EXPERT REVIEWS

Perispinal etanercept: a new therapeutic paradigm in neurology

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Etanercept is a potent antagonist of TNF, a pleotropic immune signaling molecule that is also a pivotal regulator of synaptic function. Excess TNF is centrally involved in the pathogenesis of a variety of inflammatory neurological disorders, including Alzheimer's disease, sciatica, traumatic brain injury and spinal cord injury. Perispinal etanercept produces rapid improvement in both Alzheimer's disease and sciatica and in other forms of disc-related pain. Basic research and the observed clinical effects suggest that etanercept has the surprising ability to penetrate into the cerebrospinal fluid after perispinal administration. Perispinal administration is a novel method of delivery designed to introduce this anti-TNF molecule into the bidirectional cerebrospinal venous system and the cerebrospinal fluid to facilitate its selective delivery to either spinal structures or the brain. The scientific rationale, physiologic mechanisms, clinical effects and potential clinical indications of this therapeutic approach are the subject of this article.

Keywords: Alzheimer's • cerebrospinal venous • choroid plexus • dementia • etanercept • radiculopathy • sciatica • synaptic • TNF

TNF is a pleotropic immune signaling molecule. Best known for initiating and amplifying the inflammatory response, excess TNF is also centrally involved in the pathogenesis of many human diseases, through its influence on a wide variety of physiological processes [1]. Excess TNF has been a major therapeutic target in medicine for more than two decades, since its cardinal role in inflammatory diseases was established [1]. One of the major accomplishments in medicine in the 1990s was the development of safe and effective biologic antagonists of TNF. In November 1998 the US FDA approved the first anti-TNF biologic, etanercept, for human use. Etanercept functions *in vivo* as a potent and selective antagonist of TNF [2]. It is a dimeric fusion protein consisting of the extracellular ligand-binding portions of two soluble TNF receptors fused to an Fc fragment of an IgG1 molecule. It is a large molecule, with a molecular weight of 150,000 Da.

At the time of etanercept's FDA approval, in 1998, the role of TNF in neurological disorders and in Alzheimer's disease (AD) was incompletely understood. For example, in 1999, when TNF was first discovered to be present in 25-fold excess in the cerebrospinal fluid (CSF) of patients with AD, this finding was interpreted to imply that TNF had a neuroprotective function, that it was produced as a physiologic counter-response to the pathology responsible for the disease [3]. It was only several years later, when the same authors documented that excess CSF TNF was associated with more rapid AD progression, that the deleterious role of excess CSF TNF in AD pathogenesis began to become more widely appreciated [4]. There is now substantial accumulated scientific evidence that suggests that excess TNF is involved in the pathophysiology of a variety of neurological diseases, including AD [5–12]. TNF is recognized as one of only a handful of gliotransmitters that regulate synaptic function [13–15]. Glial–neuronal interactions involving TNF are involved in the pathogenesis and progression of neurodegenerative diseases [16–22]. The pivotal role of TNF in the regulation of neuronal function is now fully evident (**Box 1**) [5–22].

The appreciation of the essential role of TNF in the regulation of neuronal function and in the pathogenesis of neuroinflammatory disorders was, however, not sufficient for the development of etanercept as a neurologic therapeutic. Novel methods of drug delivery were needed because of etanercept's high molecular weight and the difficulty large molecules have of traversing the BBB. Perispinal methods of delivery were invented

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Box 1. Physiologic synaptic effects of TNF.

- Inhibition of long-term potentiation [56,59,60,162]
- Modulation of AMPA and GABA receptors [125]
- Control of synaptic strength [123]
- Modulation of synaptic scaling [124]
- Modulation of synaptic transmission by gliotransmission [13–15]
- Rapid alteration of synaptic transmission in the spinal cord dorsal horn [114]
- Rapid modulation of enzymes (nSmase2) (within seconds) involved in NMDA trafficking [110]

that were designed for selective delivery of etanercept [23,24]. The scientific rationale, physiologic mechanisms, clinical effects and potential future clinical indications of perispinal etanercept are the subject of this article.

Perispinal etanercept for disc-related pain

Scientific rationale: the role of TNF in disc-related pain

Substantial experimental data suggests that excess TNF is centrally involved in the pathogenesis of neuropathic pain [25,26]. In experimental models, TNF causes pain and mechanical allodynia when deposited at the normal dorsal root ganglia [27]; enhances ongoing allodynia when administered at compressed dorsal root ganglia [27]; induces abnormal discharges in rat dorsal horn neurons [28]; and reduces nerve conduction velocity when applied to the cauda equina [29]. Epineurial application of TNF elicits acute mechanical hyperalgesia in the awake rat [30]. Sciatica and other types of pain associated with intervertebral disc disease, such as disc herniation or annular tear, are forms of neuropathic pain [25,26]. Radiculopathy associated with disc herniation has been shown to be caused by the inflammatory effects of the nucleus pulposus, which are mediated by TNF [31,32]. In experimental models, selective inhibition of TNF prevents nucleus pulposus-induced histologic changes in the dorsal root ganglia [32]; prevents mechanical and thermal hyperalgesia caused by disc incision and nerve displacement [33]; and prevents adverse behavioral changes caused by experimental disc herniation [34]. In addition, excess TNF has been implicated in the development of pain associated with spinal stenosis and facet degeneration [35,36].

There is additional specific evidence from basic science experiments that utilized etanercept itself. In experimental models, etanercept reduced hyperalgesia in experimental painful neuropathy and ameliorated the reduction in nerve conduction velocity caused by nucleus pulposus [32,37]. Most recently, locally administered etanercept reached the endoneurium of the injured nerve, preferentially bound to transmembrane and trimer TNF isoforms, and inhibited pain-related behaviors in a rat sciatic nerve crush model [38]. Recently it was also demonstrated in an experimental model that immediate etanercept therapy enhanced axonal regeneration after sciatic nerve crush injury [39]. The data from these studies is concordant with the various neuronal effects of TNF which have been established in other experimental models (**Box 1**).

The external vertebral venous plexus, which drains the perispinal area, is in anatomic continuity with the intraspinal veins and the radicular veins (**Figure 1**) [23,40]. The lack of venous valves makes bidirectional flow in these interconnected veins possible [41,42]. The rapid effects of perispinal etanercept observed in patients with disc-related pain are best explained by local delivery of etanercept to the inflamed nerve roots, dorsal root ganglia and dorsal horn of the spinal cord via the vertebral venous system [23].

Clinical evidence & effects

Clinical studies

In 2003, the first reports of rapid and sustained clinical improvement in patients with intractable disc-related pain, including sciatica, cervical radiculopathy, back and neck pain, were published [24,43]. Since that time many peer-reviewed, published scientific studies from multiple academic centers, including several controlled trials, have documented favorable clinical results of perispinal etanercept for disc-related pain and sciatica (**Table 1**) [24,43–49]. Disc-related sciatica and low back pain have been selected as off-label indications for etanercept supported by the best evidence available by consensus expert opinion (this selection was compiled by rheumatologists and bioscientists from 23 countries in the Updated Consensus Statement on Biological Agents for the Treatment of Rheumatic Diseases, 2009) [50].

The favorable results of these studies are in agreement with the author's decade of clinical experience utilizing perispinal etanercept in over 3000 patients with intractable disc-related pain [23]. The details of this experience follow.

Rapid & sustained clinical improvement

In more than half of the patients who respond to etanercept treatment, pain relief is evident within minutes of perispinal administration, often beginning at 2–3 min after the dose, with relief then escalating [23,24]. It is not uncommon for patients to report 80–100% pain relief 20 min after their first dose [23,24]. The temporal nature of this response suggests that perispinal administration results in rapid local delivery of etanercept to the vertebral venous system and the CSF, with rapid local delivery to sites of TNF excess [23]. Rapid response suggests immediate neutralization of excess TNF, resulting in normalization of synaptic mechanisms whose homeostasis had been perturbed by the presence of TNF in a concentration in excess of its normal physiological range (see section entitled 'Rapid clinical response' and **Box 1**) [23].

The rapid response is not limited to pain relief; there is often rapid improvement in the typical sensory disturbance (numbness and paresthesias) and the radicular motor weakness that accompany sciatica and other forms of radiculopathy [23,24,43,44]. Rapid changes in mood and affect may also occur (see section entitled 'Mood and affect') [23].

Both clinical experience and the published data from controlled clinical trials suggest that the majority of patients treated respond favorably (78% in a study conducted at Walter Reed Army Medical Center [DC, USA] at 1 month, with 72% reporting persistence of beneficial effects at 6 months) [23,24,43–46,48]. Positive effects can last indefinitely, with the possibility of complete resolution of pain

and disability, even in patients presenting with years of severe, intractable pain [23,24]. In a 143-patient, open-label study, rapid improvement (within 20 min) and significant and sustained reductions in pain, sensory disturbance and weakness were documented in a patient population with an average pain duration of 9.8 years [44]. The patient population included individuals with lumbar and cervical radiculopathy, disc bulge, disc protrusion, disc extrusion, disc herniation, annular tear, degenerative disc disease, spinal stenosis and spondylolisthesis. In total, 69% of the studied patients had previously had epidural steroid injections and 30% had previously had spinal surgery [44]. These results and patient characteristics are representative of our clinical experience [23].

With regard to the safety of perispinal etanercept, the data developed for the Walter Reed study of epidural etanercept is reassuring [48]. The safety data requested by the FDA included careful study of both dogs and humans to whom epidural etanercept was administered [48]. No human or animal toxicity was noted [48].

Potential candidates

Perispinal etanercept is utilized for selected patients with pain that has not adequately responded to standard medical or surgical treatment, or for those patients desiring an alternative to surgery or epidural steroid injections. The most common off-label indication is for intervertebral disc-related pain, which presents as back pain, sciatica or neck pain. Presenting patients have most often had chronic low back or neck pain, but the back pain can be in any location, from the sacrum, up the spine, to the neck. Patients with radicular neck pain (cervical radiculopathy) often have radiation of pain to the trapezius area, shoulder, tricep, down the arm to the fingers and, less commonly, associated headaches (cervicogenic headache, which is often misdiagnosed as migraine headache). Patients with thoracic disc herniations can develop thoracic radiculopathy, with pain radiating in a dermatomal distribution around the rib cage horizontally. The source of pain may be from single or multiple discs, and may be associated with a disc bulge, protrusion, herniation or an annular tear. Patients who have failed spinal surgery, including microdiscectomy, endoscopic discectomy or spinal fusion, are potential candidates, as are individuals with intractable spinal stenosis and severe fibromyalgia [23,24,43,44].

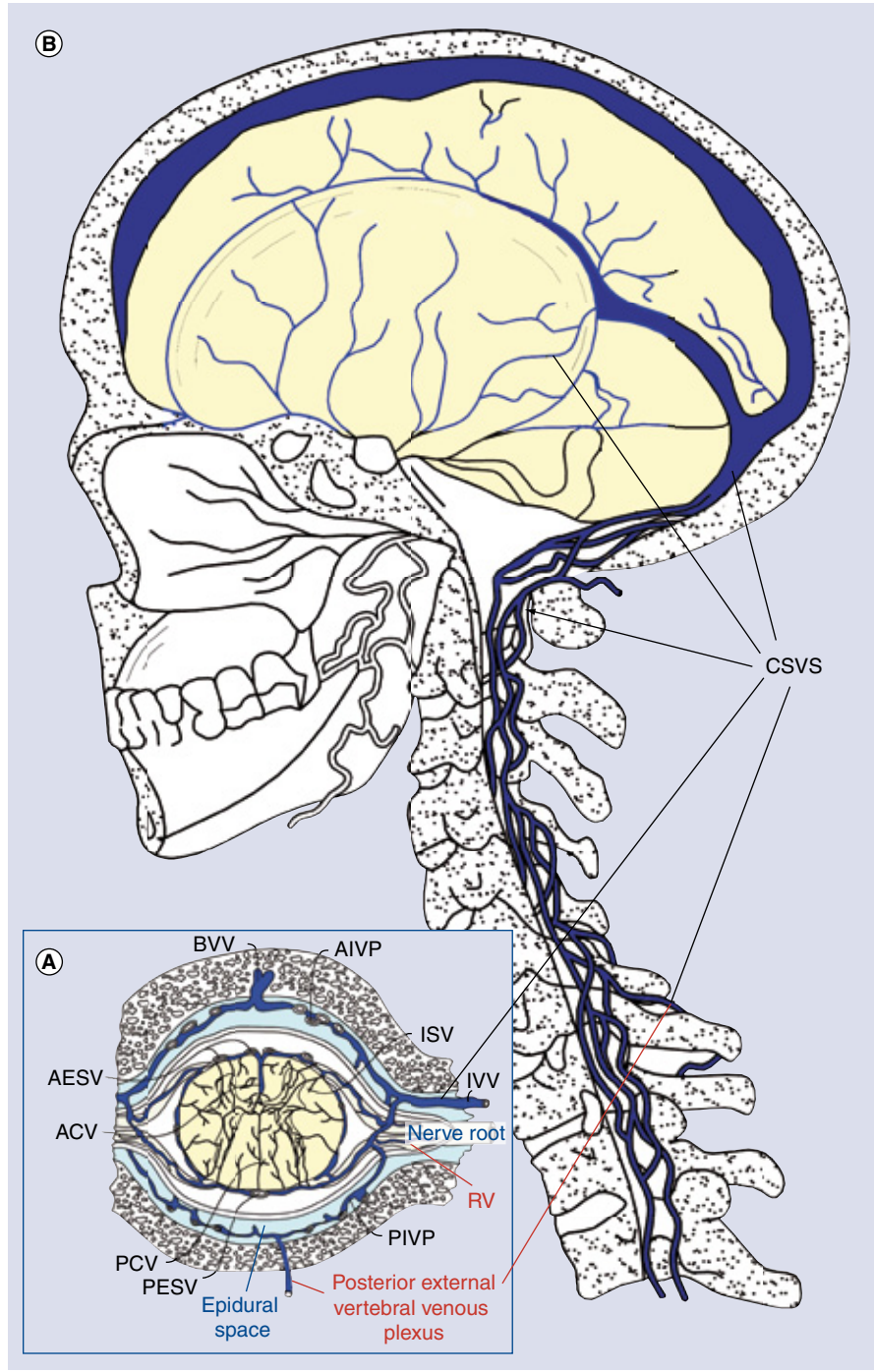

Figure 1. The cerebrospinal venous system. (A) The spinal portion of the cerebrospinal venous system, including the vertebral venous plexuses, the epidural space and their relationship to the spinal cord and the nerve roots. Horizontal section through the spine. **(B)** The anatomic continuity of the spinal and cerebral venous plexuses. ACV: Anterior central vein; AESV: Anterior external spinal vein; AIVP: Anterior internal vertebral plexus; BVV: Basivertebral vein; CSVS: Cerebrospinal venous system; ISV: Internal spinal vein; IVV: Internal vertebral vein; PCV: Posterior central vein; PESV: Posterior external spinal vein; PIVP: Posterior internal vertebral plexus; RV: Radicular vein. **(A)** Adapted from [163].

Table 1. Etanercept for sciatica and related forms of neuropathic pain.

Lead author (year)	Country/ academic center	N	Type of study	Overall result	Route	Dose/number of doses	Length of study	Ref.
Cohen (2009)	USA/Walter Reed/Johns Hopkins	24	RCT	Favorable	Epidural	2, 4 or 6 mg Two doses, 2 weeks apart	6 months	[48]
Tobinick (2009)	USA	NA	Review	Favorable	Perispinal	25 mg	NA	[23]
Dahl (2009)	USA/Johns Hopkins	6	Observational	Favorable	Perineural	5 mg One to three doses	3 months	[164]
Kume (2008)	Japan/ Hiroshima	28	RCT	Favorable	Epidural	25 mg One dose	1 month	[45]
Cohen (2007)	USA/Walter Reed/Johns Hopkins	36	RCT	Negative	Intradiscal	0.1–1.5 mg One dose per positive disc	6 months	[165] [161]
Malik (2007)	USA/ Northwestern	1	Case report	Negative	Epidural	25 mg One dose	3 weeks	[166]
Serratrice (2007)	France	1	Case report	Favorable	Subcutaneous	25 mg Biweekly	8 months	[167]
Shin (2005)	S. Korea/ USA/Rush Univ.	3	Case–control	Favorable	Intravenous	3 mg/kg One dose	1 year	[46]
Genevay (2004)	Switzerland	10	Case–control	Favorable	Subcutaneous	25 mg Three doses, 3 days apart	6 weeks	[47]
Tobinick (2004)	USA	143	Observational	Favorable	Perispinal	25 mg 2.3 ± 0.7 doses	1 month	[44]
Tobinick (2003)	USA	20	Observational	Favorable	Perispinal	25 mg One to five doses mean 1.8	30–518 days, mean 230 days	[24]
Tobinick (2003)	USA	2	Observational	Favorable	Perispinal	25 mg One dose	8 months–1 year	[43]

N: Number of patients; NA: Not available; RCT: Randomized controlled trial; Univ.: University.

Novel clinical response patterns

It was apparent, even with the first patient treated, that perispinal etanercept had unprecedented clinical effects, because of the rapidity of response. As clinical experience grew, there were additional clinical effects that gave further clues to the paradigm-shifting nature of this new therapeutic modality. One of these clues was the anatomically widespread nature of pain relief, which has been repeatedly observed in patients with concurrent disc herniations in both the neck and lower back [23,24,43,44]. A perispinal injection of etanercept in the lumbar area for these patients often results in relief of both neck and back pain within 3 or 4 min of a single dose [23,24,43,44]. This rapid effect was puzzling at first, because it could not be explained by the carriage of etanercept via the CSF alone [51]. The study of CSF flow around the spinal cord has been investigated. Rostral flow of CSF does occur, but is more than an order of magnitude too slow to account for the widespread pain relief seen in patients with multiple disc herniations following perispinal etanercept administration [50]. It was only when one considered the possibility of widespread carriage of etanercept via the vertebral venous system followed by subsequent CSF delivery that a rational explanation for the rapidity of these effects emerged [23].

Perispinal etanercept for AD & other dementias

The impetus for the initiation of investigation of perispinal etanercept for the treatment of AD was the fact that, at the time of conception of this anti-TNF approach, there was an enormous unmet need for a more effective therapeutic strategy. This is still the case [52]. The current FDA-approved drugs do not prevent or reverse the disease, and do not prevent long-term clinical deterioration [52]. This is, in large part, due to the fact that the cause (or causes) of AD remains incompletely understood, despite many years of intensive investigation [53]. The leading hypothesis remains the pathological events that surround the accumulation of amyloid peptides in the AD brain. These pathological events include inflammation, synaptic dysfunction, vascular dysfunction and interference with molecular

mechanisms of memory [53]. An anti-TNF therapeutic approach is attractive because not only has TNF been implicated in the mediation of each of these pathological mechanisms (inflammation, synaptic dysfunction, vascular dysfunction and molecular memory mechanisms), etanercept and other anti-TNF molecules have shown evidence of amelioration of these disturbances in a variety of basic science models [54–60]. In addition, excess TNF may result in increased amyloid production, and amyloid may result in excess TNF, producing a deleterious feedback loop that could potentially be interrupted by an anti-TNF therapeutic [17,61–65]. Of interest, etanercept has shown efficacy in the treatment of various complications of systemic amyloidosis [66,67]. An anti-TNF strategy might also potentially be useful as a method to reduce brain inflammation engendered by other therapeutic approaches [68].

One should note that the goal of any anti-TNF therapeutic strategy in dementia is not to drive TNF levels to zero; rather it is to reduce excess levels of TNF, so as to attempt to restore TNF homeostasis [5,62]. It is the author's conception that optimal brain function requires that TNF be maintained within a normal physiologic range [5,62]. Physiologic levels of TNF are required for neuronal repair and neurogenesis [69]. Although the literature includes conflicting data regarding TNF levels in the blood in AD, a series of studies have suggested that TNF is significantly elevated in the CSF in both AD and mild cognitive impairment, and have provided data that disease progression correlates with CSF TNF elevation [3,4,6]. Peripheral levels of TNF may not correlate with CSF TNF levels; in the study by Tarkowski and colleagues that demonstrated a 25-fold excess of TNF in the CSF of the AD patient group, this same group did not show a significant elevation of serum TNF, implying intrathecal production of TNF [3]. This is not to imply that excess serum TNF may not exacerbate AD; indeed, recent data does suggest that the systemic inflammatory events that are associated with elevation of serum TNF may be associated with an increased rate of cognitive decline in AD [70].

Perispinal etanercept is, therefore, theorized to potentially intervene in a variety of intermediate mechanisms mediated or initiated by excess TNF that are involved in the pathogenesis of AD. Interference in intermediate TNF-mediated disease mechanisms is also the way that etanercept works for its FDA-approved indications, such as rheumatoid arthritis, psoriasis and ankylosing spondylitis. Despite the fact that the underlying cause of all of these diseases has remained elusive, anti-TNF strategies have proven remarkably effective. A more detailed analysis of the evidence supporting an anti-TNF therapeutic approach in AD follows. This analysis is not meant to provide a balanced, comprehensive review of all of the possible pathogenetic mechanisms in AD, because these mechanisms remain unsettled [53]. Rather, this analysis is limited to a concise discussion of the evidence supporting an anti-TNF therapeutic approach in AD. It is clearly acknowledged that this therapeutic strategy remains off-label and is not yet supported by randomized, placebo-controlled data. In this sense, perispinal etanercept for AD remains in an earlier stage of development than perispinal etanercept for sciatica, for which development was accelerated by financial support from the US Army [48]. It is hoped that a detailed compilation of the positive clinical effects that have consistently been observed by a variety of physicians and scientists, as well as the related discussion herein, will help accelerate the initiation of the extremely costly controlled trials necessary to further clinical development of this pioneering therapeutic strategy.

Scientific rationale

Role of TNF in AD

The pathophysiology of AD is complex, with abnormalities in multiple brain pathways. Inflammatory pathways have long been suspected of playing a key role in AD progression [71]. Recent data from transgenic murine AD models suggest that elevation of pro-inflammatory cytokines, including TNF, IL-1β, IL-6 and S100B, may precede the appearance of amyloid-β plaques [72]. Although the relative importance and inter-relationship of inflammatory pathways in AD is still being elaborated, a decade of accumulating scientific evidence suggests that excess TNF constitutes another target (in addition to amyloid and tau) that is a central mediator of AD pathogenesis (**Table 2**) [3–5,57,70,73–78]. This previously reviewed evidence includes:

- Basic science evidence from multiple independent academic centers [3–5,57,70,75–78]. Animal studies utilizing parenteral or intracerebroventricular delivery of anti-TNF biologics (**Table 2**) are of particular interest in view of the imaging data that suggest that etanercept is capable of penetration into the cerebral ventricles after peripheral administration [5,54–56];

- Genetic evidence correlating specific polymorphisms in TNF promoter genes causing increased TNF production with increased AD risk, in multiple studies from several academic centers, supported by a recent meta-analysis [73,74,79–82];

- Epidemiologic evidence correlating AD risk with elevated serum TNF [83]; the capacity of immune cells to produce TNF with future risk of AD [75,77]; and the rapidity of cognitive decline with adverse clinical events associated with excess TNF [70];

- Clinical evidence that has been previously reviewed, with rapid and sustained clinical improvement in patients with mild, moderate and severe AD following perispinal administration of etanercept documented [5,23,61,62,84,85]. Some of these patients have now had sustained clinical improvement for more than 5 years [5]. In addition to improvement in AD, improvement in patients with semantic dementia, frontotemporal dementia and primary progressive aphasia treated with perispinal etanercept has been documented, but clinical experience with these disorders is limited [5,23,85,86]. Swedish data reporting elevated CSF TNF in AD and correlating excess CSF TNF with disease progression constitutes additional clinical evidence [3,4,76]. The Swedish data has now been extended to include the findings that patients with mild cognitive impairment who subsequently developed either AD or vascular dementia had higher levels of soluble TNF receptors in both CSF and plasma at baseline when compared with age-matched controls, and that the levels of both soluble TNF receptors correlated with the axonal damage marker tau in the CSF [6].

Table 2. Excess TNF and dementia.

Type of evidence	Evidence	Ref.
Genetic		
	TNF promoter polymorphisms causing increased TNF production are associated with increased AD risk	[73,74,79–82]
Epidemiologic		
	Both acute and chronic systemic inflammation, associated with increases in serum TNF, are associated with an increase in cognitive decline in AD	[70]
	Higher spontaneous production of TNF by peripheral blood mononuclear cells found to be a marker of future risk of AD in older individuals	[75]
	Production of TNF in whole blood stimulated by LPS in middle age is a risk factor for AD	[77]
Clinical		
	Increased rate of disease progression from MCI to AD associated with increased CSF TNF	[4,6]
	Increased CSF TNF associated with both AD and vascular dementia	[3]
	Increased CSF TNF associated with frontotemporal dementia	[9]
	Decreased age of AD-onset associated with increased TNF	[74,81]
	Improvements in cognition following initiation of weekly perispinal etanercept injections in AD ranging from mild to severe	[61,62,84,85]
Basic science		
Anti-TNF biologics in animal models	ICV pretreatment with anti-TNF antibody improved the impairment of spatial learning produced by amyloid-β	[58]
	ICV infliximab or peptide TNF antagonist prevent inhibition of LTP at hippocampal synapses produced by ICV amyloid	[56,59]
	ICV injection of an anti-TNF antibody prevented the nitration of proteins in the hippocampus and impairment of recognition memory induced by two forms of amyloid-β	[54]
	Weekly intraperitoneal injections of a chimeric monoclonal anti-TNF antibody in transgenic mice overproducing amyloid-β reduced the pathological behavioral anomalies that develop in this model	[55]
Additional basic science studies	Excess TNF is associated with *in vitro* disruption of synaptic mechanisms, neuronal death, neuronal inflammation, neuronal dysfunction, microglial activation, increased tau production, microvascular dysfunction and glutamate excitotoxicity	[5,7,8,18,23,168]

AD: Alzheimer's disease; CSF: Cerebrospinal fluid; ICV: Intracerebroventricular; LPS: Lipopolysaccharide; LTP: Long-term potentiation; MCI: Mild cognitive impairment.

Perispinal administration

Perispinal denotes anatomically localized administration in the vicinity of the spine, and encompasses intrathecal, epidural and local delivery into Batson's plexus via methods designed to deliver etanercept (or other therapeutic molecules) selectively to the spine, spinal cord, spinal nerve roots and, particularly with Trendelenburg positioning, to the cerebral venous system. In the case of sciatica, the efficacy of perispinal (including epidural) administration of etanercept has been demonstrated in multiple studies performed at academic centers around the world (**Table 1**) [24,43–47].

The conventional methods of perispinal delivery of drugs are the intrathecal and epidural routes. The intrathecal route, in which the therapeutic is delivered directly into the CSF, is invasive and carries the risk of dural tear, leading to postspinal puncture headache. For treatment of sciatica, perispinal administration of etanercept via the epidural route has resulted in encouraging controlled data [45,48]. Perispinal administration of etanercept (and other biologics) via Batson's plexus is less invasive than both the epidural or intrathecal routes [23,24,43,44]. This route involves the use of much shorter and smaller diameter needles than those required for epidural or intrathecal administration. In order to understand how this route works, one must be familiar with the anatomy of the spinal venous system (**Figure 1**).

Cerebrospinal venous system

Substances injected into the area posterior to the spine drain into the external vertebral venous plexus [23,40–42]. The external vertebral venous plexus is part of Batson's plexus (the vertebral venous plexus). Batson's plexus is an extensive interconnected plexus of veins that surrounds the spine and is distributed along the entire length of the spine, from the sacrum to the neck, communicating freely with the pelvic and prostatic venous plexuses caudally and with the cerebral venous system via extensive interconnections at the base of the cranium [23,40–42]. Among the unique features of Batson's plexus is the fact that it lacks venous valves, so flow within this system is bidirectional [23,40–42,87,88]. The functional and anatomic continuity of the vertebral venous system with the cerebral venous system led this author to select the name 'cerebrospinal venous system' to designate the combination of the cerebral venous system with the vertebral venous plexus [40]. The cerebrospinal venous system has important physiologic roles in both health and disease. It provides a direct route for the distribution of substances (blood, therapeutics or cancer cells) from the spine to the brain or *vice versa* [23,40,41,88].

The external vertebral venous system is connected with the internal vertebral venous system, which anastomoses and is in direct continuity with the spinal veins that drain (and supply) venous blood to the spinal cord, the dorsal root ganglia and the spinal nerve roots (Figure 1). The rapid clinical effects of perispinal etanercept on sciatica and other forms of intervertebral disc-related pain were a clue that perispinal etanercept was being distributed through Batson's plexus [23]. Appreciation of the anatomic and functional continuity of Batson's plexus with the cerebral veins led to the concept that perispinal administration of etanercept could be used to deliver etanercept to the cerebral venous system (Figure 1) [23]. The cerebral venous system contains no valves, and there are widespread anastomoses of the great cerebral veins with the more superficial cerebral veins, the choroid plexus and the cerebral capillaries [23,41,42,89,90].

The advantage of anatomically localized delivery is the selectivity of delivery, that is, the achievement of higher local concentrations of etanercept (and other biologics) to the targets selected within the distribution of the cerebrospinal venous system, when delivered locally rather than systemically [23,24,38,91].

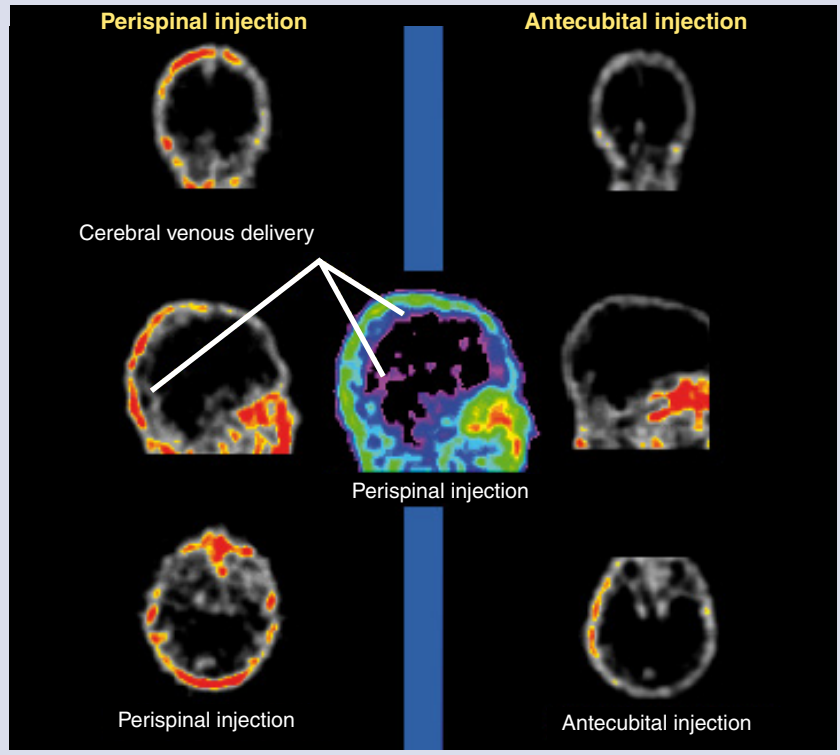

Figure 2. Single proton-emission computerized tomography imaging results following perispinal and antecubital injection of 99mTc-DTPA in a human. Delivery of radiolabeled DTPA into the cerebral venous system following perispinal administration is demonstrated. The imaging pattern suggests enhanced cerebral venous delivery following perispinal administration compared with antecubital administration. The three images on the left and the central image followed perispinal injection and inversion. The three images on the right followed antecubital injection and inversion. DPTA: Diethylenetriaminepentaacetic acid; Tc: Technicium.

Experimental evidence: radionuclide PET & single proton-emission computerized tomographic imaging

To investigate the anatomic distribution of etanercept following perispinal administration, a series of imaging experiments were conducted. The first, conducted using a human volunteer following institutional review board approval, involved single proton-emission computerized tomographic imaging of a human subject to whom radiolabeled technicium diethylenetriaminepentaacetic acid (DPTA; 99mTc-DTPA) had been administered, first by perispinal administration via Batson's plexus in the posterior neck, and then by antecubital intravenous injection. 99mTc-DTPA is a well-established radiotracer that has been used for demonstrating the integrity of the BBB. Under normal conditions 99mTc-DTPA does not cross the BBB [92]. It was postulated prior to initiation of this experiment that perispinal administration followed by inversion would result in retrograde movement of the radiotracer into the cerebral venous system. In addition, based upon the clinical effects of perispinal etanercept in AD, and with knowledge that a previous trial of systemic etanercept for AD had failed [93], it was postulated that perispinal administration could be a more efficient method of delivering a therapeutic to the cerebral venous system than systemic delivery. The results of this experiment provided preliminary scientific support for these hypotheses. Single proton-emission computerized tomographic brain imaging, conducted 5–10 min after perispinal injection of 99mTc-DPTA followed by inversion, produced a pattern of cerebral venous distribution of radiotracer that was more intense than that seen following antecubital injection (Figure 2). The result also demonstrated that perispinal administration followed by inversion results in rapid delivery of the radioisotope to the cerebral venous system (Figure 2).

Following this human experiment using DPTA, experimental investigation of the distribution of radiolabeled etanercept *in vivo* was undertaken by the author. In collaboration with investigators at Stanford, etanercept was labeled with a positron emitter, ^{64}Cu, to enable visualization of its distribution using a micro-PET scanner [23,94,95]. A total of 150 µl of ^{64}Cu-labeled-etanercept solution (ca. 1 mCi) was injected into each of two rats, the first overlying the cervical spine of a Sprague-Dawley rat at the C6–7 level using a 30 gauge needle at a depth of 6 mm and the second via a ventral tail vein, while the rats were anesthetized with 2.5% isoflurane inhalation anesthesia. The rats were then placed in the head-down position by tail suspension for 3 min, immediately followed by placement in the bed of a micro-PET imaging scanner. Following perispinal administration, a distinctive pattern of tracer

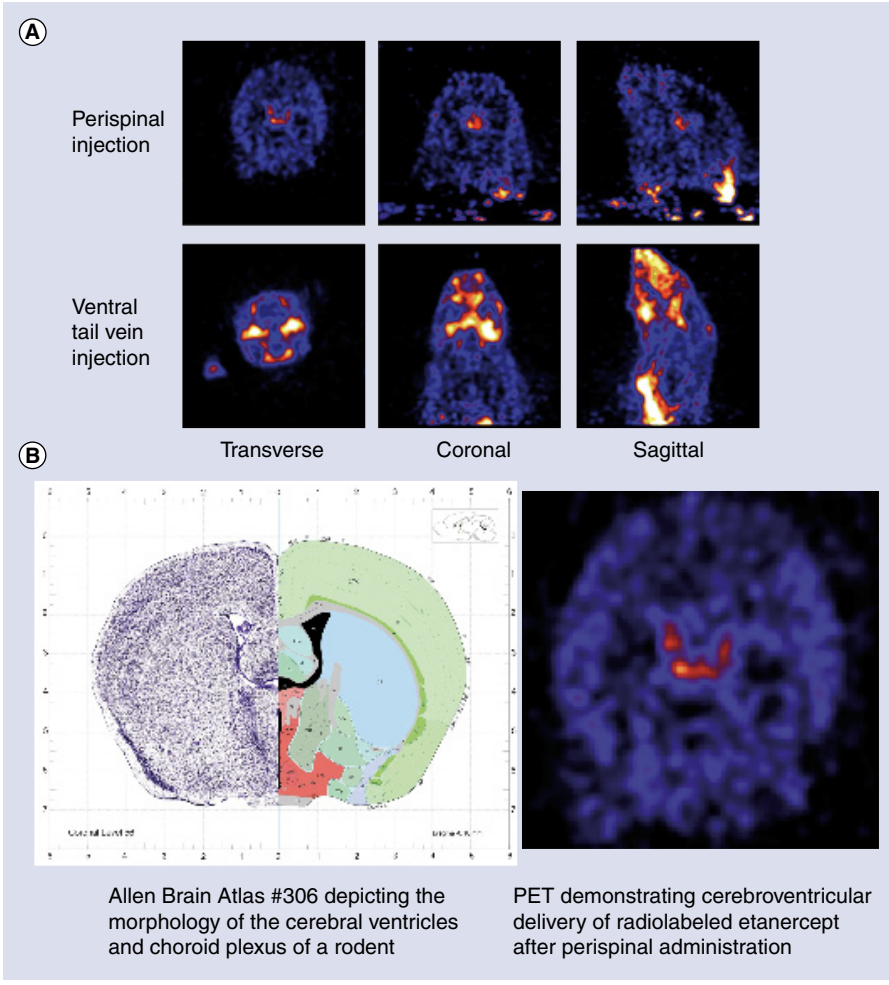

Figure 3. PET images of a living rat brain following peripheral administration of ^{64}Cu-DOTA-etanercept. The distinctive central pattern of brain distribution suggests penetration of ^{64}Cu-DOTA-etanercept into the CSF in the lateral and third ventricles and accumulation of tracer within the choroid plexus following perispinal administration. **(A)** The pattern following perispinal administration is distinct from that following ventral tail vein injection. **(B)** Comparison of the transverse PET image following perispinal injection with section 306 from the Allen Brain atlas [201].
CSF: Cerebrospinal fluid; DOTA: 1,4,7,10-tetraazadodecane-N,NI,NII,NIII-tetraacetic acid.

distribution was seen, *in vivo*, in the rat brain within minutes of peripheral delivery (Figure 3A). The PET transverse section revealed a distinctive horseshoe-shaped distribution of tracer in the central brain, with the central distribution confirmed on the coronal and sagittal sections (Figure 3A). Comparison of this distinctive pattern of distribution with published MRI, autoradiographic and brain atlas images suggested that this pattern of distribution was most compatible with delivery into the choroid plexus and the lateral and third ventricles of the rat (Figure 3B) [5,95–100,201]. In addition, careful evaluation of the PET images also revealed central linear accentuation of radiotracer, a pattern that was highly suggestive of accumulation within the choroid plexus [5,95–100,201]. The PET results after perispinal injection were distinct from the results seen after ventral tail vein injection, in which vascular delivery was evident but selective ventricular delivery was absent. A limitation of these imaging studies with regard to AD is the fact that these were normal animals. BBB abnormalities may occur in AD [101,102]. The effects of any such abnormalities on the distribution of etanercept are not presently known. Despite the small size and preliminary nature of these studies, they provide a direction for future research, and suggest the intriguing possibility that intracerebroventricular penetration may account for the rapid clinical effects seen after perispinal administration of etanercept. IL-1 Ra, another large molecule (molecular weight of 17,000 Da), also penetrates into the cerebral ventricles after peripheral administration, providing additional evidence that certain large molecules may traverse the blood–CSF barrier as part of normal physiology [103]. Several groups have reported significant effects of intracerebroventricular delivery of anti-TNF biologics on AD memory mechanisms in animal models [54,56–59]. This evidence highlights the potential clinical significance of intracerebroventricular delivery of etanercept.

One may speculate regarding the implications of these findings. If rapid intracerebroventricular delivery after perispinal administration is indeed responsible for the rapid favorable clinical response seen following perispinal etanercept in dementia, then this implicates excess TNF in the choroid plexus, the cerebral ventricles or possibly in the periventricular regions or the regions surrounding the circumventricular organs in the pathogenesis of AD. These enumerated regions are the anatomic areas with the fewest physiological barriers to diffusion of etanercept that has reached the CSF [5,100,104]. The choroid plexus is known to be the source of synthesis of numerous cytokines and other immunomodulatory molecules [100,105,106]. Based on the preliminary data so far developed, it is hypothesized that certain forms of dementia may involve a choroid plexitis associated with excess TNF that may be exacerbated by peripheral inflammatory events or by β-amyloid or amyloid oligomers. Excess TNF in the choroid plexus, the periventricular regions, or the regions surrounding the circumventricular organs could have adverse glial or synaptic effects that could result in widespread neuronal, cortical or neural network dysfunction [62].

Clinical effects of perispinal etanercept in AD

The author has now had more than 5 years of clinical experience treating patients with AD with perispinal etanercept. This experience has recently been reviewed [5,23,61,107]. The patients have included a broad clinical spectrum, including mild, moderate

and severe AD. In those patients responding favorably, clinical improvements typically occur across multiple domains, including improvements in executive function, verbal abilities, attention, mood, memory and motor function [5,23,61,62,84,85,107]. The quantitative data has been published previously [5,23,61,62,84,85,107]. A detailed qualitative discussion of the diverse clinical effects that have been observed after initiation of perispinal etanercept follows.

These observations are documented not as a representation of exactly what will occur for any given patient, but rather as a guide to facilitate further basic science and clinical investigation into the underlying scientific mechanisms that are operative. For example, the changes in mood and affect seen in some patients suggest the possibility of TNF-mediated effects on serotonergic pathways, a link that has recently been confirmed [108]. Of related interest is new data suggesting that an antidepressant, imipramine, may prevent cognitive decline and amyloid-β accumulation in a murine AD model, in part by inhibiting TNF [109]. Moreover, the rapidity of these effects, and other clinical effects that may occur within minutes of perispinal etanercept administration, such as improvements in cognition and attention, suggests the existence of novel TNF-mediated pathways that have not been fully characterized and are highly deserving of investigation [5,23,61,62,85,110–114]. Investigational techniques that are capable of demonstrating rapid brain changes, such as functional MRI and evoked potentials, may be capable of documenting such effects.

It should be noted that one of the problems that physicians and researchers face is the heterogeneity of the dementia patient population. There are multiple forms of dementia (e.g., AD, vascular, frontotemporal, Lewy Body and corticobasal degeneration) and, indeed, multiple forms of AD (e.g., early-onset, late-onset and familial) that reflect different genetic drivers of neurodegeneration [115–117]. In addition, any given patient may have more than one type of dementia [118]. Current approaches to disease classification are inadequate to precisely define the disease burden [118]. Biomarkers for determining disease classification are still in the process of being developed and characterized [119–121]. As the recent bapineuzumab clinical trial results highlight, differences in genotype may translate into different responses to treatment, including differences in adverse effects [68,122]. Therefore, it should be emphasized that despite the fact that clinical improvement following perispinal etanercept has been verified by objective observers, and that long-term positive responses may occur, further study in randomized controlled trials is needed [5,61,107]. Ideally, large and carefully designed clinical trials will include the investigation of multiple biomarkers and patient genetics, and correlation of baseline genotypes and biomarker patterns with clinical response, to help define optimal patient selection.

Rapid clinical response

A discernable clinical response is customarily seen within 10 min of the first dose. The first signs of improvement are often subtle, but include improved attention, reduced latency of response to questions, more rapid speech with enhanced content, improved affect and a more rapid gait [5,23,61,62,84–86]. This rapid response has been verified by multiple, objective observers over the course of 5 years, and is congruent with the rapid synaptic effects of TNF that have been documented in multiple experimental models [5,23,61,62,84–86,107,110–114].

Rapid clinical effects, within minutes, following a single perispinal etanercept dose are also the rule in patients with disc-related pain [23,24,44]. Patients with sciatica or cervical radiculopathy with a history of chronic and intractable constant and daily pain, often for months or years, routinely report pain reduction beginning within minutes following the first dose of perispinal etanercept [23,24,44]. One should note that perispinal etanercept is administered without any local anesthetic. The narrow gauge needles used produce minimal discomfort and make local anesthesia unnecessary. Therefore, the rapid reduction in pain (often accompanied by rapid objective improvement in motor strength) must be a direct effect of etanercept. The rapidity of the response is directly related to the nature of etanercept, as well as the local, perispinal route of administration [23,24,44]. Etanercept is a biologic, a therapeutic developed through recombinant DNA biotechnology. Etanercept is a direct molecular antagonist of its target, excess TNF, which it binds (and thereby inactivates) immediately [2]. This immediate efficacy is in contrast to the prolonged time (usually hours to days) required for pharmaceuticals (drugs) to act by influencing enzyme systems or other upstream or downstream processes.

Basic science studies suggest several known effects of TNF on synaptic mechanisms that may help explain the rapid clinical responses produced by perispinal etanercept. TNF is known to modulate both synaptic strength and synaptic scaling [2,123,124]. One of the experimental effects of TNF is the modulation of the surface expression of neurotransmitter receptors at synapses [7,125]. TNF causes a rapid exocytosis of AMPA receptors in hippocampal pyramidal neurons [125]. Rapid synaptic effects of TNF, within minutes, were reported in 2008 in an experimental rat spinal cord model [114]. More recently, even more rapid synaptic effects of TNF have been reported [110,112]. TNF-induced neutral sphingomyelinase-2 was found to modulate synaptic plasticity by controlling the membrane insertion of NMDA receptors, with effects beginning within seconds [110,112]. TNF has also been recently reported to have rapid, nitric oxide-dependent effects on suprachiasmatic nuclei neuronal activity [111].

Attention

Improvement in attention is regularly observed following perispinal etanercept in patients with dementia [5,62,85]. Patients seem more alert to their surroundings, they are able to concentrate on the task at hand more efficiently (some are able to begin reading books again, for example), and they respond to questions more quickly and more appropriately. Family members often relate that when returning from their office visit and riding in the car the patients pay attention to the outside environment and comment appropriately, sometimes for the first time in months or years.

Cognition & executive function

The 2006 open-label clinical trial of perispinal etanercept for AD documented progressive improvement during the 6 months in several standard measures of cognition, with the majority of

improvements noticeable within 3 months of initiation of treatment [84]. At 6 months the Mini-Mental State exam score increased by 2.13 ± 2.23, the AD Assessment Scale-Cognitive subscale (ADAS-Cog) improved (decreased) by 5.48 ± 5.08, and the Severe Impairment Battery increased by 16.6 ± 14.52 [84]. We often perform limited repeat cognitive testing approximately 20 min after the first dose of etanercept. Routinely we observe significant improvement, such as greatly reduced time to complete a Trails B task, improved clock drawing or improved ability to perform numerical calculations [62]. In a published case study, perispinal etanercept led to an eight-point improvement in the Montreal Cognitive Assessment (MOCA) [126] test, measured 2 h after the dose was administered [62]. The MOCA test measures eight cognitive domains, and is particularly sensitive to changes in executive function. The eight-point improvement was notable because it exceeded the normal test–retest variation (0.9 ± 2.5 points [126]) by more than three standard deviations, and it correlated with improvements noted in multiple clinical domains [62]. Improvement, however, may only be initially noted in a single domain, or may be more widespread. Our clinical trial published in 2006 began in 2004; our patient with the longest record of continued weekly treatment has now been treated for more than 54 months, and his Mini-Mental State exam, after more than 4.5 years, is still improved from his baseline before treatment [5,84].

The prolonged clinical improvement observed in this patient might legitimately be argued to be influenced by selection bias, rater reliablity, diagnostic uncertainty and individual daily variation. All of these factors may be operative. Nevertheless, this patient has sustained clinical improvement verified by standardized cognitive testing for more than 4.5 years, his improvement has additionally been verified by his family and multiple, independent observers, and he had been progressively clinically declining prior to initiation of perispinal etanercept for a period of several years. Furthermore, our clinical experience with additional patients suggests that long-term benefit, over a period of years, as long as maintenance treatment with perispinal etanercept is continued, may occur [5,61]. Large, Phase III randomized controlled studies in AD typically cost hundreds of millions of dollars [127]. Randomized controlled data for perispinal etanercept in AD is not yet available. If suitable funding can be found for such studies, it would add valuable data to the observational and open-label clinical data already assembled. As noted previously, further study in larger patient populations whose baseline genetic and biomarker status are defined may help to define optimal patient selection and prediction of patients who are more likely to receive long-term benefit. Such studies are urgently needed.

Verbal function

A 6-month, open-label clinical trial in 12 subjects with probable AD documented significant improvements in verbal learning, memory and fluency in this cohort, all of whom were treated with weekly perispinal etanercept [85]. Significant effects were documented on multiple objective measures, with the most significant effect ($p < 0.0007$) observed in verbal fluency, as measured by the FAS instrument [85]. Our clinical experience over 5 years parallels these results; characteristically there is improvement in verbal fluency, most easily documented using the simple letter fluency FAS test that elicits lexical words that begin with a given letter (F, A, S) over a period of 60 s each [5,62,85]. The FAS test is a standardized instrument that gives a validated measure of the quantity of different words produced in the time period selected [128]. This test requires a cognitive search of the stored lexicon, and is often reduced in patients with AD and frontotemporal dementia [129]. The case reports included in this published study also document improvements in the verbal abilities in a patient with severe aphasia due to semantic dementia and a patient with nonfluent aphasia accompanying AD [85]. Speech was more fluent following perispinal etanercept in both patients, with additional improvements in attention, conversational ability, cognition and behavior noted. Decreased word-finding difficulties and improved naming abilities have been repeatedly noted in the Alzheimer's patients we have treated with perispinal etanercept, and have also been documented in patients with primary progressive aphasia treated with perispinal etanercept [5,62,85,86].

Memory

Improvement in both short- and long-term memory are perhaps the least dramatic of all of the clinical effects seen following perispinal etanercept for AD. Short-term memory difficulties are one of the first signs of AD, and may reflect particular sensitivity of the hippocampus to damage from AD pathological processes. Memory improvements are often subtle and often require careful testing using standardized instruments for their detection [85]. It is advisable to counsel families, prior to treatment, that readily observable changes in memory abilities are not to be expected, particularly early in the course of treatment.

Activities of daily living

The families of patients treated with perispinal etanercept consistently relate that perispinal etanercept has resulted in significant improvements in their family member's abilities to function and perform the usual activities of daily living [5,61,62,84,85]. Future studies should incorporate objective measures of daily living abilities among the parameters studied.

Motor function

There is only a single characteristic change in motor function seen following perispinal etanercept: patients with AD often ambulate more quickly following initiation of treatment [85]. In our office,

Box 2. Perispinal etanercept: key therapeutic targets in neurology.

- Neurological pain and dysfunction of spinal origin, including sciatica, lumbar radiculopathy, back pain, spinal stenosis, neck pain, cervical radiculopathy and cervicogenic headache [23,24,29,31,35,37–39,44,48]
- Neuropathic pain [25,26,37,164]
- Alzheimer's disease and other forms of dementia (vascular dementia, mixed dementia and frontotemporal dementia) [3,4,6,10,55,56,59,62,70,73,80,82,84,85,107,169,170]
- Spinal cord injury [7,143,144,146–150]
- Traumatic brain injury [136]
- Stroke [137–140]

we quantitate this with a measured time to walk 20 m, a validated instrument [130]. We often observe a 25–50% decrease in time to complete following the first perispinal etanercept dose. This response also seems to correlate with improvements in attention and executive function, and often occurs rapidly. It is, therefore, suspected that this may be another manifestation of a synaptic or neural network effect mediated by TNF.

Mood & affect

Changes in mood and affect following perispinal etanercept were first noted in patients treated for intractable disc-related pain. Patients repeatedly reported less depression and improved mood following perispinal etanercept treatment. One might attribute this solely to the pain relief experienced. However, because of the repeatable and somewhat unusual nature of the clinical response, it was suspected that these changes in mood and affect were the result of a separate and direct clinical effect of perispinal etanercept on brain function, not simply an absence of pain. One of the reasons for this conjecture was that patients with disc-related pain have reported improved clarity of thought and ability to concentrate following perispinal etanercept. More specifically, a unique clinical effect occurs on a routine basis when treating patients with disc-related pain with perispinal etanercept: a transient mild but noticeable euphoria, lasting 5–10 min following the dose. This same mild euphoria/mood elevation is often seen following perispinal etanercept in AD patients, and although often transient, the improvement in mood may also be long-lasting [85]. Of related interest are additional pieces of evidence associating excess TNF with depression and/or changes in brain function. These include literature reports of antidepressant effects of etanercept administered for psoriasis [131]; a report that chronic back pain is accompanied by brain atrophy [132]; and a new meta-analysis that reports that major depression is associated with the elevation of serum TNF [133]. Quantification of these effects on mood and affect in future studies of perispinal etanercept would be of interest.

Safety considerations

For its FDA-approved indications, such as rheumatoid arthritis, the safety of chronic administration of etanercept, with clinical experience now encompassing 1.6 million patient years of use, is well characterized [134]. Prior to initiating chronic etanercept treatment, it is necessary to avoid treatment in patients with latent TB and to assess the patient's health status. Patients who are immunocompromised or have uncontrolled diabetes mellitus are at increased risk of infectious complications. Etanercept is contraindicated in patients with an active infection. More extensive safety information is available in the package insert. For off-label indications, including the off-label neurological uses discussed herein, safety data is incomplete and further study is necessary. Some data that may be relevant were published in 2009. The FDA required that animal and human safety studies addressing the safety of neuraxial delivery of etanercept be performed prior to completion of the randomized controlled study of epidural etanercept for sciatica conducted at Walter Reed Army Medical Center [48]. No behavioral, neurologic or histologic evidence of drug-related toxicity was seen [48]. There is only scant data regarding the chronic use of anti-TNF molecules in animal AD models [55]. The dilemma, of course, is that AD is a chronic, progressive and invariably fatal disease and none of the FDA-approved therapeutics for this condition are capable of preventing long-term clinical deterioration [52]. A potential advantage of off-label use of an existing drug, compared with enrollment in a clinical trial of an experimental drug, is the more extensive knowledge of safety developed through on-label experience [135]. Off-label use by different routes of administration, with different dosing schedules, for off-label indications, however, presents new safety issues not addressed by on-label experience. Careful consideration of these issues is necessary.

Perispinal etanercept: additional therapeutic targets in neurology

Increasing scientific evidence supports consideration of the study of perispinal etanercept in animal models and human clinical trials for the treatment of neuronal injury, including stroke and traumatic brain injury (**Box 2**) [136–140]. Multiple basic science studies have implicated TNF in the neuronal injury that follows spinal cord trauma [141–143]. In addition to the studies implicating TNF in its pathogenesis, accumulating basic evidence documents improvement in spinal cord injury (SCI) by anti-TNF biologics [144–146]. Etanercept has been studied specifically in animal models of SCI. Administered by intraperitoneal injection 1 h before and 6 h after injury, etanercept reduced the severity of spinal cord trauma [147]. In a separate set of experiments evaluating motor function, etanercept significantly reduced hind limb motor disturbances occurring following SCI [147]. A combination of dexamethasone and etanercept was more effective than either alone as a single treatment, resulting in reduced tissue injury and improved motor recovery [148]. In a third animal study, immediate intrathecal administration of etanercept resulted in markedly reduced mechanical allodynia 1, 2, 3 and 4 weeks after injury and reduced spinal microglial activation [149]. Treatment with etanercept that was delayed for 14 days after injury had no effect [149].

Significant motor recovery, including recovery of the ability to walk, was reported in a patient who had fortuitously received etanercept shortly before a catastrophic automobile accident [150]. The accident produced a complete and displaced transection of the vertebral column, resulting in an initial T7 complete paraplegia. Etanercept was postulated to have significantly reduced the post-traumatic spinal cord inflammation and the perilesional area [150]. Despite this favorable preliminary data, further study involving the use of biologic TNF antagonists in SCI is necessary to establish the optimal dose and timing of administration, as these factors may influence the clinical effects [151]. Perispinal administration may have the potential to enhance selective delivery of etanercept to the spinal cord via retrograde carriage in the vertebral venous system and merits investigation in animal models and clinical trials (**Figure 1**) [23].

Expert commentary

The clinical effects produced by perispinal etanercept illuminate the existence of rapidly reversible, TNF-mediated pathophysiologic processes in both AD and in disc-related pain. In

addition, these clinical effects underscore the fundamental role that TNF plays in the regulation of neuronal function [5,152].

These realizations represent new advances in our understanding of immune regulation of brain and neuronal function, and offer unique opportunities to help an enormous, currently underserved population of patients with unmet medical needs. The ability of perispinal etanercept to alleviate suffering, observed while treating thousands of patients with intractable disc-related pain over a period of 10 years, and after thousands of doses of perispinal etanercept administered over a period of nearly 5 years in patients with AD, has been repeatedly demonstrated [23,61,107]. It is urgent that initiation and completion of the difficult and costly clinical trials necessary to secure FDA approval for these indications be undertaken. Only the pharmaceutical industry or the government can accomplish this. This is the only way we can ensure consistent third-party reimbursement, without which this novel treatment approach will remain out of reach for many who need it.

Perispinal etanercept represents a new therapeutic paradigm in neurology. It offers the opportunity to radically change the management of certain neurological disorders, including AD, related forms of dementia and intervertebral disc-related pain in all of its forms, including intractable low back pain, neck pain and sciatica. For AD, our clinical experience to date suggests that perispinal etanercept is the first therapeutic approach that is disease modifying. Identification of excess TNF as a central mediator of disease pathogenesis in AD opens the possibility of the concurrent use of perispinal etanercept in combination with other therapeutic approaches. In addition, because of the ability of anti-TNF treatment to ameliorate inflammation, perispinal etanercept has the potential to complement other therapeutic strategies that may themselves engender brain inflammation [68]. For intractable disc-related pain, perispinal etanercept represents a uniquely effective nonsurgical treatment modality that is capable of both rapid and sustained symptom reduction. The ability to see first hand the difference perispinal etanercept has made in the lives of our patients has been the driving force that has sustained the efforts necessary to pioneer this remarkable therapeutic modality.

Five-year view

"The advancement of scientific knowledge is an uphill struggle against 'accepted wisdom'."

– Wolinsky [113].

The favorable clinical results produced by perispinal etanercept provide proof-of-concept of the utility of an anti-TNF approach for neuroinflammatory disorders. These favorable results have also attracted pharmaceutical company interest and the initiation of their first efforts to gain FDA-approval for an anti-TNF indication for sciatica. The comparative simplicity of the necessary clinical trial design and the favorable existing basic science and clinical data accumulated over a period of nearly a decade give these commercialization efforts an excellent chance of yielding a new FDA-approved anti-TNF pain indication within a 5-year time frame.

Speculation regarding FDA approval of anti-TNF treatment for brain and spinal cord disorders is more difficult. This will require the completion of large, multicenter trials that, for AD, typically require hundreds of millions of dollars of funding [127]. As recent experience has demonstrated, the design of AD clinical trials is challenging [68,127]. Will future etanercept clinical trials for neurological indications be properly designed? Careful patient selection, proper selection of dose and route of administration and adequate trial size will be necessary to achieve optimal results. The previous clinical trial failure of subcutaneous etanercept for AD is likely to be a reflection of the difficulty that large molecules have in crossing the BBB or blood–CSF barrier in sufficient concentration when administered systemically [93,153–157]. Note that, in general, large molecules, when administered systemically, only achieve a small fraction of their serum concentration in the CSF. For albumin this fraction is 0.5% [154]; for rituximab (MW 145 kDa) it is 0.1% [156]. The successful use of rituximab delivered into the CSF for treatment of CNS lymphoma [157] demonstrates that CSF delivery of a biologic can successfully treat CNS parenchymal disease. Basic science and clinical evidence supports the concept that perispinal administration of etanercept may have therapeutic advantages over systemic administration for neurological applications [5,23,24,38,40,42–44,48,54,56,61,62,84–86,91,107,153,155,157–161]. Perispinal administration of large molecules, such as etanercept, is, therefore, likely to be the route of choice for the treatment of brain and spinal indications.

Despite the evidence supporting a perispinal anti-TNF therapeutic rationale for AD, the source of the enormous funding necessary to move toward FDA approval remains uncertain. What is clear, however, is that further experimental investigation of the neuronal and CNS effects of TNF and anti-TNF biologics in neurology and related fields (such as psychiatry) will continue. As a result, one can predict that despite uncertainties about timing, in the near future investigations into the role of TNF will result in further advances in the understanding of brain and neuronal physiology, immune regulation of synaptic and brain function and the pathophysiology of neurological diseases.

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The author has multiple issued and pending US and foreign patents detailing methods of use of etanercept and other anti-TNF biologics for neurological indications, including epidural etanercept for sciatica, perispinal etanercept for Alzheimer's disease, disc-related pain, traumatic brain injury, stroke and spinal cord injury, including US patents 6015557, 6177077, 6419934, 6419944, 6537549, 6982089, 7214658, 7629311 and Australian patent 758523, all assigned to TACT IP, LLC. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- TNF, an immune signaling molecule, plays a central role in the pathogenesis of a variety of neuroinflammatory disorders.
- TNF is a gliotransmitter that regulates synaptic function.
- Excess TNF constitutes another target (in addition to amyloid and tau) that is a central mediator of Alzheimer's disease (AD) pathogenesis.
- Perispinal administration of etanercept results in its delivery into the cerebrospinal venous system.
- Perispinal etanercept may result in rapid improvement in AD and sciatica.
- Penetration of etanercept into the cerebral ventricles and the choroid plexus after perispinal delivery may play a role in its rapid cerebral effects.
- Spinal cord and traumatic brain injury constitute therapeutic targets for perispinal etanercept that are in addition to its documented efficacy for disc-related pain, lumbar and cervical radiculopathy and dementia.

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