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ORIGINAL RESEARCH ARTICLE

Selective TNF Inhibition for Chronic Stroke and Traumatic Brain Injury

An Observational Study Involving 629 Consecutive Patients Treated with Perispinal Etanercept

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Abstract

Background Brain injury from stroke and traumatic brain injury (TBI) may result in a persistent neuroinflammatory response in the injury penumbra. This response may include microglial activation and excess levels of tumour necrosis factor (TNF). Previous experimental data suggest that etanercept, a selective TNF inhibitor, has the ability to ameliorate microglial activation and modulate the adverse synaptic effects of excess TNF. Perispinal administration may enhance etanercept delivery across the blood–CSF barrier.

Objective The objective of this study was to systematically examine the clinical response following perispinal administration of etanercept in a cohort of patients with chronic neurological dysfunction after stroke and TBI.

Methods After approval by an independent external institutional review board (IRB), a chart review of all patients with chronic neurological dysfunction following stroke or TBI who were treated open-label with perispinal etanercept (PSE) from November 1, 2010 to July 14, 2012 at a group medical practice was performed.

Results The treated cohort included 629 consecutive patients. Charts of 617 patients following stroke and 12 patients following TBI were reviewed. The mean age of the stroke patients was 65.8 years ± 13.15 (range 13–97). The mean interval between treatment with PSE and stroke was 42.0 ± 57.84 months (range 0.5–419); for TBI the mean interval was 115.2 ± 160.22 months (range 4–537). Statistically significant improvements in motor impairment, spasticity, sensory impairment, cognition, psychological/behavioural function, aphasia and pain were noted in the stroke group, with a wide variety of additional clinical improvements noted in individuals, such as reductions in pseudobulbar affect and urinary incontinence. Improvements in multiple domains were typical. Significant improvement was noted irrespective of the length of time before treatment was initiated; there was evidence of a strong treatment effect even in the subgroup of patients treated more than 10 years after stroke and TBI. In the TBI cohort, motor impairment and spasticity were statistically significantly reduced.

Discussion Irrespective of the methodological limitations, the present results provide clinical evidence that stroke and TBI may lead to a persistent and ongoing neuroinflammatory response in the brain that is amenable to therapeutic intervention by selective inhibition of TNF, even years after the acute injury.

Conclusion Excess TNF contributes to chronic neurological, neuropsychiatric and clinical impairment after stroke and TBI. Perispinal administration of etanercept produces clinical improvement in patients with chronic neurological dysfunction following stroke and TBI. The therapeutic window extends beyond a decade after stroke and TBI. Randomized clinical trials will be necessary to further quantify and characterize the clinical response.

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1 Background

Stroke is a leading cause of disability throughout the world [1]. Motor impairment, typically affecting the control or movement of the face, arm and leg of one side of the body is seen in about 80 % of patients [2]. Cognitive impairment is common and may be long-lasting and progressive [3–6]. Additional impairments that are common and disabling include central post-stroke pain, hemiplegic shoulder pain, painful spasticity, fatigue, incontinence, sleep-disordered breathing, depression and emotionalism (pseudobulbar affect [PBA]) [1–11]. There is currently no drug treatment that is specifically approved to treat the spectrum of chronic neurological dysfunction that affects the 4.5 million survivors of stroke in the USA [1–11].

Tumour necrosis factor (TNF), a key regulator of varied physiological mechanisms in multiple organ systems, is an immune signalling molecule produced by glia, neurons, macrophages and other immune cells [12]. During the past 3 decades there has been increasing recognition that excess TNF plays a key role in the pathophysiology of disease [13]. TNF exerts its physiological effects by binding to two cell-surface receptors, the p55 and p75 TNF receptors (TNFR), now more commonly referred to as TNFR1 and TNFR2. TNFR are found on all nucleated cells, including neurons in the brain [14, 15]. Constitutive expression of p55 TNFR messenger RNA has been detected in the brain in the circumventricular organs, choroid plexus, leptomeninges, ependymal lining cells in the walls of the cerebral ventricles and along the blood vessels [16].

As of the late 1990s there remained conflicting opinions regarding whether excess TNF was neuroprotective or neurodestructive [17–21]. Animal models suggested that inhibition of TNF had potential therapeutic utility for treating multiple sclerosis (MS). However, a 1998 human trial of the biologic selective TNF inhibitor lenercept, a p55 TNFR fusion protein in clinical development, resulted in MS exacerbation, and its clinical development was abandoned [20, 21]. In 1998, the first biologic selective TNF inhibitors, etanercept and infliximab, were approved by the US FDA for the treatment of rheumatoid arthritis in humans. Both of these agents are large molecules, with a molecular weight of 150,000 Da, a property that would be expected to limit their ability to cross the blood–brain barrier and reach the brain after systemic administration [22]. A study of etanercept confirmed that it did not cross the blood–brain barrier [23]. Intrathecal delivery was a potential method to achieve brain delivery. However, at the time there would have been great concern about neuraxial delivery of any biologic TNF inhibitor due to the CNS toxicity of lenercept and an earlier study suggesting the potential of infliximab to produce adverse CNS effects [24].

The complex role played by TNF in the brain is still in the process of being deciphered [25–36]. However, now, more than a decade after the introduction of biologic TNF inhibitors into clinical practice, there is substantial evidence that excess TNF plays a key role in brain dysfunction, and also that physiological levels of TNF are involved in normal brain physiology [14, 15, 25, 26, 29, 31, 32, 35, 37–49]. In the brain, among other functions, TNF serves as a gliotransmitter, secreted by glial cells that envelope and surround synapses, and TNF is known to regulate synaptic communication between both neurons and neuronal networks [12, 27, 29, 31, 44, 50–53]. During the past 10 years, a relatively non-invasive method of delivery of etanercept, perispinal extrathecal administration, was developed for the treatment of neuroinflammatory disorders [54]. In 2003, clinical evidence suggested the potential of perispinal etanercept (PSE) for rapid relief of pain and neurological dysfunction due to herniated nucleus pulposus and spinal pain due to bone metastases [55–57]. In 2004, the rapidity of relief of sciatic pain and associated sensory and motor dysfunction, often evident within minutes, was confirmed in additional patients [58]. Prevailing concepts of drug distribution were unable to explain the novel pattern of clinical effects that rapidly ensued after PSE [48, 54, 55, 57–60]. The pattern, rapidity and distribution of clinical effects best fit with rapid delivery of etanercept via retrograde distribution into the radicular and intraspinal veins from the external vertebral venous division of Batson's plexus [54, 59, 61–64]. Further study of the anatomy and physiology of Batson's plexus led to a new insight: the lack of venous valves, enabling bidirectional flow, and the anatomical continuity of Batson's plexus with the cerebral venous system introduced the possibility that this unique vascular pathway might be utilized for delivery of etanercept, and other large molecules, into the brain [46, 54, 59, 62–64]. The potential use of this unique, bidirectional venous system, named the "cerebrospinal venous system" in 2006 [65], for the treatment of Alzheimer's disease was investigated in an open-label, 6-month PSE clinical trial [66]. Rapid and sustained improvement in cognitive function was seen [51, 66]. The potential value of PSE for treating other forms of dementia has been suggested [40, 46, 48, 51, 54, 59, 60, 66, 67]. Basic science and clinical investigation suggests that PSE, followed by Trendelenburg positioning, may result in rapid delivery of etanercept into the CSF within the cerebral ventricles [26, 46, 59, 68]. Paravascular pathways, recently reported to clear interstitial solutes from the brain, may facilitate parenchymal brain delivery of etanercept that reaches the CSF through cerebrospinal venous delivery [26, 47, 59, 65, 69, 70].

Independent clinical and basic science investigation of etanercept and other biologic TNF inhibitors for the treatment of neuroinflammatory disorders, at academic centres around the world, paralleled the clinical development of PSE. These additional investigators developed independent supporting evidence [25, 28, 34, 35, 37–39, 41, 49, 62, 71–83]. This evidence includes both randomized, controlled, clinical trial data [71, 74], animal and human data supporting the safety of neuraxial delivery of etanercept [71, 74] and favourable etanercept data in an animal traumatic brain injury (TBI) model [37]. In this TBI model, etanercept was found to reduce TBI-induced cerebral ischaemia, cellular damage, motor and cognitive function deficits, and microglial activation [37].

Increasing evidence regarding TNF as a therapeutic target after stroke and TBI also developed in parallel with the evidence of the potential of etanercept as a neurotherapeutic. A major step in recognizing the involvement of TNF was recognition of the stroke penumbra as a site of microglial activation and neuroinflammation [84]. In 2006, it was suggested that neuroinflammation in the stroke penumbra was a potential therapeutic target [84]. In 2008, scientists specifically implicated excess TNF as a therapeutic target in the stroke penumbra [41]. This research identified activated microglia in the stroke penumbra as a source of neurotoxicity, killing neurons through an apoptotic mechanism that was mediated by TNF [41].

Thus, three parallel bodies of work during the past decade converged to present a scientific rationale for PSE as a treatment for chronic neurological dysfunction after stroke and TBI: (1) the clinical development of perispinal administration of etanercept, including recognition and basic science investigation of the potential of the cerebrospinal venous system as a route for therapeutic delivery of large molecules to the brain, and clinical experience using PSE for selected neuroinflammatory disorders; (2) basic science and clinical evidence developed at independent academic centres regarding the potential and safety of etanercept as a neurotherapeutic; and (3) the identification of neuroinflammatory mechanisms (microglial activation, and TNF mediation of neurotoxicity) in the stroke penumbra and in TBI, and recognition that this was a potential therapeutic target [37, 41, 43, 84, 85].

The clinical results in the first three patients with chronic post-stroke neurological dysfunction who were given PSE were published in 2011 [47], and have been followed by nearly 2 years of favourable clinical experience. This is a report detailing that experience. The objective of this study was to systematically examine the clinical response following perispinal administration of etanercept in a cohort of patients with chronic neurological dysfunction after stroke and TBI.

2 Methods

2.1 Study Design

This is an observational study consisting of a review of the medical charts of all patients with chronic neurological dysfunction following stroke or TBI who were treated open-label with PSE from November 1, 2010 to July 14, 2012 at a private medical practice.

2.2 Setting

The study was performed at a private medical practice at three clinics (Los Angeles, CA, USA; Newport Beach, CA, USA; and Boca Raton, FL, USA) in collaboration with the assistance of an independent biostatistician. The chart review was conducted after approval by an independent external institutional review board (IRB).

2.3 Participants

There were 468 patients treated in California and 161 patients treated in Florida, for a total of 629 patients.

All patients had chronic neurological dysfunction that had failed to adequately respond to all forms of previous treatment and were treated with PSE as part of the usual practice of medicine. Prior to treatment, all patients were advised of the known potential adverse clinical effects of etanercept, including death, infection, decreased blood counts, reactivation of tuberculosis, seizures, lymphoma, cancer and congestive heart failure, and that treatment was off-label and clinical experience for this indication was limited. All patients were treated, after informed written and oral consent, with PSE 25 mg as previously described [47]. 617 patients had chronic neurological dysfunction following stroke; 12 patients had chronic neurological dysfunction after TBI. The quantitative data were as recorded in the medical charts of all patients; the qualitative data was tabulated from a summary form that was present in each chart that reflected the treating physician's clinical evaluation of the patient's response to treatment immediately, 1 week and 3 weeks following the first dose of PSE that had been completed at the time of each patient's office visits.

2.4 Variables

The following assessments were performed immediately following the first dose of PSE, and at 1 week and 3 weeks after the first dose: quantitative data on time to walk a measured 20-m distance [86], hand grip strength measured by dynamometer, visual analogue score (VAS) for pain, Montreal Cognitive Assessment (MoCA) [87, 88] and the

controlled oral word association test (FAS) [89]. Patients were also qualitatively assessed for improvement in motor impairment, spasticity, walking impairment, cognitive impairment, psychological or behavioural difficulties, sensory impairment, aphasia, pain and other impairments at these three time points. Patients with improvement in one or more areas of qualitative impairment were classified as having improvement in clinical impairment. Clinical responses recorded as 'immediate' reflect clinical findings within 30 min of treatment.

2.5 Data Sources/Measurement

The data sources were the patient charts as well as the clinical observations made by the treating physicians and nurse practitioner. The number of parameters assessed after treatment varied during office visits following treatment and were adapted to each patient, depending upon the patient's pattern of clinical impairment.

2.6 Statistical Analysis

Quantitative measures were summarized, and absolute change from pre-treatment and percentage change from pre-treatment calculated. The Wilcoxon signed rank test was used to evaluate whether absolute and percentage changes from pre-treatment were significantly different from zero, at each time point. Differences in gaits and gait changes between two subgroups of patients (those within 6 months of stroke, and those more than 5 years after stroke) were evaluated using the Wilcoxon rank sum test at each time point. Patients confined to wheelchairs were excluded from the gait analysis.

Qualitative measures, assessed as either improved or not improved since treatment, were tabulated at each time point. Proportions of patients experiencing improvement of clinical symptoms were evaluated for differences from 0.5 using exact binomial tests. Therefore, the p values displayed for qualitative measures indicate whether significantly more than 50 % of patients showed improvement, and should not be taken to indicate if significantly more than 0 % of patients showed improvement.

SAS® version 9.2 (SAS, Cary, NC, USA) was used to perform all analyses. A significance level of $\alpha = 0.05$ was used to evaluate all statistical tests. All statistical tests performed were two-sided.

2.7 Bias

The treatment was open-label. One of the authors (ET) invented the treatment method and has issued US and foreign patents covering the treatment method; the medical clinic has licensed these patents.

3 Results

3.1 Participants

There were 629 consecutive participants, 468 in California and 161 in Florida.

The complete demographic and baseline profile of the patient cohort is detailed in Table 1. Charts of 617 patients following stroke and 12 patients following TBI were reviewed. The mean age of the stroke cohort was 65.8 ± 13.15 (range 13–97). The mean age of the TBI cohort was 34.7 ± 13.8 (range 19–52). The mean time since stroke was 42.0 ± 57.84 months (range 0.5–419) and since TBI was 115.2 ± 160.22 months (range 4–537).

3.2 Outcome Data

The outcome data are described in Tables 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and Tables S1–S4 (see Online Resource 1).

In the post-stroke cohort, the time to walk 20 m was significantly reduced following PSE. Both absolute change from pre-treatment and percentage change from pre-treatment showed statistically significant improvements in the overall cohort (Table 2), the subgroup of patients within 12 months of stroke (Table S1), the subgroup of patients more than 12 months since stroke (Table 4), the subgroup of patients more than 5 years since stroke (Table 5) and the subgroup of patients more than 10 years since stroke (Table 7). These improvements were apparent immediately following treatment, and at 1 week and 3 weeks post-treatment in all subgroups, with the exception that the absolute change from pre-treatment to 1-week post-treatment among patients more than 10 years after stroke did not reach statistical significance ($p = 0.0532$). The same pattern of improvement was apparent in the time to walk a second 20 m, immediately following the first 20 m, with the exception that the percentage change from pre-treatment to 1-week post-treatment among subjects more than 10 years after stroke also did not reach statistical significance ($p = 0.0663$). Improvements among times to walk both the first and second 20 m were shown both among patients with limited walking impairment (those who walked unassisted or with the use of a cane) and those with more severe impairment (requiring use of a quad cane, walker or manual assistance).

In addition, the times to walk 20 m were compared between patients within 6 months of stroke, and those more than 5 years since stroke. Although the latter group had longer mean walking times, the differences between walking times, changes from pre-treatment and percentage changes from pre-treatment between the two groups were not significantly different at any time point (Table S3).

Additional quantitative assessments, such as the FAS, MoCA, left and right hand grip strengths, and VAS for pain

Table 1 Demographics and baseline characteristics

Characteristic	Statistic/ category	Patients with stroke ($N = 617$)	Patients with TBI ($N = 12$)
Age (years)	Mean (SD)	65.8 (13.15)	34.7 (13.81)
	Minimum, maximum	13, 97	19, 52
<18	n (%)	1 (0.2)	0 (0)
18–65	n (%)	262 (42.5)	12 (100.0)
>65	n (%)	354 (57.4)	0 (0)
Sex	Male	372 (60.3)	6 (50.0)
	Female	245 (39.7)	6 (50.0)
Months since stroke or TBI[a]	Mean (SD)	42.0 (57.84)	115.2 (160.22)
	Minimum, maximum	0.5, 419	4, 537
≤3	n (%)	17 (2.8)	0 (0)
4–6	n (%)	175 (28.4)	4 (33.3)
7–9	n (%)	23 (3.7)	0 (0)
10–12	n (%)	27 (4.4)	0 (0)
13–60	n (%)	229 (37.1)	2 (16.7)
61–120	n (%)	101 (16.4)	3 (25.0)
>120	n (%)	45 (7.3)	3 (25.0)
Stroke type or TBI			
Haemorrhagic stroke	n (%)	167 (27.1)	0 (0)
Ischaemic stroke	n (%)	377 (61.1)	0 (0)
Unknown stroke type	n (%)	73 (11.8)	0 (0)
TBI	n (%)	0 (0)	12 (100.0)
Coumadin (warfarin) use			
Yes	n (%)	115 (18.6)	0 (0)
No	n (%)	502 (81.4)	12 (100.0)
Pain medication use			
Yes	n (%)	104 (16.9)	0 (0)
No	n (%)	513 (83.1)	12 (100.0)

SD standard deviation, *TBI* traumatic brain injury

[a] One patient, whose months since stroke were recorded as <12, was imputed as 6 months

showed statistically significant improvements from pre-treatment to each of the post-treatment assessments (Tables 8, 9, 10). Improvement in PBA was observed in a subgroup of patients (Table S4).

Qualitative changes were assessed by site personnel as improved or not improved at each time point. The percentage of patients showing improvement was then compared with 50 %, to determine if the percentage of patients showing improvement was significantly different from 50 %. The post-stroke cohort showed statistically significant improvements in clinical impairment, motor impairment, spasticity, walking impairment, cognitive impairment, psychological impairment, sensory impairment, aphasia and other impairments (with 'other impairments' defined as any stroke-related clinical impairment noted in the patient chart prior to treatment that did not fall into any of the named categories, such as pseudobulbar palsy, dysphonia, diplopia or urinary incontinence) at all three time points. Half of the patients showed an improvement in pain immediately following treatment, with significantly more than half showing an improvement in pain at 1 week and 3 weeks post-treatment (Table 3). Patients within 12 months of stroke showed statistically significant improvements in all qualitative assessments except sensory impairment at all three time points, with improvements in sensory impairment at 1 week and 3 weeks post-treatment (Table S2). Patients more than 5 years since stroke showed statistically significant improvements in all qualitative assessments except psychological impairment and pain at all three time points, with significant improvements in the remaining two assessments at 1 week and 3 weeks post-treatment (Table 6).

Patients in the TBI cohort showed a generally similar pattern of response to PSE as those in the stroke cohort. Although four of five patients showed improvement in the time to walk 20 m immediately following treatment, and four of four and five of five patients assessed at the remaining time points showed improvement in walking times, the changes were not statistically significant (Table 11). Patients in this cohort also showed statistically significant improvement in a number of qualitative assessments. Motor impairment and spasticity were statistically significantly improved in the TBI cohort at all three time points after PSE administration (Table 12).

Demographics of the best 10 % and worst 10 % of patients, based on percentage improvement in walk time immediately after PSE administration, were also compared and no significant differences were seen.

3.3 Descriptive Data

Improvements in motor impairment, spasticity, sensory impairment, walking, cognition, pain, aphasia, balance, handwriting, left-sided neglect, PBA (Table S4), special senses (vision, hearing, taste and smell), micturition, urinary incontinence (Case Report 1), dysphagia, drooling (Case Report 3, web supplement), dysarthria, speech impairment (pronunciation, slurring, enunciation, slowness), dysphonia, headache, fatigue, appetite, ataxia, breathing, chewing without biting side of mouth, clonus, cold intolerance, pallor of a limb, warmer extremities, decrease in extremity oedema, coordination, diplopia, driving ability, hair growth and pigmentation (one patient), muscle twitching, neglect and sleep were observed in the post-stroke patient cohort. Changes in the post-TBI cohort were generally similar and are described in Tables 11 and 12 and in Case Report 2.

Table 2 Time to walk 20 m (s) before and after a single dose of perispinal etanercept, stroke cohort

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	320	312	190	147
Mean (SD)	57.2 (52.52)	49.4 (44.74)	52.0 (55.68)	49.0 (45.31)
Median	36.1	32.2	32.7	32.4
Minimum, maximum	8.6, 325.0	6.4, 260.0	6.2, 405.1	7.4, 298.1
Absolute change from pre-treatment[a]				
N		312	187	144
Mean (SD)		−7.5 (18.22)	−9.1 (17.02)	−7.2 (19.82)
Median		−3.2	−4.8	−3.7
Minimum, maximum		−145, 80.8	−135, 19.3	−144, 80.1
p value[b]		<0.0001	<0.0001	<0.0001
Percentage change from pre-treatment[a]				
N		312	187	144
Mean (SD)		−10.4 (14.37)	−13.9 (15.94)	−10.1 (19.53)
Median		−9.6	−13.1	−11.2
Minimum, maximum		−65.4, 53.2	−69.7, 42.8	−69.5, 70.9
p value[b]		<0.0001	<0.0001	<0.0001

SD standard deviation

[a] Negative numbers indicate improvement

[b] *p* value is from Wilcoxon signed rank test

3.4 Clinical Improvements Following Perispinal Etanercept (PSE)

Improvements in motor function, spasticity, walking, cognition, psychological/behavioural function, sensation, aphasia and pain were commonly observed in the patient cohort.

3.4.1 Motor Function

Rapid motor improvement, beginning within minutes, was routinely observed in this patient cohort, including both the post-stroke patients and the TBI patients (Tables 2, 3, 4, 5, 6, 7, 9, 11, 12 and Tables S1–S3). Motor improvement manifested in a variety of ways, including improvements in walking, leg strength, hand grip strength, hand function and swallowing. Walking speed and gait were improved in the majority. Improved facial symmetry in patients with hemiparesis and unilateral facial paresis was characteristic and appreciated within minutes of the first dose of PSE. Improved ease of arising from a low chair was often observed. Increased strength was often clinically evident. Improved tongue strength and reduced tongue deviation in those with severe facial paresis was observed in several patients. Improvement in range of motion (ROM) of affected limbs (e.g. shoulder abduction and wrist and finger flexion and extension) was commonly observed, but some of the improvement in ROM was likely due to reduced spasticity. At times, development of partial motor ability for the first time since stroke was seen. For example, several patients were able to partially dorsiflex at the ankle joint whereas prior to treatment they had complete foot drop and ankle inversion. Some of the most satisfied responders were patients who began with a baseline of significant residual, but incomplete, hand function, some of whom recovered the ability to perform fine motor movements, such as buttoning and unbuttoning buttons with their affected hand after PSE administration. This degree of recovery was not seen in patients whose baseline hand function was very limited. Notable were several patients with dysphonia, in whom voice amplitude, reduced by their stroke, was markedly increased after PSE administration. One patient whose voice was severely affected by her stroke, to the point that she was unable to be heard in normal conversation and unable to be heard on the telephone, recovered her ability to phonate within minutes of the first PSE dose, and was able to resume using the telephone. Improvements in dysarthria were noted in multiple patients.

3.4.2 Spasticity

Improvement in spasticity was routinely observed and usually occurred within minutes of PSE administration in both stroke and TBI patients (Tables 3, 6, 12 and Table S2). Improvement has been observed in all affected joints on the hemiplegic side, including the fingers, elbow, shoulder, knee, hip, ankle and toes, neck and torso. In multiple patients painful curling of toes due to spasticity was alleviated, facilitating improved walking ability with less pain. Spasticity improvement was objectively apparent to all examining physicians, to the patients and to the patients' family members. A related sign of hyperreflexia, clonus, which in some patients extended to involve the entire limb

Table 3 Changes in impairment, by impairment type and time point, after a single dose of perispinal etanercept, stroke cohort

Impairment type	Immediately post-treatment, n (%)	After 1 week, n (%)	After 3 weeks, n (%)
Clinical impairment	614	484	339
Improved[a]	610 (99.3)	466 (96.3)	322 (95.0)
Not improved	4 (0.7)	18 (3.7)	17 (5.0)
p value[b]	<0.0001	<0.0001	<0.0001
Motor impairment	589	453	328
Improved	550 (93.4)	407 (89.8)	292 (89.0)
Not improved	39 (6.6)	46 (10.2)	36 (11.0)
p value[b]	<0.0001	<0.0001	<0.0001
Spasticity	487	380	274
Improved	417 (85.6)	315 (82.9)	222 (81.0)
Not improved	70 (14.4)	65 (17.1)	52 (19.0)
p value[b]	<0.0001	<0.0001	<0.0001
Walking impairments	511	398	289
Improved	417 (81.6)	326 (81.9)	232 (80.3)
Not improved	94 (18.4)	72 (18.1)	57 (19.7)
p value[b]	<0.0001	<0.0001	<0.0001
Cognitive impairment	390	333	240
Improved	293 (75.1)	288 (86.5)	206 (85.8)
Not improved	97 (24.9)	45 (13.5)	34 (14.2)
p value[b]	<0.0001	<0.0001	<0.0001
Psychological impairment	140	144	117
Improved	97 (69.3)	128 (88.9)	110 (94.0)
Not improved	43 (30.7)	16 (11.1)	7 (6.0)
p value[b]	<0.0001	<0.0001	<0.0001
Sensory impairment	402	318	227
Improved	243 (60.4)	241 (75.8)	178 (78.4)
Not improved	159 (39.6)	77 (24.2)	49 (21.6)
p value[b]	<0.0001	<0.0001	<0.0001
Aphasia	288	225	156
Improved	173 (60.1)	172 (76.4)	121 (77.6)
Not improved	115 (39.9)	53 (23.6)	35 (22.4)
p value[b]	0.0008	<0.0001	<0.0001
Pain	279	215	156
Improved	140 (50.2)	155 (72.1)	114 (73.1)
Not improved	139 (49.8)	60 (27.9)	42 (26.9)
p value[b]	>0.999	<0.0001	<0.0001
Other impairment	406	342	246
Improved	318 (78.3)	324 (94.7)	230 (93.5)
Not improved	88 (21.7)	18 (5.3)	16 (6.5)
p value[b]	<0.0001	<0.0001	<0.0001

[a] Denotes improvement noted in the patient chart in any domain

[b] *p* value is from exact binomial test

when an ankle reflex was elicited, was typically reduced and in some patients completely resolved.

3.4.3 Walking

Observable improvement in walking, not only in walking speed but also in the quality and character of the gait was observed after PSE administration in both stroke and TBI patients (Tables 2, 3, 4, 5, 6, 7, 12 and Tables S1–S3). The consensus opinion of the treating physicians and nurse practitioner was that walking improvement was attributable not only to motor strength improvement but also to improvements in balance, stability, coordination and particularly to a decrease in spasticity in the hemiparetic

Table 4 Time to walk 20 m (s) before and after a single dose of perispinal etanercept, patients in stroke cohort more than 12 months since stroke

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	268	259	161	124
Mean (SD)	58.0 (53.83)	50.6 (46.65)	53.8 (59.17)	51.5 (48.12)
Median	35.9	32.1	32.5	33.8
Minimum, maximum	8.6, 325.0	6.4, 260.0	6.2, 405.1	7.4, 298.1
Absolute change from pre-treatment[a]				
N		261	159	123
Mean (SD)		−7.2 (17.80)	−8.6 (15.12)	−6.5 (17.34)
Median		−3.1	−4.8	−3.5
Minimum, maximum		−145, 80.8	−135, 19.3	−119, 80.1
p value[b]		<0.0001	<0.0001	<0.0001
Percentage change from pre-treatment[a]				
N		261	159	123
Mean (SD)		−10.0 (14.38)	−13.6 (16.18)	−9.3 (19.78)
Median		−9.3	−13.1	−10.3
Minimum, maximum		−65.4, 53.2	−69.7, 42.8	−69.5, 70.9
p value[b]		<0.0001	<0.0001	<0.0001

SD standard deviation

[a] Negative numbers indicate improvement

[b] *p* value is from Wilcoxon signed rank test

Table 5 Time to walk 20 m (s) before and after a single dose of perispinal etanercept, patients in stroke cohort more than 60 months since stroke

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	102	98	66	51
Mean (SD)	54.0 (47.94)	46.3 (39.58)	51.5 (62.72)	46.3 (40.34)
Median	33.8	30.4	27.3	27.2
Minimum, maximum	8.6, 256.7	6.4, 218.6	6.2, 387.7	7.4, 193.1
Absolute change from pre-treatment[a]				
N		100	65	51
Mean (SD)		−7.7 (17.85)	−7.6 (12.37)	−5.8 (17.11)
Median		−3	−4.4	−4.5
Minimum, maximum		−142, 27.0	−49.8, 19.3	−49.6, 80.1
p value[b]		<0.0001	<0.0001	<0.0001
Percentage change from pre-treatment[a]				
N		100	65	51
Mean (SD)		−10.8 (14.23)	−14.4 (17.59)	−10.4 (23.32)
Median		−8.1	−14.7	−10.3
Minimum, maximum		−65.4, 28.7	−69.7, 21.5	−69.5, 70.9
p value[b]		<0.0001	<0.0001	<0.0001

SD standard deviation

[a] Negative numbers indicate improvement

[b] *p* value is from Wilcoxon signed rank test

limbs, allowing greater flexibility and ROM. Increased knee flexion, increased movement of the affected leg forward, decreased side swing of the affected leg and decreased hip hike were observed after PSE administration. In some patients foot drop partially resolved with the patient no longer dragging the foot and able to clear the floor more easily to move forward. Improvements in hip strength on examination were also observed but not quantitated and this may have also helped in ambulation.

3.4.4 Pain

Pain improvement was observed after PSE administration in both stroke and TBI patients (Tables 3, 6, 10, 12 and Table S2). The most common improvement in pain observed was improvement in hemiplegic shoulder pain and improvement in pain associated with spasticity. Hemiplegic shoulder pain, either at rest or with passive or active motion and in some patients associated with

Table 6 Changes in impairment, by impairment type and time point after a single dose of perispinal etanercept, patients in stroke cohort more than 60 months since stroke

Impairment type	Immediately post-treatment, n (%)	After 1 week, n (%)	After 3 weeks, n (%)
Clinical impairment	145	129	90
Improved[a]	144 (99.3)	125 (96.9)	80 (88.9)
Not improved	1 (0.7)	4 (3.1)	10 (11.1)
p value[b]	<0.0001	<0.0001	<0.0001
Motor impairment	139	120	89
Improved	128 (92.1)	108 (90.0)	78 (87.6)
Not improved	11 (7.9)	12 (10.0)	11 (12.4)
p value[b]	<0.0001	<0.0001	<0.0001
Spasticity	121	106	78
Improved	106 (87.6)	96 (90.6)	66 (84.6)
Not improved	15 (12.4)	10 (9.4)	12 (15.4)
p value[b]	<0.0001	<0.0001	<0.0001
Walking impairments	122	107	79
Improved	107 (87.7)	93 (86.9)	68 (86.1)
Not improved	15 (12.3)	14 (13.1)	11 (13.9)
p value[b]	<0.0001	<0.0001	<0.0001
Cognitive impairment	68	72	53
Improved	55 (80.9)	64 (88.9)	48 (90.6)
Not improved	13 (19.1)	8 (11.1)	5 (9.4)
p value[b]	<0.0001	<0.0001	<0.0001
Psychological impairment	39	47	35
Improved	24 (61.5)	41 (87.2)	34 (97.1)
Not improved	15 (38.5)	6 (12.8)	1 (2.9)
p value[b]	0.1996	<0.0001	<0.0001
Sensory impairment	107	96	70
Improved	70 (65.4)	74 (77.1)	59 (84.3)
Not improved	37 (34.6)	22 (22.9)	11 (15.7)
p value[b]	0.0018	<0.0001	<0.0001
Aphasia	48	44	29
Improved	32 (66.7)	36 (81.8)	24 (82.8)
Not improved	16 (33.3)	8 (18.2)	5 (17.2)
p value[b]	0.0293	<0.0001	0.0005
Pain	59	55	39
Improved	27 (45.8)	41 (74.5)	27 (69.2)
Not improved	32 (54.2)	14 (25.5)	12 (30.8)
p value[b]	0.6029	0.0004	0.0237
Other impairment	104	94	68
Improved	82 (78.8)	89 (94.7)	64 (94.1)
Not improved	22 (21.2)	5 (5.3)	4 (5.9)
p value[b]	<0.0001	<0.0001	<0.0001

[a] Denotes improvement noted in the patient chart in any domain

[b] *p* value is from an exact binomial test

subluxation of the shoulder joint, characteristically improved in this patient cohort following PSE administration. Reductions in pain, hyperesthesia and allodynia were observed. Pain associated with spasticity, including shoulder pain, wrist pain and finger pain, was routinely reduced. Multiple patients with neuropathic pain reported improvement; improvement in pain in patients with thalamic pain syndrome was variable and often transient. Rapid relief of pain elicited when a spastic extremity or digit was stretched was characteristic.

3.4.5 Sensation

Improvement in sensation was observed after PSE administration in both stroke and TBI patients (Tables 3, 6, 12 and Table S2). At least one of the patients in the cohort was

Table 7 Time to walk 20 m (s) before and after a single dose of perispinal etanercept, patients in stroke cohort more than 120 months since stroke

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	32	31	21	16
Mean (SD)	62.8 (53.69)	53.1 (40.77)	63.6 (55.96)	56.0 (44.72)
Median	43.4	40.3	45.7	44.3
Minimum, maximum	8.6, 231.7	6.4, 173.0	6.2, 210.8	7.4, 150.0
Absolute change from pre-treatment[a]				
N		32	21	16
Mean (SD)		−10.1 (26.16)	−6.2 (13.69)	−11.1 (13.53)
Median		−4.2	−2.4	−6.8
Minimum, maximum		−142, 27.0	−36.3, 19.3	−38.6, 4.7
p value[b]		<0.0001	0.0532	0.0022
Percentage change from pre-treatment[a]				
N		32	21	16
Mean (SD)		−11.9 (16.13)	−11.0 (18.46)	−14.0 (16.54)
Median		−11.1	−9	−11.8
Minimum, maximum		−61.4, 28.7	−54.2, 21.5	−47.9, 20.9
p value[b]		<0.0001	0.0121	0.0034

[a] Negative numbers indicate improvement

[b] *p* value is from Wilcoxon signed rank test

SD standard deviation

able to resume shaving with a manual razor due to recovery of facial sensation.

3.4.6 Cognition

Improvements in various cognitive domains were observed after PSE administration in both stroke and TBI patients (Tables 3, 6, 8, 12 and Table S2). The professional medical staff and family members noted improvements in executive ability, language, attention, focus, orientation and conversation. Improvement in verbal fluency (letter fluency) as measured by the FAS and improvement in the MoCA [88–92] was seen.

3.4.7 Aphasia

Partial improvement in aphasia, particularly in patients with significant residual language function before PSE administration, was seen (Tables 3, 6, 12 and Table S2). Improvement was noted in both receptive and expressive aphasia, in verbal fluency (Table 8) and in ease of word finding.

3.4.8 Psychological/Behavioural Function

Rapid improvement of mood, affect and attitude was commonly observed. Patients and families commonly reported improvement of depression, anxiety, irritability, motivation, initiative, hopefulness, and return of pre-morbid personality ("his personality is back") and sense of humour (Tables 3, 6, 12 and Table S2). Common observations are that individuals treated became more interactive and more willing to do physical therapy and engage in life activities.

3.4.9 Pseudobulbar Affect

Six patients in the stroke cohort were identified with PBA [11, 93]. After one treatment with PSE, immediate clinical improvement in PBA was noted in members of this subgroup (Table S4). This improvement continued through 3 weeks in several of the patients, with both caregivers and the treating physicians noting a decrease in frequency and duration of emotional incontinence.

3.5 Case Report 1: Resolution of Post-Stroke Urinary Incontinence After Perispinal Etanercept (PSE)

A 39-year-old woman suffered an ischaemic stroke with a large infarction of the right middle cerebral artery territory on August 17, 2011, 6 months after heart surgery. Brain magnetic resonance angiography (MRA) and brain magnetic resonance imaging (MRI) on hospital admission showed acute infarction in the distribution of the right middle cerebral artery, with diminished size and flow in the right internal carotid artery. The right carotid bulb had an abnormal appearance that suggested intimal dissection and/or thrombus. On April 28, 2012, approximately 8 months after her stroke, she presented for consideration of PSE to treat her residual stroke symptoms, which included left hemiparesis, left-sided neglect, anxiety and urinary incontinence. She had lost bladder sensation with the stroke and took an anti-muscarinic medication, tolteridine, to help control her

Table 8 Cognitive measures before and after a single perispinal etanercept dose, stroke cohort

Measure	Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
FAS	Actual value				
	N	138	128	66	38
	Mean (SD)	15.7 (11.60)	17.5 (12.43)	15.3 (12.30)	16.3 (10.12)
	Median	15	16	12	15
	Minimum, maximum	0.0, 58.0	0.0, 58.0	0.0, 63.0	0.0, 46.0
	Absolute change from pre-treatment[a]				
	N		128	66	38
	Mean (SD)		1.9 (4.26)	1.9 (4.66)	2.1 (4.25)
	Median		1	1	3
	Minimum, maximum		–11.0, 15.0	–12.0, 20.0	–6.0, 10.0
	p value[b]		<0.0001	0.0005	0.0048
	Percentage change from pre-treatment[a]				
	N		121	61	35
	Mean (SD)		21.7 (67.93)	28.5 (88.44)	60.8 (177.78)
	Median		13.6	6.3	17.9
	Minimum, maximum		–100, 550.0	–100, 500.0	–40.0, 1000
	p value[b]		<0.0001	0.0030	0.0008
MoCA	Actual value				
	N	107	85	51	32
	Mean (SD)	16.1 (6.84)	17.5 (7.19)	17.5 (7.09)	19.6 (6.37)
	Median	17	18	19	21.5
	Minimum, maximum	0.0, 30.0	0.0, 29.0	0.0, 29.0	8.0, 28.0
	Absolute change from pre-treatment[a]				
	N		85	51	32
	Mean (SD)		2.6 (2.75)	2.9 (3.61)	3.5 (3.45)
	Median		2	3	4
	Minimum, maximum		−3.0, 10.0	−10.0, 10.0	−5.0, 9.0
	p value[b]		<0.0001	<0.0001	<0.0001
	Percentage change from pre-treatment[a]				
	N		84	51	32
	Mean (SD)		21.0 (25.74)	28.5 (44.82)	30.1 (39.71)
	Median		16.5	20	19.5
	Minimum, maximum		−27.3, 128.6	−100, 200.0	−33.3, 150.0
	p value[b]		<0.0001	<0.0001	<0.0001

[a] Positive changes indicate improvement

[b] *p* value is from Wilcoxon signed rank test

FAS controlled oral word association test, *MoCA* Montreal Cognitive Assessment, *SD* standard deviation

incontinence. Despite tolteridine, her urinary incontinence required urination every 20 min in order to avoid accidents. On examination, she had left-sided facial droop, left eyelid ptosis, severe spasticity and left hemiparesis, with severe paresis of the left arm, wrist and fingers, limited knee flexion, limited ankle dorsiflexion and left-sided neglect. Approximately 15 min after the injection, the patient noted that it was "easier" and felt "better" to walk, that there was more "movement in her ankle" and that the (left) "foot was straighter". She stated that it required less effort to move her left arm. On examination, there was decreased left facial paresis and decreased spasticity in her left hand. She stated that, a couple of hours after the injection, she could sense for the first time that her bladder was full and her urinary incontinence had disappeared. She discontinued tolteridine at that time. Two hours after the first PSE dose, the patient noted that she no longer had left-sided neglect. She noted that she was able to read a book without difficulty, whereas prior to injection, she would lose her place when she reached the left side of the page. Two days after the first PSE dose, the spasticity in her left arm and leg significantly improved. There was a baseline of severe hand and finger spasticity, with the fingers constantly held in a tight fist. Two days after PSE, the hand was open, with fingers relaxed and pliable. Her spasticity had resolved to the degree that she no longer needed to go to her spasticity clinic. She normally had to

Table 9 Hand grip strength (kg) before and after a single perispinal etanercept dose, stroke cohort

Hand	Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Left	Actual value				
	N	270	255	117	78
	Mean (SD)	22.1 (13.44)	24.4 (14.16)	25.7 (13.97)	27.1 (13.21)
	Median	22	25	27	27
	Minimum, maximum	0.0, 60.0	0.0, 56.0	0.0, 58.0	0.0, 62.0
	Absolute change from pre-treatment[a]				
	N		251	110	73
	Mean (SD)		2.3 (3.79)	3.1 (5.61)	3.5 (5.45)
	Median		2	2	3
	Minimum, maximum		−7.0, 28.0	−6.0, 35.0	−9.0, 34.0
	p value[b]		<0.0001	<0.0001	<0.0001
	Percentage change from pre-treatment[a]				
	N		232	101	69
	Mean (SD)		20.5 (58.24)	27.7 (77.26)	23.2 (40.09)
	Median		8.5	11.1	12
	Minimum, maximum		−25.0, 560.0	−25.0, 580.0	−42.9, 261.5
	p value[b]		<0.0001	<0.0001	<0.0001
Right	Actual value				
	N	278	266	111	76
	Mean (SD)	23.1 (13.98)	26.0 (14.38)	25.8 (13.94)	25.9 (13.19)
	Median	22	25.5	24	24
	Minimum, maximum	0.0, 65.0	0.0, 65.0	0.0, 64.0	0.0, 58.0
	Absolute change from pre-treatment[a]				
	N		262	104	71
	Mean (SD)		2.6 (3.47)	3.0 (4.07)	3.4 (4.56)
	Median		2	2	2
	Minimum, maximum		−8.0, 22.0	−4.0, 20.0	−8.0, 18.0
	p value[b]		<0.0001	<0.0001	<0.0001
	Percentage change from pre-treatment[a]				
	N		250	101	69
	Mean (SD)		19.3 (36.53)	22.4 (48.62)	22.9 (41.94)
	Median		10	12.8	13
	Minimum, maximum		−25.0, 350.0	−23.1, 400.0	−21.1, 300.0
	p value[b]		<0.0001	<0.0001	<0.0001

[a] Positive changes indicate improvement

[b] *p* value is from Wilcoxon signed rank test

SD standard deviation

wear an ankle foot orthosis to straighten her left ankle, which would otherwise invert, but after the first PSE dose, she could take steps without the ankle brace. Two days after the first injection, her left hamstring muscle was significantly stronger and this allowed her to flex the knee better, which allowed greater ease of walking. Approximately 2 weeks after the first PSE dose, pain and subluxation in the left shoulder resolved. On May 26, 2012, 1 month after her first treatment, she returned to the clinic requesting a second PSE dose. At that time she reported that all improvements from the prior PSE dose had been maintained. A second PSE dose was given and she again noted during the evening after the injection that spasticity in her foot and left leg improved. Several hours after the treatment the toes in her left foot no longer curled up when she walked and she was able to place her foot flat onto the floor. This effect persisted for approximately 3 months. Her family noted that her sense of humour had returned and that she had a more relaxed demeanor such that she seemed to be more like herself prior to the stroke. She noted that her ability to keep track of tasks had improved. She presented for a third injection 4 months later (September 15, 2012), at which time she reported that she continued to have complete absence of urinary incontinence and also maintained all improvements from the first treatment as well as the second, except for return of toe spasticity. Approximately 30 min after the third injection, she noted that her left leg and foot felt lighter and that it was easier to walk. Several hours afterwards, she also noted that again the spasticity in

Table 10 Visual analogue score (VAS) for pain before and after perispinal etanercept, stroke cohort

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	38	21	23	13
Mean (SD)	7.1 (2.09)	3.1 (2.49)	4.0 (2.63)	2.3 (2.81)
Median	7	3	4	1
Minimum, maximum	2.0, 10.0	0.0, 9.0	0.0, 9.0	0.0, 8.0
Absolute change from pre-treatment[a]				
N		21	23	13
Mean (SD)		−3.7 (2.62)	−3.8 (2.98)	−5.3 (3.40)
Median		−4	−4	−6
Minimum, maximum		−8.7, 0.0	−9.0, 2.0	−10.0, 1.0
p value[b]		<0.0001	<0.0001	0.0012
Percentage change from pre-treatment[a]				
N		21	23	13
Mean (SD)		−53.0 (33.90)	−46.2 (39.60)	−67.9 (41.48)
Median		−50	−44.4	−75
Minimum, maximum		−100, 0.0	−100, 50.0	−100, 16.7
p value[b]		<0.0001	<0.0001	0.0012

[a] Negative changes indicate improvement

[b] *p* value is from Wilcoxon signed rank test

SD standard deviation

Table 11 Time to walk 20 m (s) before and after a single dose of perispinal etanercept, traumatic brain injury cohort

Statistic	Pre-treatment	Immediately post-treatment	After 1 week	After 3 weeks
Actual value				
N	6	6	4	5
Mean (SD)	35.0 (26.18)	35.6 (29.53)	28.7 (28.34)	23.7 (19.21)
Median	26.5	25.5	15.4	15.7
Minimum, maximum	10.3, 81.0	9.1, 83.0	12.9, 71.2	9.0, 56.0
Absolute change from pre-treatment[a]				
N		5	4	5
Mean (SD)		−7.4 (8.69)	−9.1 (5.95)	−8.6 (9.80)
Median		−5.3	−9.1	−5.4
Minimum, maximum		−19.0, 2.0	−16.3, −1.8	−25.0, −1.3
p value[b]		0.1875	0.1250	0.0625
Percentage change from pre-treatment[a]				
N		5	4	5
Mean (SD)		−24.3 (23.23)	−28.3 (20.27)	−22.9 (15.05)
Median		−25	−25.6	−17
Minimum, maximum		−59.9, 2.5	−51.4, −10.5	−45.3, −8.7
p value[b]		0.1250	0.1250	0.0625

[a] Negative numbers indicate improvement

[b] *p* value is from Wilcoxon signed rank test

SD standard deviation

her toes resolved and she was able to place her foot flat on floor without pain. As of this publication, additional responses were to be assessed in the ensuing weeks.

3.6 Case Report 2: Clinical Response to PSE 45 Years after Traumatic Brain Injury

A 50-year-old man suffered TBI at the age of 6 years when he was hit as a pedestrian by a motor vehicle on September 30, 1967. The accident resulted in a jaw fracture, pneumothorax, subdural hematoma, coma for 3 weeks and residual debilitating neurological and neuropsychiatric effects. On June 13, 2012, 45 years after TBI, he presented for consideration of treatment with PSE. Upon presentation, he had left-sided hemiparesis, left foot drop that required him to use an electrical stimulation device for walking, left hand dysfunction with severe spasticity and clicking of joints, left-sided sensory deficit, left-sided allodynia, constant pain and frequent daily spasms in the left ankle, foot and back, and episodic decrease in visual acuity of the left

Table 12 Changes in impairment, by impairment type and time point after a single dose of perispinal etanercept, traumatic brain injury cohort

Impairment type	Immediately post-treatment, n (%)	After 1 week, n (%)	After 3 weeks, n (%)
Clinical impairment	12	11	9
Improved[a]	12 (100.0)	11 (100.0)	9 (100.0)
Not improved	0 (0)	0 (0)	0 (0)
p value[b]	0.0005	0.0010	0.0039
Motor impairment	11	11	8
Improved	10 (90.9)	11 (100.0)	8 (100.0)
Not improved	1 (9.1)	0 (0)	0 (0)
p value[b]	0.0117	0.0010	0.0078
Spasticity	9	9	6
Improved	9 (100.0)	9 (100.0)	6 (100.0)
Not improved	0 (0)	0 (0)	0 (0)
p value[b]	0.0039	0.0039	0.0312
Walking impairments	11	10	8
Improved	8 (72.7)	8 (80.0)	8 (100.0)
Not improved	3 (27.3)	2 (20.0)	0 (0)
p value[b]	0.2266	0.1094	0.0078
Cognitive impairment	10	11	8
Improved	7 (70.0)	10 (90.9)	7 (87.5)
Not improved	3 (30.0)	1 (9.1)	1 (12.5)
p value[b]	0.3437	0.0117	0.0703
Psychological impairment	6	6	5
Improved	5 (83.3)	5 (83.3)	4 (80.0)
Not improved	1 (16.7)	1 (16.7)	1 (20.0)
p value[b]	0.2188	0.2188	0.3750
Sensory impairment	4	4	3
Improved	3 (75.0)	3 (75.0)	3 (100.0)
Not improved	1 (25.0)	1 (25.0)	0 (0)
p value[b]	0.6250	0.6250	0.2500
Aphasia	6	7	5
Improved	3 (50.0)	4 (57.1)	4 (80.0)
Not improved	3 (50.0)	3 (42.9)	1 (20.0)
p value[b]	>0.999	>0.999	0.3750
Pain	6	6	4
Improved	2 (33.3)	3 (50.0)	3 (75.0)
Not improved	4 (66.7)	3 (50.0)	1 (25.0)
p value[b]	0.6875	> 0.999	0.6250
Other impairment	11	11	8
Improved	10 (90.9)	9 (81.8)	8 (100.0)
Not improved	1 (9.1)	2 (18.2)	0 (0)
p value[b]	0.0117	0.0654	0.0078

[a] Denotes improvement noted in the patient chart in any domain

[b] *p* value is from an exact binomial test

eye. He reported that he also suffered from deep depression that had lasted for many years. He lacked confidence and had a poor social life as he was extremely self-conscious about his deficits, such as his hyperflexed hand and wrist and would hide it in his pocket when he could. His foot spasms were so severe that he wished at times for amputation. He also reported being diagnosed with post-traumatic stress disorder due to the accident. On examination, he was noted to have left-sided facial droop, left arm weakness, left leg weakness with ankle inversion and foot drop as well as spasticity in the toes, including recurrent episodes where the great toe would hyperextend spontaneously, and severe sensory deficit in the left hand and leg. His 20-m gait time prior to treatment measured 21 s. Grip strength was measured as 40 kg on his right hand and 26 kg on his left hand. On June 13, 2012, the patient received his first PSE

treatment. Immediately after the injection, the patient noted that he had improved left ankle movement, decrease in foot spasms, improved ROM and fine motor control with his left hand, significant decrease in spasticity and clicking of joints of his left hand, improvement in function, control and coordination of his left hand, improved facial symmetry, relaxation of his toes and improved sensation in the ball of his foot. His 20-m gait time decreased from 21 to 15 s. His grip strength increased from 26 to 42 kg in his left hand and remained at 40 kg in his right hand. He also noted immediate improvement of mood, and complete resolution of pain in his back and left foot. At 1-week post-treatment, he had improved fine motor movement in his left hand and reported that this was allowing him to better play his guitar. He noted increased strength and movement in his left leg along with a decrease in spasticity. His foot drop was almost completely resolved. The spasms in his foot were significantly decreased in frequency and now stoppable by his own will. His 20-m gait test time decreased further to 13 s, which was even more notable since he was now walking without using the electrical stimulator for foot drop. At 3 weeks, he noted no longer having pain in his ankle or back, resolution of spasms and resolution of numbness in his left foot. His gait test time decreased further and was now 11.6 s, and was also still without use of the electrical stimulator.

At his last follow-up on September 24, 2012, more than 3 months after a single PSE dose, the patient continued to report sustained improvement in spasticity and numbness, noting that his fingers, hand and leg felt even looser. Compared with his 3-week follow-up, he reported even more improvement in fine motor movement and in his general ability to use his left arm. He continues to ambulate without the electrical stimulator, using it only when he exercises. He reports sustained improvement in his vision as the episodic blurriness in his left eye resolved a few weeks after the treatment. He reports sustained relief in his hand, foot, hip, back and ankle pain on the left side. He maintains his positive outlook on life, is happier and more independent, and reports no residual signs or symptoms of depression. He no longer experiences suicidal thoughts and is hopeful for ongoing improvement.

For Case Report 3, see Online Resource 2. A digital video accompanying Case Report 2 can be seen in Online Resource 3.

4 Discussion

4.1 Key Results

Statistically significant clinical improvements in multiple domains were documented following perispinal administration of etanercept in this patient cohort, even in patients treated years after stroke and TBI. Surprising improvements in motor function, spasticity, cognition, psychological/behavioural impairments, pain, pseudobulbar affect, sialorrhea, dysphonia, dysarthria, diplopia, urinary incontinence, neglect, special senses (vision, taste, hearing, smell) and swallowing were observed in the patient cohort, all suggesting the existence of a novel and effective therapeutic response.

4.2 Limitations

The present study has significant limitations. Clinical testing was not identical for all patients, reflecting the usual variance of the daily medical practice from which the data were taken. Qualitative improvement in impairment was assessed by unblinded site personnel. Sample size was limited for the quantitative measures, particularly VAS pain scores, MoCA scores, FAS scores and hand grip. On the cognitive tests (MoCA and FAS), test–retest learning and recall may have occurred, particularly in the patients with more limited cognitive impairment. Before and after measurement of walking time, hand grip strength, VAS pain score, MoCA [87, 88] and the FAS score were not routinely measured in the Florida patient cohort and were not included in the data analysis. The limited time of observation, 3 weeks, limits conclusions regarding a length of clinical response longer than 3 weeks; the case reports, however, included longer observation periods. There are acknowledged conflicts of interest. The treatment was open-label. That a portion of the observed clinical effects was due to a placebo effect cannot be ruled out; however, the nature, diversity and constellation of clinical effects observed in the patient cohort argue against their attribution to a placebo response. Placebo effects have been found to be more prominent in studies that involve patient-reported outcomes [94]. The clinical results reported herein, such as time to walk 20 m, are not predominantly patient-reported measures. Recent systemic reviews found little evidence in general that placebos had powerful clinical effects [94–98]. Numerous instances of physiological therapeutic response to PSE in this patient cohort were observed that could only be characterized as powerful clinical effects. Historically, some pharmacological interventions have been so powerful that randomized trials were not necessary to establish a therapeutic effect [99]. Patient expectations, physician expectations and the open-label nature of the intervention may well have introduced bias into the reported clinical results that cannot be quantified. Therefore, randomized, placebo-controlled trials will be necessary to further quantify and characterize the clinical response to PSE following stroke and other forms of brain injury.

There are many questions that require further research: What is the optimal dose regimen? Are there patient

characteristics that are predictive of a better response to selective TNF inhibition? It is worthy of note that the commercially available TNF inhibitors are not clinically equivalent [100]. There is now more than a decade of clinical experience with perispinal administration of etanercept, and safety studies of epidural etanercept, in both animals and humans, have been published [71, 74]; comparable epidural data are not available for the other biologic TNF inhibitors. Although etanercept given for its labelled indications has a well established safety record, and our clinical experience with PSE has generally been favourable, further study will be needed to define the safety of PSE in this patient population [59, 101–107]. In particular, there are conflicting data in the literature regarding the role of TNF in neuronal repair [72, 73, 108]; some of the data in the literature are from TNF-knockout experimental models [108]. It may well be that the effects of TNF on neuronal function are concentration dependent; low levels of TNF appear necessary for optimal neuronal function, but excess levels may be deleterious [45, 48, 72, 73]. Although the data of the present study document beneficial clinical effects from the first dose of PSE in this patient population, it does not define what the optimal dosing regimen is for these indications; further research will be needed to illuminate this question.

4.3 Interpretation

Open-label results, and case studies, may be the first published reports of new uses of existing drugs [109, 110]. The present results support the concept that off-label use and small pilot studies may facilitate the discovery of new indications for existing drugs and biologics [109, 111]. It is notable that the current era of widespread use of biologic TNF inhibitors across multiple indications was ushered in by an open-label, uncontrolled, non-randomized pilot study published in *The Lancet* in 1994 involving only seven patients for a new indication, rheumatoid arthritis [112].

The present results provide clinical evidence that stroke and TBI may lead to a persistent and ongoing neuroinflammatory response that is amenable to therapeutic intervention by selective inhibition of TNF, even years or decades after the acute injury. The extent, duration, spectrum and reversibility of this pathophysiology are novel findings that suggest new directions for research. Additional methods of addressing TNF excess in the brain, some of which are already being developed for the treatment of Alzheimer's disease, including the use of other selective TNF inhibitors, merit investigation as potential treatment agents for post-stroke neurological dysfunction [28, 34, 38, 49, 80, 113].

The time to walk 20 m has been previously studied in an elderly population and global and executive functions predicted declines in gait speed [86]. Gait performance tests have been studied and found to be reliable in patients with hemiparesis after stroke [114]. The MoCA is a validated instrument for use in quantitating cognitive impairment, and has been used in stroke trials [87, 88, 90–92, 115–117]. The FAS is a validated instrument that has previously been used in a study of PSE for Alzheimer's disease [60, 89].

Improvements in motor function, spasticity, cognition, psychological and behavioural changes, sensation, aphasia and pain are evidence of a novel therapeutic effect in this patient population. In addition, individual improvements in less common clinical conditions, such as pseudobulbar palsy, were notable. Resolution of urinary incontinence within hours of PSE administration, rapid improvement in swallowing and ability to handle secretions, and improvements in special senses that were noted in the patient cohort following PSE administration would not have been expected and suggest the existence of a novel therapeutic effect [118–121].

The mechanisms involved in rapid neurological improvement following PSE have recently been reviewed in the literature and discussed at a 2012 international conference [25, 26, 30, 59, 131]. Rapid improvement, beginning within minutes of PSE, has precedence in the clinical results seen following PSE for sciatica and Alzheimer's disease, but is more easily appreciated in many stroke patients due to the readily observable and appreciable changes in motor function and spasticity. The parallels with dementia patients treated with PSE include rapid improvement in mood, affect, cognition, verbal abilities and gait [26, 40, 46, 48, 51, 54, 59, 60, 66, 67]. The parallels with patients with sciatica and other forms of disc-related pain treated with PSE are also multiple: rapid clinical effects, beginning within minutes after a single dose, including improvements in pain, sensory impairment and motor strength [54–56, 58, 59]. Additional dosing may be of potential benefit, but further study will be required to define optimal dosing regimens.

These clinical results suggest, for the first time, that the treatment window for addressing neurological dysfunction after stroke and TBI lasts for more than a decade.

4.4 Generalizability

With a mean time of administration of 42 months after stroke and 115 months after TBI, PSE was used long after the time one would expect to see sudden additional clinical improvement, particularly sudden improvement involving multiple domains. For this reason, in addition to the rapidity, diversity, constellation, spectrum and surprising nature of the clinical effects, it is not plausible to postulate a null treatment response. One would expect this patient

population, in general, to have reached a point where their neurological status was stable [122–124]. Previous research has indicated that the majority of recovery of overall functional ability, arm function, walking and speech occurs within 3 months following a stroke [122–124]. For this reason, in contrast to acute stroke and TBI, the patients in this cohort have a stable neurological baseline so they may function as their own controls, and change from their baseline status in minutes, days or 3 weeks is likely to be a valid measure. Well designed observational studies may not overestimate the magnitude of the effects of treatment as compared with randomized controlled trials on the same topic [125]. The sample size of the stroke cohort, and the confirmation of the clinical observations by multiple observers in two different patient populations (stroke and TBI), also support the stated conclusions. Since the qualitative descriptive data depended upon each clinician's qualitative assessment of the response to treatment without reference to a standardized instrument, the generalizability of these data is limited. The sample size of all of the quantitative measures, especially the TBI walking time, VAS pain scores, MoCA scores, FAS scores and hand grip scores, was limited, limiting the generalizability of these results. Test–retest learning and recall may limit the generalizability of the MoCA and FAS results. These considerations affect specific portions of the results. However, the nature and repeatability of the clinical results in this stroke cohort with a large sample size, and a spectrum of similar results in the TBI cohort, support the conclusions as written, without limitation. In view of the unmet medical need, funding of the costly randomized controlled trials necessary to obtain regulatory approval is urgently needed.

Historically, the advancement of scientific knowledge has often been an uphill struggle against 'accepted wisdom' [126–129]. For example, when tissue plasminogen activator (TPA) was first proposed for use in acute stroke, the prevailing scientific belief was that TPA given hours after stroke was well beyond the time when intervention could be of therapeutic benefit. The concept that salvage of the stroke penumbra could be performed hours after stroke was contrary to the long-held dogma that neuronal death after vascular occlusion occurred within minutes and therapeutic intervention after that time was futile. It took more than a decade for this dogma to be overcome and for TPA to be widely accepted [130]. The TPA experience demonstrated how the identification of new concepts of pathophysiology can lead to new methods of treatment. In identifying the persistence of brain neuroinflammation amenable to therapeutic modulation more than a decade after stroke and TBI, the present authors are again challenging long-held dogma and opening the door to new therapeutic possibilities.

5 Conclusion

Excess TNF contributes to chronic neurological, neuropsychiatric and clinical impairment after stroke and TBI. Perispinal administration of etanercept produces clinical improvement in patients with chronic neurological dysfunction following stroke and TBI. The therapeutic window extends beyond a decade after stroke and TBI. Randomized clinical trials will be necessary to further quantify and characterize the clinical response.

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