Clin Drug Investig (2014) 34:361–366
DOI 10.1007/s40261-014-0186-1

CASE REPORT

Immediate Neurological Recovery Following Perispinal Etanercept Years After Brain Injury

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Published online: 20 March 2014

Abstract Positron emission tomographic brain imaging and pathological examination have revealed that a chronic, intracerebral neuroinflammatory response lasting for years after a single brain injury may occur in humans. Evidence suggests the immune signaling molecule, tumor necrosis factor (TNF), is centrally involved in this pathology through its modulation of microglial activation, role in synaptic dysfunction, and induction of depressive symptoms and neuropathic pain. Etanercept is a recombinant TNF receptor fusion protein and potent TNF inhibitor that has been found to reduce microglial activation and neuropathic pain in multiple experimental models. We report that a single dose of perispinal etanercept produced an immediate, profound, and sustained improvement in expressive aphasia, speech apraxia, and left hemiparesis in a patient with chronic, intractable, debilitating neurological dysfunction present for more than 3 years after acute brain injury. These results indicate that acute brain injury-induced pathologic levels of TNF may provide a therapeutic target that can be addressed years after injury. Perispinal administration of etanercept is capable of producing immediate relief from brain injury-mediated neurological dysfunction.

Key Points

Acute brain injury may lead to a chronic, intracerebral neuroinflammatory response involving excess tumor necrosis factor (TNF) and microglial activation that persists for years after injury

Etanercept, in addition to binding TNF, may reduce microglial activation

Perispinal administration of etanercept is capable of producing rapid favorable neurological improvement in select patients with chronic brain dysfunction

Electronic supplementary material The online version of this article (doi:10.1007/s40261-014-0186-1) contains supplementary material, which is available to authorized users.

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1 Introduction

Positron emission tomographic brain imaging and pathological examination have revealed that a chronic, intracerebral neuroinflammatory response lasting for years after a single brain injury may occur in humans [1–6]. Evidence suggests the immune signaling molecule, tumor necrosis factor (TNF), is centrally involved in this pathology through its modulation of microglial activation, role in

synaptic dysfunction, and induction of depressive symptoms and neuropathic pain [7, 8]. Etanercept is a recombinant TNF receptor fusion protein and potent TNF inhibitor that has been found to reduce microglial activation and neuropathic pain in multiple experimental models [7–11]. Basic science and clinical evidence suggest the chronic neuroinflammatory response that occurs following acute brain injury may be amenable to therapeutic intervention utilizing biological TNF inhibitors [7, 8]. We report the clinical effects of a single dose of perispinal etanercept, used off-label, in a patient who had suffered acute brain injury years earlier.

2 Case Report

A 52-year-old woman presented to our medical clinic in January 2014 for evaluation, with a chief complaint of severe and intractable speech and language difficulties. Forty months earlier, in September 2010, at the age of 49 years, the patient, a school teacher, was found actively seizing on the school floor, 45 min after she entered the bathroom. Multiple seizures were witnessed by the ambulance emergency medical personnel on the way to the hospital. Upon admission she presented with dense left hemiplegia, left hemisensory loss, aphasia, and confusion. An intravenous benzodiazepine was given. Head computed tomography on admission was negative. The next day, partial motor function had returned but left hemiparesis and left-sided hyperesthesia persisted. Brain magnetic resonance imaging (MRI) and electroencephalogram were normal. Her chronic seizure medications, zonisamide and levetiracetam, were continued with an increased dose of levetiracetam. Eleven days after admission she was discharged. Severe impairment of language function, expressive aphasia, marked circumlocution, prolonged latency of response to verbal questions, moderate impairment of visuospatial/constructional tasks, severe impairment of attention, residual left hemiparesis, and left hemisensory loss were noted on the day of hospital discharge. Despite months of rehabilitation, including physical, occupational, and speech therapy, her cognitive, speech, motor, and gait abnormalities never resolved. Four months prior to her visit to our medical clinic, independent medical evaluation revealed noticeable memory and cognitive impairment, mild left hemiparesis, 'profound linguistic impairments' with marked expressive aphasia, slow and hesitating speech, and difficulty naming objects ("it took her approximately 30 seconds to speak the word 'watch'….").

Prior to the brain injury she had been in good health, other than a 10-year history of complex partial seizures. Ten days prior to the brain injury she had been seen by her neurologist, at which time no neurological deficits were noted and seizure control on her medication regimen was reported as excellent. MRI of the brain 6 years earlier had been normal and there was no history of head trauma.

At presentation to our clinic in January 2014, the patient was accompanied by her husband, mother, and brother. They related that her neurological, speech, and cognitive dysfunction had continued without change for at least the past year; she later related that she was and had been experiencing chronic discomfort, including paresthesias in her left arm and left leg following brain injury, with left lower extremity pain that woke her from sleep on repeated occasions.

Complete blood count and tuberculin skin test were normal (negative). Cognitive and neurological evaluation was performed. Vital signs and general physical examination were normal. Motor examination was most notable for a mild left hemiparesis, motor apraxia, and gait abnormality, with a noticeable limp on the left and absence of left-arm swing. Most remarkable were her speech and language difficulties. There was marked apraxia of speech. Attempts to read words or initiate utterances required great effort and prolonged time. The prosody of speech was highly segmented with very slow intervals. She was asked to read a 14-item word list out loud, a task that took 466 seconds for her to complete (see electronic supplementary video). Multisyllabic words were extremely difficult for her to pronounce. She used compensatory mechanisms, for example gesturing the shape of a cube with her hands when trying to speak the word 'cube'. She counted from 1 to 10 out loud with difficulty, requiring 62 s for completion. She struggled with initiating the sounds, with a stutter-like quality to her utterances, and there were many pauses between sounds. She had similar difficulty reciting the alphabet. Verbal fluency was severely impaired, as measured by a standardized instrument, the Controlled Oral Word Association Test (COWAT)-FAS version [12]. Her markedly slow processing of verbal and cognitive tasks and prolonged latency of response to questions and verbal commands prevented completion of the usual cognitive test battery. There was severe difficulty with a written exercise of subtraction of 7 from 100. She was able to write the correct answer (93) but it took her 95 s to answer. Deficits in visuospatial function, memory, attention, and executive function were observed. A summary of selected measures that were quantitated before and after treatment is contained in Table 1.

Prior to treatment, the scientific rationale, risks, and potential benefit of perispinal etanercept were discussed with the patient and her family members, and informed consent was obtained. After skin preparation with chlorhexidine, etanercept (25 mg) was administered external to the ligamentum flavum, using sterile technique, by injection with a 27 gauge, 0.5 inch needle through the skin in

Table 1 Change in selected clinical measures following a single dose of perispinal etanercept

Clinical measures	Pre-Tx (21 January 2014)	4 min post-Tx	14–18 min post-Tx	30–45 min post-Tx	3 days post-Tx	6 days post-Tx
Gait	15 m: 19.4 sec		15 m: 12 s		15 m: 8.1 s	15 m: 8.1 s
	15 m: 17.4 sec,		15 m: 12 s		15 m: 8.2 s	15 m: 7.6 s
	Total: 30 m = 36.8 sec (with a limp)		Total: 30 m = 24 s (without a limp)		Total: 30 m = 16.3 s (without a limp)	Total: 30 m = 15.7 s (without a limp)
14-item word list (time to read)	466 s			16 s, 14 s, 10 s	7 s	6 s
Counting from 1 to 10	62 s	25 s	8 s	10 s	3 s	
Alphabet	111 s			13 s	6 s	
Finger to nose (repetitions) [13]	L: 0/10 s			L: 10/10 s	L: 13/10 s	L: 12/10 s
	R: 3/10 s			R: 11/10 s	R: 13/10 s	R: 13/10 s
Heel on shin (repetitions) [14]	L: 0.5/5 s			L: 7/5 s	L: 5/5 s	L: 6/5 s
	R: 2/5 s			R: 8/5 s	R: 6/5 s	R: 6/5 s
Foot tapping (repetitions) [15]	L: 8/5 s			L: 21/5 s	L: 19/5 s	L: 22/5 s
	R: 12/5 s			R: 22/5 s	R: 22/5 s	R: 21/5 s
Controlled Oral Word Association Test [16]	Patient wrote the words			Patient verbalized the words		Patient verbalized the words
	F: 4			F: 11		F: 15
	A: 4			A: 8		A: 13
	S: 5			S: 16		S: 20
	Total = 13			Total = 35		Total = 48
Grip strength (Jamar) [17]	L: 12 kg					L: 30 kg
	R: 29 kg					R: 28 kg
BDI-II [18]	9 out of 63					0 out of 63
RPQ [19]	RPQ-3: 4 out of 12					RPQ-3: 1 out of 12
	RPQ-13: 27 out of 52					RPQ-13: 2 out of 52
Temperature dorsal aspect of foot	L: 94.6 °F		L: 94.6 °F			L: 95.2 °F
	R: 95.2 °F		R: 94.8 °F			R: 95.2 °F

Tx treatment, *L* left, *R* right, *BDI-II* Beck Depression Inventory-II, *RPQ* Rivermead Post-Concussion Symptom Questionnaire

the midline between the adjoining spinous processes overlying the C7–T1 spinal level. Following injection, the patient was put into the Trendelenburg position on the examination table for 7 min.

Four minutes after injection, while still in the Trendelenburg position, there was notable improvement in apraxia and quality of speech. She counted from 1 to 10 in 25 s with decreased apraxia, decreased stutter, and increased fluidity of speech. She remarked "it's bright in here", referring to a marked change in her visual perception. There was noticeable euphoria. During the hour following etanercept administration, the patient was carefully observed. Her elevated mood was sustained. There was marked and progressive improvement in neurological function during this hour, with notable changes apparent every few minutes, particularly in apraxia of speech and verbal fluency. Fourteen minutes after injection her speech was dramatically improved, and she counted 1 to 10 in 8 s. At 16 min she noted improvement in her chronic left-sided paresthesias in both the arm and leg. At 17 min, improvement in gait was evident; her limp was gone, and her gait was normal, with normal left-arm swing. Speech, verbal fluency, cognition, and motor function progressively improved during the next hour, and remained remarkably improved from baseline at 3 and 6 days after treatment (Table 1). Within the first hour, all of the neurological impairments noted on baseline examination had either resolved completely or were markedly improved (Table 1). Each of the authors was present and witnessed the baseline neurological evaluation and the immediate and progressive neurological improvement exhibited by the patient on the day of treatment. Most remarkable was the improvement in apraxia of speech and verbal fluency; for example, the time required to read a list of 14 words improved from 466 s

prior to treatment to 10 s when measured 41 min after perispinal etanercept, and further improved to 7 s at 3 days. The baseline examination and the response to treatment were documented by digital video recording. A segment of that recording, documenting the patient's baseline function and the dramatic difference in expressive aphasia, verbal apraxia, and speech within the first hour after perispinal etanercept administration is included as a supplementary file accompanying this article (electronic supplementary video). Improvement in multiple additional measures was documented at intervals during the first hour after treatment and at 3 and 6 days (Table 1). At 3 and 6 days, sustained improvement in left hemiparesis, sensation, speech, gait, pain, vision, and cognition were noted. There were no adverse effects from treatment.

Fifteen days after etanercept administration, her family practitioner confirmed remarkable clinical improvement. The patient reports her improvements in apraxia, speech, gait, motor function, pain, sensation, vision, and executive function have been sustained through today, currently 6 weeks following her single perispinal etanercept dose.

3 Discussion and Conclusion

We report that a single dose of perispinal etanercept resulted in an immediate, profound, and sustained improvement in expressive aphasia, speech apraxia, and left hemiparesis in a patient with long-standing, chronic, debilitating neurological dysfunction due to acute brain injury (Table 1). The patient had chronic neurological dysfunction that failed to resolve despite intensive treatment and months of rehabilitation. After a single perispinal etanercept injection, significant neurological recovery was readily apparent to all observers within minutes. Recovery continued to progress during the first hour, was sustained at 3 and 6 days, and has been sustained through to the present time (currently 6 weeks after treatment). The rapidity and spectrum of the treatment effect, across multiple neurological domains (speech, language, affect, cognition, motor, and sensory function), are typical of the results seen after perispinal etanercept treatment of patients with chronic neurological dysfunction after stroke or traumatic brain injury [7, 8]. However, the magnitude of improvement, with nearly complete recovery in every domain, was remarkable and may reflect the circumstances of the patient's brain injury [20, 21]. Seizures may result in upregulation of TNF, including TNF production from activated microglia and astrocytes, neurovascular injury, and cognitive impairment [20–26]. Our results suggest that excess TNF may be centrally involved in the pathogenesis of chronic brain dysfunction mediated by status epilepticus. The collective results of perispinal etanercept establish pathologic TNF concentration as a long-standing therapeutic target following acute brain injury [7, 8, 27–32]. Amazingly, this therapeutic approach may be applied years after brain injury, with great efficacy.

An objective review of the peer-reviewed medical literature establishes that the biological plausibility of the rapid favorable neurological effects seen here and in others treated with perispinal etanercept is unequivocal, and is supported by extensive literature [32] (for complete references, please see the electronic supplementary material):

1. Published, peer-reviewed reports of improvement in cognition in humans following the use of etanercept or TNF antibodies by independent academic sources other than the present authors.
2. Favorable results of etanercept and other recombinant TNF inhibitors in animal models of stroke, traumatic brain injury, Alzheimer's disease, and neuropathic pain.
3. Published, peer-reviewed reports of rapid, significant, and sustained neurological and clinical improvement following perispinal etanercept in patients with chronic neurological dysfunction following stroke, traumatic brain injury, Alzheimer's disease, sciatica, and other forms of spinal pain.
4. Positron emission tomographic imaging data and data from direct pathological examination of brain tissue demonstrating chronic microglial activation in the brain following stroke and traumatic brain injury in humans that may last for years after a single brain injury.
5. Etanercept's demonstrated ability to reduce microglial activation in multiple experimental models, including in models of brain injury.
6. Known effects of TNF on synaptic function.
7. Known rapid effects of TNF on neuronal and synaptic function.
8. Recognition in the scientific community of the therapeutic potential of perispinal etanercept for the treatment of neurological disorders, as indicated by scientific citation.
9. Four randomized, clinical trials reporting favorable effects of etanercept for spinal neuropathic pain supporting earlier reports of the effectiveness of perispinal etanercept for these indications.
10. A known anatomic pathway for carriage of etanercept following perispinal injection, the vertebral venous plexus (Fig. 1).

Venous drainage of the anatomic area posterior to the spine is accomplished by the external vertebral venous plexus, a division of the cerebrospinal venous system [33]. The external vertebral venous plexus penetrates through the ligamentum flavum, providing a vascular route for

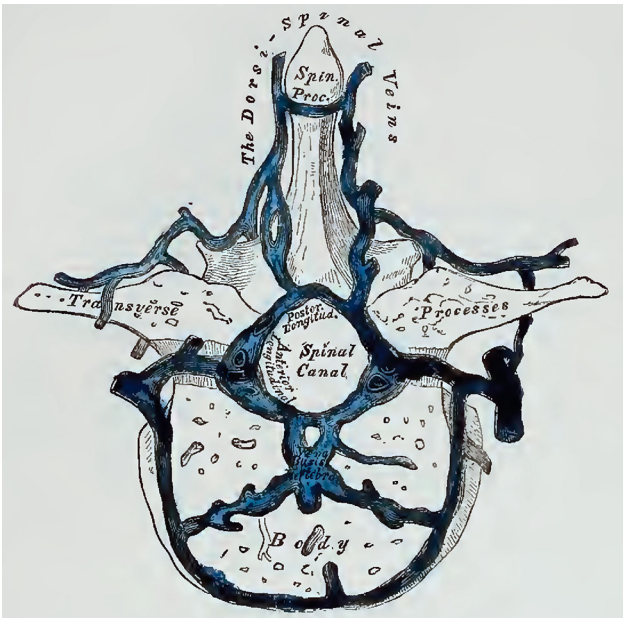

Fig. 1 The vertebral veins (reproduced from Gray and Holmes [45])

delivery of pharmaceuticals to the central nervous system (Fig. 1) [31, 34].

There is no available pharmaceutical treatment that has a US FDA indication encompassing the broad range of neurological, speech, and cognitive dysfunction that may occur in patients with brain injury [35]. Etanercept has rare risks of death, infection, demyelination, seizures, infection, etc., but its known side effect profile when used chronically for its approved indications is favorable [36]. However, the side effect profile for the dozens of reported off-label uses of etanercept remains incompletely defined, despite limited favorable safety data from four randomized trials [8, 37]. The decision to use a medication off-label requires individual assessment by the patient's treating physician and informed consent by the patient [38]. Off-label use is commonplace and necessary for optimal care of patients with neurological disorders, offering patients a therapeutic alternative when response to standard treatment is inadequate [39]. Off-label use as part of a physician's practice of medicine is not considered investigational or experimental [39, 40]. Off-label use of perispinal etanercept in patients with chronic neurologic dysfunction following acute brain injury has a firm scientific and ethical rationale, is supported by sound medical evidence, addresses unmet medical needs, and merits further investigation [41–44].

Acknowledgments Dr. Edward Tobinick has multiple issued and pending US and foreign patents, assigned to TACT IP LLC, which claim methods of use of etanercept for the treatment of neurological disorders, including, but not limited to, US patents 6419944, 6537549, 6982089, 7214658, 7629311, 8119127, 8236306, and 8349323, all assigned to TACT IP LLC; and Australian patent 758523. Dr. Tobinick is the founder of the Institute of Neurological Recovery, a group of medical practices that utilize perispinal etanercept as a therapeutic modality, and also train physicians; he is also the Chief Executive Officer of TACT IP LLC. Helen Rodriguez-Romanacce and Arthur Levine are employees of the Institute of Neurological Recovery, Boca Raton, FL, USA. The professional activities of Tracey Ignatowski and Robert Spengler include their work as co-directors of neuroscience at NanoAxis, LLC, a company formed to foster the commercial development of products and applications in the field of nanomedicine, which include novel methods of inhibiting TNF.

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