 30% of the patients had previous spinal surgery, and 69% had received previous epidural steroid injections. Magnetic resonance imaging documented disc bulge, protrusion, extrusion, or herniation in 67%; degenerative disc disease (DDD) in 51%; central spinal stenosis and DDD in 13%; spondylolisthesis and DDD in 13%; and annular tear of the intervertebral disc capsule in 6%. The patients received a mean of $2.3 \pm 0.7$ doses of perispinal etanercept with a mean interval between doses of $13.6 \pm 16.3$ days. Visual Analog Scales (VAS) for intensity of pain, sensory disturbance, and weakness were used to measure treatment response. The mean VAS intensity of pain, sensory disturbance, and weakness were significantly reduced after perispinal etanercept at 20 min, one day, one week, two weeks, and one month with a $p < 0.0001$ at each time interval for the first dose in this patient population [36].

The efficacy of perispinal etanercept for the treatment of disc-related sciatica has been confirmed by a recent randomized, controlled study performed in Japan as well as by a randomized, placebo-controlled study performed at Johns Hopkins/Walter Reed Army Medical Center [77,78].

### *Perispinal etanercept for cancer metastatic to the spine*

Also in 2003 the results of perispinal etanercept for treatment of refractory pain due to cancer metastasis to the spine in two patients were published [79]. One patient had lung cancer metastatic to the thoracic spine and was treated with perispinal

etanercept in October 2001; the second patient had breast cancer metastatic to the lumbar spine; each had daily, constant, severe pain that had proven refractory to all attempts at treatment, including opioids, before etanercept. It was hypothesized that anatomically targeted administration of etanercept might be able to interfere with tumor-induced osteoclast activation, and thereby interrupt the cycle of osteoclast activation, further bone invasion, resultant release of tumor growth factors, and further cancer growth and pain [79]. Perispinal etanercept was administered overlying the area of spinal pain. Both patients experienced rapid (within minutes), sustained, and nearly complete pain relief. Reduction in tumor activity at the site of perispinal etanercept administration was suggested by follow-up positron emission tomographic imaging at one year post-injection, and correlated with relief of clinical symptoms [79]. This was one of the first reports of the successful use of an anti-TNF treatment strategy for cancer, an approach whose rationale was supported by subsequent research [15,80–82]. The rapid pain relief experienced, beginning within minutes, suggests that the pain experienced by these patients involved, at least partly, neuroinflammation, and suggests that TNF-mediated glial activation, involving mechanisms similar to those present in TNF-mediated disc-related pain, may have been modulated by perispinal etanercept in these patients [1,11,12,79,83].

Involvement of excess TNF in the pathogenesis of both spinal cord injury and traumatic brain injury provide two additional potential therapeutic applications for perispinal etanercept treatment [84–86].

### *Cautions*

Potential side effects of the off-label use of perispinal etanercept, as discussed herein, include all of the risks inherent in the use of etanercept for its labeled indications, which may include, but are not limited to, death, infection, decreased blood counts, congestive heart failure, eye inflammation, lymphoma, demyelinating disease, cancer and reactivation of tuberculosis [87]. PPD skin testing before initiation of etanercept treatment is mandatory, and a black box warning highlighting the risk of tuberculosis, sepsis, and severe infection has recently been added to the package insert [87]. Dosage and dosing intervals need to be individualized for each patient. Perispinal administration of etanercept is an emerging treatment strategy; its proper performance and implementation require hands-on training.

## Conclusions

Excess TNF is centrally involved in the pathogenesis of a variety of neuroinflammatory disorders, including Alzheimer's disease, other forms of dementia, sciatica, neuropathic pain and related disorders. Perispinal administration of etanercept, a potent anti-TNF fusion protein, is a treatment modality whose rapid clinical effects may be related to modulation of synaptic dysregulation produced by excess TNF. This treatment approach utilizes therapeutic delivery of etanercept across the dura via the cerebrospinal venous system. Further study of perispinal etanercept for disorders involving neuroinflammation, including not only Alzheimer's disease, disc-related pain, and related disorders but also spinal cord injury and traumatic brain injury, is warranted. The unique clinical effects of perispinal etanercept in neuroinflammatory disorders suggest the possibility that perispinal delivery of other biologics, such as vascular endothelial growth factor antagonists, interleukin antagonists, or neurotrophic factors, might be useful for the treatment of additional CNS disorders, including CNS malignancies. Further study in experimental models is warranted.

## Disclosure

Author Edward Tobinick has multiple issued and pending patents, assigned to TACT IP LLC, which describe the parenteral and perispinal use of etanercept for the treatment of Alzheimer's disease, sciatica, neuropathic pain and other neurological disorders, including, but not limited to, U.S. patents 6015557, 6177077, 6419934, 6419944, 6537549, 6982089, and 7214658 and Australian patent 758523. He owns stock in Amgen, the manufacturer of etanercept. In addition, he has pending patents that describe the use of the cerebrospinal venous system and/or perispinal administration to deliver other therapeutic or diagnostic agents to the brain, eye, spinal cord, and other anatomic structures.

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