

Rapid Improvement of Chronic Stroke Deficits after Perispinal Etanercept

Three Consecutive Cases

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Abstract

Background: Thrombolytic therapy reduces stroke size and disability by reperfusion and salvage of ischaemic penumbra. Emerging evidence suggests that retrieved penumbra may be the site of ongoing inflammatory pathology that includes extensive microglial activation. Microglial activation may be associated with excessive levels of tumour necrosis factor (TNF) and resultant neurotoxicity. Etanercept, a potent biologic TNF antagonist, reduces microglial activation in experimental models and has been therapeutically effective in models of brain and neuronal injury. Perispinal administration of etanercept, previously reported to be beneficial for the treatment of Alzheimer's disease, may facilitate delivery of etanercept into the brain.

Objective: The objective of this report is to document the initial clinical response to perispinal etanercept in the first chronic stroke cohort so treated.

Methods: Three consecutive patients with stable and persistent chronic neurological deficits due to strokes that had failed to resolve despite previous treatment and rehabilitation were evaluated at an outpatient clinic. They were treated off-label with perispinal etanercept as part of the clinic's practice of medicine.

Results: All three patients had chronic hemiparesis, in addition to other stroke deficits. Their stroke distributions were right middle cerebral artery (MCA), brainstem (medulla) and left MCA. The two patients with MCA strokes had both received acute thrombolytic therapy. Each of the three patients was treated with an initial dose of perispinal etanercept 13, 35 and 36 months following their acute stroke, respectively. Significant clinical improvement following perispinal etanercept administration was observed in all patients. Onset of clinical response was evident within 10 minutes of perispinal injection in all patients. Improvements in hemiparesis, gait, hand function, hemi-sensory deficits, spatial perception, speech, cognition and behaviour were noted among the patients treated. Each patient received a second perispinal etanercept dose at 22–26 days after the first dose that was followed by additional clinical improvement.

Conclusions: Open-label administration of perispinal etanercept resulted in rapid neurological improvement in three consecutive patients with chronic neurological dysfunction due to strokes occurring 13–36 months earlier.

These results suggest that stroke may result in chronic TNF-mediated pathophysiology that may be amenable to therapeutic intervention long after the acute event. Randomized clinical trials of perispinal etanercept for selected patients with chronic neurological dysfunction following stroke are indicated.

Introduction

Acute arterial occlusion in the brain produces a topographical gradient of decreased cerebral blood flow, resulting in not only an ischaemic core of irreversibly damaged tissue, but also an ischaemic penumbra of potentially salvageable brain.^[1-3] Timely reperfusion of the penumbra via acute thrombolytic therapy can lead to a significant reduction in stroke size and disability.^[4] There is increasing recognition that the rescued penumbra may remain a locus of inflammatory pathology, including extensive microglial activation (MA).^[5-8] The recognition of this inflammatory pathology introduces the possibility of therapeutic intervention aimed at reducing neuroinflammation.^[7] Inhibition of tumour necrosis factor (TNF), the key cytokine that initiates and amplifies the inflammatory response, has been proposed as a potential method to reduce neuron death induced by MA in the ischaemic penumbra.^[7]

TNF is released by microglia and macrophages following middle cerebral artery (MCA) occlusion and is elevated following other forms of neuronal injury, including spinal cord and traumatic brain injury.^[9-11] The level of TNF is increased in the CSF of ischaemic stroke patients and correlates with the volume of the evolving brain infarct.^[12] In a recent macrosphere-induced stroke model, TNF level was found to be rapidly and persistently elevated following acute stroke, with activated microglia present in a thick rim around the ischaemic infarct core by day 7.^[13] Experimental evidence from diverse models suggests that glial-produced TNF may maintain MA and produce neurotoxicity; and that both this auto-activation process and the resultant neurotoxicity may be reversible by blockade of TNF.^[7,14,15] Etanercept, a potent biologic antagonist of TNF, has been shown to reduce MA in experimental models and to have therapeutic effects in a variety of models of neurological injury.^[11,15-18] Perispinal

administration of etanercept followed by Trendelenburg positioning, previously reported to be beneficial for the treatment of Alzheimer's disease, may facilitate delivery of etanercept into the brain.^[19-26] The duration of inflammation following brain injury is unknown, but the available evidence suggests that it may persist longer than the duration of acute ischaemia.^[6,27,28] MA in the ischaemic core, the peri-infarct zone and the contralateral hemisphere 30 days after acute stroke has been demonstrated in a study of four stroke patients.^[6] Excess TNF, released by activated glia, may perpetuate inflammation and produce a cycle of continued glial activation.^[14]

In this paper, the clinical effects of perispinal etanercept administered to three consecutive patients with long-standing neurological deficits that resulted from a previous stroke are reported.

Methods

Three consecutive patients presenting to a private outpatient clinic at 100 UCLA Medical Plaza in Los Angeles, CA, USA with chronic neurological deficits following stroke were evaluated and treated as part of the clinic's usual practice of medicine. Each of the patients had persistent chronic neurological deficits that had failed to resolve despite previous inpatient and outpatient treatment and rehabilitation. The neurological deficits of all patients had been stable for longer than 6 months. Patients were only considered for anti-TNF treatment if there were no history of immunosuppression, lymphoma, blood disorder, hepatitis, congestive heart failure or recent infection and skin testing for tuberculosis was negative. Following oral and written informed consent from the patient, each patient was treated off-label with an initial perispinal, interspinous, extrathecal injection of 25 mg of etanercept powder (Immunex, Seattle, WA, USA)

mixed with sterile water overlying the posterior cervical spine followed by Trendelenburg head-down positioning for 5 minutes. Each patient treated requested and received a second etanercept dose 22–26 days after the first. This perispinal methodology and its scientific rationale have been previously discussed in detail.^[19-26,29,30] Clinical evaluation was individualized for each patient. Among the measures utilized was neurocognitive testing using two standardized instruments, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA), and a standardized measure of gait, time to walk a measured 20-metre distance.^[31-36] There were no changes made to the patients' drug regimens following treatment. The clinical results and case histories for each of these three patients are reported retrospectively as pilot findings 2 months after treatment of the first patient.

Results

Case 1

A 61-year-old man presented to the clinic 3 years after a major left MCA stroke. Thirty-six months earlier, following sudden onset of profound aphasia, confusion and motor weakness, the patient was taken to a local emergency room (ER). In the ER, he was found to have right hemiplegia and complete aphasia. CT brain scan ruled out intracranial haemorrhage. The patient was transferred to a regional hospital for consideration of intra-arterial thrombolytic treatment because the 3-hour cut-off for initiation of intravenous thrombolytic treatment was missed. Arteriography demonstrated occlusion of the anterior branch of the left MCA. Intra-arterial reteplase infusion resulted in partial resolution of thrombus and partial reperfusion. Repeat CT scans demonstrated acute cerebral infarction in the distribution of the left MCA with oedema in the left frontal, temporal and parietal lobes and midline shift. Maximal midline shift was 11 mm 6 days following the stroke (figure 1). The patient required 10 days of intensive care and 1 month of inpatient rehabilitation. While in the intensive care unit he could not talk and had no purposeful

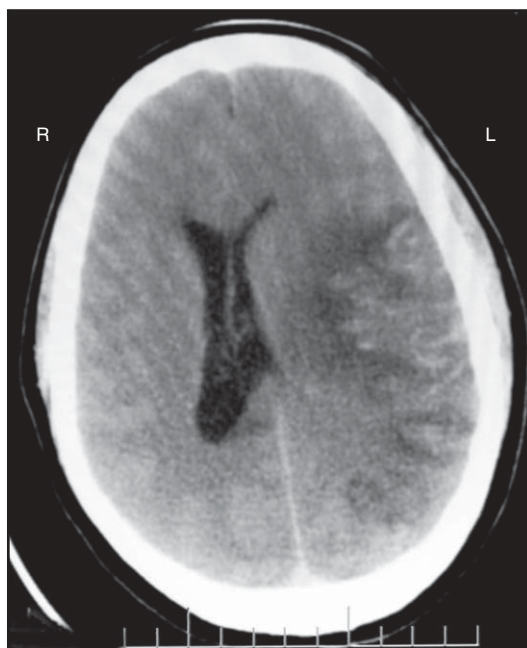


Fig. 1. CT scan of the brain, case 1, 6 days after acute stroke, axial view: subacute cerebral infarction in the distribution of the left middle cerebral artery with mass effect causing an 11 mm midline shift to the right. There is hypoattenuation involving the left frontal, parietal and temporal lobes, with substantial effacement of the left lateral ventricle due to mass effect from the oedematous infarcted tissue. L = left; R = right.

movement in his arms or legs. After 3 weeks in the hospital he began to be able to move his legs. At the time of discharge, there was limited movement in the right leg but none in the right arm, and persistence of profound expressive aphasia. There was also cognitive impairment: for example, he could not comprehend how to use a television remote control. Two months after the stroke he could still not speak intelligible words. With time, right leg motor abilities recovered substantially, but motor function of the right upper extremity and speech remained severely limited. The patient had a previous history of hypertension, hyperlipidaemia, type 2 diabetes mellitus, coronary artery disease and myocardial infarction. Diabetes was well controlled. Current medications included aspirin and extended-release dipyridamole, extended-release niacin, escitalopram, metformin, pravastatin, glipizide and zolpidem.

At presentation to the clinic, 3 years after the stroke, his wife reported that speech and language

abilities remained severely limited; useful function of the right hand was absent and of the right upper extremity was extremely limited; there were limitations in gait including a chronic limp and inability to run; and there were persistent cognitive limitations. Included in the cognitive limitations were the inability to tell time, whether from a wristwatch or a wall clock; to dial a telephone, even when the phone number to dial was prominently displayed next to the telephone; to enter a series of four numbers into a numeric keypad, such as for a gate entry; to type a sentence on a computer keyboard, despite multiple attempts by family members to so instruct; and the inability to select the appropriate utensil for eating (he persisted in choosing a fork for sipping soup; and when using a fork or a knife would often attempt to use it oriented incorrectly [e.g. upside down]). Additionally, his wife reported that despite suffering repeated burns on his hands he continued to remove hot dishes from the oven without using insulated hand protection.

On examination there was severe, non-fluent, expressive aphasia. Motor speech was characterized by severe oral and verbal apraxia with deficits in articulatory agility and moderately impaired suprasegmental features of speech. The patient had difficulty verbalizing more than one word at a time and difficulty with correct pronunciation of single words and multiple consonants. There was a right hemiparesis involving the face, upper extremity and leg, with right hemianaesthesia involving the face, lips, upper extremity and leg. There was spasticity of the right upper extremity. The right hand was held in a persistent flexor position with inability to extend or use the fingers. The range of motion of the right upper extremity was limited; he could not bring his right arm behind his back and could not elevate his upper arm above his head without difficulty. Raising his right arm took concentrated mental effort. He walked with a decided limp and could not ambulate quickly. Neurocognitive testing was performed. The MMSE score was 26/30 and the MOCA score was 23/30, indicating mild cognitive impairment.^[31-33] An activities of daily living (ADL) inventory (Alzheimer's Disease Cooperative Study Activities of Daily Living

Scale) documented functional difficulty with daily tasks, with a score of 61/78.^[37] Time to walk a measured 20-metre distance down the office corridor was 19.8 seconds and 23.0 seconds returning.^[34-36] When asked to walk quickly the times were 16.5 seconds and 17.0 seconds returning.

Following informed consent, perispinal etanercept 25 mg was administered followed immediately by Trendelenburg positioning.^[21] Within 2 minutes, while still inclined on the treatment table, his speech was more distinct. Upon resuming the sitting position at 5 minutes he used his right arm to help reposition his body when arising from the Trendelenburg position, something that he had not been able to do in the 3 years since his stroke, and he stated "I woke up". At 9 minutes, he recited the alphabet with improved clarity of speech: the letters were more distinct and recited more quickly. At 10 minutes, he noted sensation and improved mobility in his right arm. At 16 minutes, he indicated that he had sensation in his right cheek; at 20 minutes, sensation was present in his right ear and he was able to place a cotton swab into his right ear canal with his left hand. At 20 minutes, sensation was present in his right oral cavity and in his right upper lip. At 25 minutes, there was sensation in the right leg. At 27 minutes, he was able to squat without difficulty. At 28 minutes, he was able to walk down the hallway corridor noticeably faster than he had been able to walk before treatment with perispinal etanercept. Within 30 minutes, there was reduction in right arm spasticity.

At 45 minutes, he was able to correctly dial a telephone number for the first time since his stroke. He spoke with his daughter, and then dialed his son's telephone number and spoke with him. Several minutes later he demonstrated that he was able to sit and arise from a deep sofa without difficulty and without assistance. He danced with his wife and demonstrated a golf swing. His standing balance was improved.

At 1 hour, a lunch break was taken. During the break his wife observed the following, all notable improvements when compared with his pre-treatment function: he chose and used a spoon correctly for sipping soup; he placed a soda glass correctly on the table in relation to the

dishes in a single attempt, the liquid in the glass was not spilled when moved; soda was obtained from the self-service dispenser without difficulty; the lunch menu was read correctly without difficulty with correct recitation of 'sandwich' and 'quesadilla'; he ordered his own lunch from the server and his wife did not have to help with translation; and he was able to read the clock in the cafeteria and recite the correct time for the first time since his stroke.

He returned to the clinic. At 2 hours, he was able to walk 20 metres in 10.1 seconds and return in 11.6 seconds. He and his wife returned to their hotel.

At 46 hours, they returned to the clinic. His wife reported that in the hotel 2 hours before (at 44 hours), for the first time since the stroke, he was able to recognize the letters on a computer keyboard and slowly type a sentence. His improvements in motor function, sensation, cognition and behaviour had all continued without diminution. Motor function had further improved: he had better physical endurance, was able to match his wife's normal walking pace and was able to run for the first time since his stroke. Sensation had further improved, returning in the right leg, ankle and back of heel and to his right frontal scalp. Speech was less effortful, with improved clarity. He was able to count to 50 rapidly and without difficulty. He was able to consistently tell time by looking at a clock or a watch, and his wife observed that he was more conscious of time. The patient and his wife returned home.

At home he was able to shave his entire face with a manual razor for the first time since his stroke, and did so every day. His wife attributed this to a combination of his renewed ability to feel the right side of his face, improved spatial control of his left hand and improved dexterity of his left hand. His wife noted that he had begun speaking with others during their everyday lives, and that family members noted that his speech was more distinct and more easily understood. He remembered to use an insulated hot pad when removing dishes from the oven.

He returned to the clinic 22 days later. All clinical improvements had been maintained. A repeat ADL inventory score improved to 65/78.^[37] Repeat neurocognitive testing was performed.

MMSE improved to 28/30, and MOCA improved to 27/30. The patient requested another dose of etanercept. After obtaining written consent, perispinal etanercept was administered followed by 5 minutes of Trendelenburg positioning as before. Within 10 minutes of this second etanercept dose, his speech appeared to be more distinct with improved articulation of sounds. Eight hours later, he was able to dorsiflex his right wrist for the first time since the stroke. The following day in the clinic, volitional right wrist dorsiflexion and visible activation of the right hand second dorsal interosseous muscle were observed. Speech was more distinct.

At 1 month after the first dose, there was further improvement in the strength of his right arm and in the clarity of speech. He was able to remove the twist-off tops of bottles for the first time since the stroke. At 5 weeks, he was able to correctly drive a manual transmission automobile. He had previously attempted this, but prior to etanercept administration was unsuccessful, as he was unable to co-ordinate the clutch/accelerator and shift activities properly. At 8 weeks, clinical improvement was maintained, no adverse effects had been experienced, and additional improvements in strength (the ability to move heavy furniture) and executive function (planning complex household tasks for the first time since his stroke) were reported by his wife. A digital video accompanying this case may be accessed from <http://www.vimeo.com/18550399>.

Case 2

A 49-year-old man presented to the clinic 35 months after a brainstem stroke. Three years earlier he had awoken with paraesthesia in the left arm and leg, followed by increasing weakness of the left arm and leg. In the ER, his symptoms worsened. MRI of the brain revealed a right medullary infarction (figure 2). The patient required 8 days of acute hospitalization and 1 month of inpatient rehabilitation. Left leg motor recovery began after 1–2 weeks but the patient was left with a severe residual gait disturbance and severe paresis of the left upper extremity. Initially, there was also transient left facial paraesthesia and

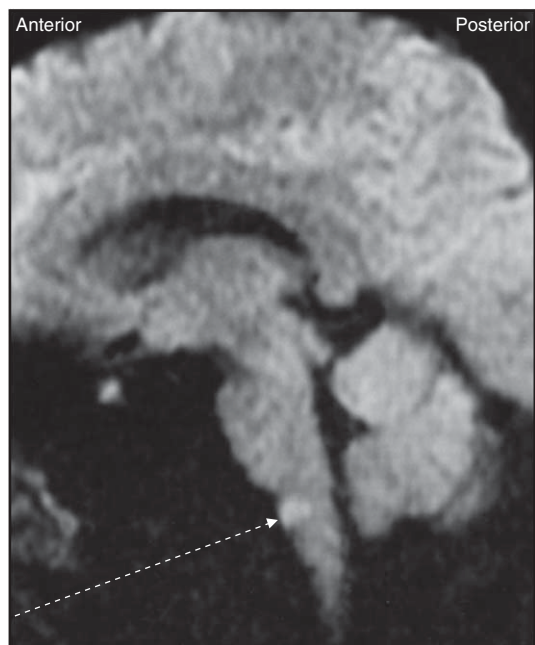


Fig. 2. MRI scan of the brain, case 2, 1 day after acute stroke, sagittal view: acute infarction in the medulla (arrow).

speech difficulty, both of which resolved within 2 weeks. At time of discharge, home walking was only possible with the assistance of a walker or a quad cane, and there was hypoaesthesia in the left upper and lower extremities, with painful paraesthesia in the left upper extremity. At presentation to the clinic, all of these neurological deficits had been stable for at least 1 year without change. The patient had a history of hypertension and type 2 diabetes. Diabetes was well controlled. Current medications included amlodipine, metformin, metoprolol, losartan, simvastatin, clonidine, gabapentin, glipizide, aspirin and extended-release dipyridamole and liraglutide.

On examination he had difficulty maintaining his balance upon standing without using his right arm for assistance. He had a left hemiparesis, with severe weakness of his left upper extremity, moderate weakness of the left lower extremity and hypoaesthesia of his left extremities. Speech and cognition appeared normal. Walking was slow, requiring 1 minute 56 seconds going and 2 minutes 3 seconds returning to walk the 20-metre office corridor distance using a standard walker for assistance.

Following informed consent, perispinal etanercept 25 mg was administered followed immediately by 5 minutes of Trendelenburg positioning. At 9 minutes following the etanercept dose, the patient stood up from the examination table. His standing balance was notably improved and was accomplished without difficulty and without use of the right arm for stabilization.

At 30 minutes, he again walked the 20-metre office corridor distance with a standard walker for assistance. Times to complete were 1 minute 20 seconds going and 1 minute 21 seconds returning. Walking required visibly less effort.

The patient returned at 10 days. He walked the 20-metre office corridor distance using a standard walker for assistance. Times to complete were 1 minute 6 seconds going and 1 minute 11 seconds returning.

At 17 days, the patient returned to the clinic. He reported maintenance of his clinical improvement, with walking continuing to be faster and to require less effort than prior to etanercept. He also said that he felt that he was able to incorporate his left arm in normal daily activities (to the extent possible) with less effort. On examination, his stride was longer and his gait more fluid than prior to perispinal etanercept administration. Improved walking speed was maintained, with time to walk 20 metres with a standard walker measured at 1 minute 13 seconds down the corridor and 1 minute 10 seconds back.

At the end of 3 weeks, the clinical improvements were maintained. At 24 days, after written informed consent, a second 25 mg dose of perispinal etanercept was administered. At 10 minutes after the dose, time to walk 20 metres with a standard walker was measured at 1 minute 3 seconds down the corridor and 1 minute 3 seconds back. At 1 month after the first dose, clinical improvement was maintained, including improvement in walking ability and subtle improvements in motor control of his left upper extremity. No adverse effects of etanercept were noted.

Case 3

A 58-year-old man presented to the clinic 13 months after a right MCA territory stroke. On

the day of the stroke, left-sided weakness began in the morning abruptly. In the ER, he had a left hemiparesis, no spontaneous movement in the left upper extremity, two-fifths movement of the left lower extremity, a left facial droop and was unable to move his eyes to the left. Brain CT initially showed no bleed and CT angiogram showed a 1–1.5 cm clot in the right MCA. Subsequent brain CT showed acute infarction in the territory of the right MCA. Acute thrombolytic therapy utilizing intravenous recombinant tissue plasminogen activator was given followed by increasing mental confusion but improved vision and control of the left lower extremity. He was transferred into the intensive care unit. Repeat CT showed a 0.75 cm² bleed in the pons in addition to the right hemispheric stroke, with a subsequent CT at 6 days showing a stroke in the distribution of the right MCA with a mass effect from cerebral oedema compressing the right lateral ventricle (figure 3). He was managed in the intensive care unit for 7 days and then transferred to inpatient rehabilitation. After 10 days, he was able to walk with some assistance. He was discharged home after 5 weeks. At the time of discharge home, he had a persistent left hemiparesis, with left facial droop; clumsiness of his left upper extremity and severe functional difficulty using his left hand; mild weakness of the left leg; hypoaesthesia of the left upper extremity, left leg and foot; and constant pain in his left arm and hand that was exacerbated by firm gripping with the left hand. The patient had a history of hypertension, hypercholesterolaemia and coronary artery disease.

Upon presentation to the clinic, the patient reported no improvement in his neurological symptoms for at least the past 6 months, with persistence of all listed neurological deficits. He reported severe difficulties using his left hand: inability to perform fine movements, such as stuffing envelopes; difficulty dressing, with inability to buckle his belt or unbutton buttons; and difficulty preparing food, with a tendency to burn his hand. He reported difficulty in placing postage stamps on an envelope in the correct orientation. He noted that he could not correctly gauge the spatial location of his hand with his eyes closed: he could not tell if it was up, down, in

front or behind his body. Since his stroke he had been unable to place his hand in his trouser pockets, either front or back due to both his inability to direct his hand in space accurately and also the fact that his fist remained clenched. He was able to hold objects in his left hand but could not maintain the grip without constant attention: when he held liquid in a cup he would spill or drop it. He could not control the pressure of the grip of his left hand. His current medications were lisinopril, simvastatin, aspirin, gabapentin and venlafaxine.

On examination there was a left facial droop, increased tone and spasticity in the left upper extremity, a mild left hemiparesis and resting closed flexion of the left hand. The left hand was clumsy, with dysdiadochokinesis. Left hand tapping rate was slow (measured at 2.8 Hz). There was marked difficulty with two-handed handling and folding of letter paper. There was left hemihypoesthesia with inability to sense pinprick.

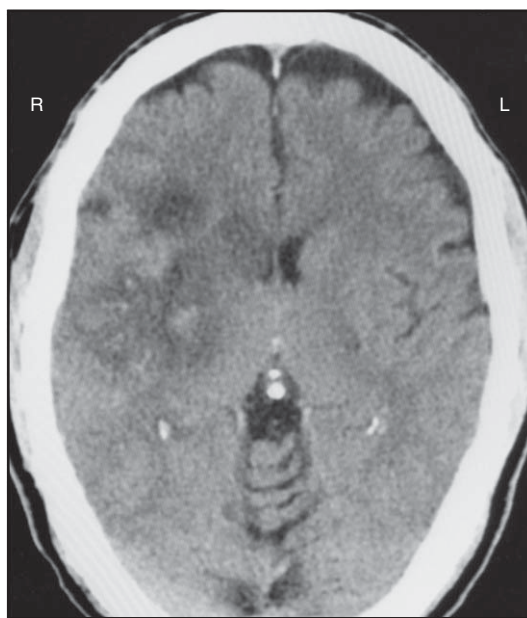


Fig. 3. CT scan of the brain, case 3, 6 days after acute stroke, axial view: subacute cerebral infarction in the distribution of the right middle cerebral artery with focal areas of haemorrhagic transformation. There is hypoattenuation involving the right frontoparietal lobe in the right middle cerebral artery distribution. There is cerebral oedema with effacement of the sulcal spaces and mild effacement of the right lateral ventricle due to mass effect from the oedematous infarcted tissue. L = left; R = right.

When the patient was seated with his eyes closed with both arms held out, the left arm drifted upward. Hand grip strength was left/right = 32/36. The left hand grip strength test produced marked discomfort in the left hand. There was balance difficulty while standing with the eyes closed. The patient walked with a persistent clenched fist and with a slight limp. Times for walking 20 metres in the office corridor were 13 seconds out and 14 seconds back. On neurocognitive testing, MMSE was 26/30 and MOCA was 23/30, indicating borderline impairment.

Following informed consent, perispinal etanercept 25 mg was administered followed immediately by 5 minutes of Trendelenburg positioning. After administration of etanercept, the following improvements were noted: beginning at 7 minutes, his left facial droop had improved; at 8–10 minutes, his left hand exhibited improved dexterity, tapping speed was faster (left hand tapping speed was videotaped and measured at 5.5 Hz), left hand diadochokinesis was faster and left hand finger-to-nose was faster; at 11–15 minutes, sensation in the left cheek, hand, arm and shin were improved, there was increased strength in the left knee extensors and the hands, with hand grip strength left/right = 36/40, and he was able to correctly perceive the spatial location of his left hand. Firm gripping during the left hand grip strength test did not produce pain. At 16 minutes, he was able to place his left hand in both his left front and left back trouser pockets for the first time since his stroke and his gait was more fluid. At 20 minutes, he was able to buckle his belt with his left hand. Within 45 minutes, he was able to open a water bottle, hold a water bottle without dropping it and page through a magazine, all with his left hand, all tasks he could not similarly accomplish prior to etanercept treatment. In addition, the pathological upward drift of his left arm with his eyes closed present prior to etanercept administration was markedly reduced.

At 48 hours, he reported maintenance of all clinical improvements. He was no longer spilling his coffee cup when held in his left hand and had less pain in this left arm and hand. He reported that his sense of balance while walking was improved.

At 7 days, all previous clinical improvements were maintained. In addition, he reported improvement in memory and conversational abilities, was able to buckle and unbuckle his belt, button and unbutton buttons, and reported improved ability to use his left hand in everyday tasks. Hand grip strength was left/right: 40/40.

At 13 days, his previous clinical improvements were maintained, and there was evidence of additional improvement. His gait was more fluid and he noted his balance while walking was better. Times for walking 20 metres were 10 seconds out and 10 seconds back. During conversation, there was notably more expressive movement with the left arm and hand. The patient's partner said that at home his improved abilities to use his left arm and hand were remarkable, and that 1 week after the dose of etanercept he was able to pick up single playing cards and deal cards with his left hand, tasks he had been unable to perform with that hand prior to receiving etanercept. On repeat neurocognitive testing MMSE was stable at 26/30 and MOCA was significantly improved at 29/30, and on examination he was able to deal playing cards with his left hand and pick up single playing cards with his left hand as his partner had reported.

At 20 days, the patient reported that the clinical improvement in his left hand had begun to diminish. At 26 days, he returned to the clinic. He was able to manipulate shoe laces with his left hand with some difficulty, a task he was unable to perform prior to etanercept treatment, but he reported that motor control of his left hand was not as good as it had been 10 days earlier. After written informed consent, a repeat 25 mg dose of perispinal etanercept was administered. Within 30 minutes following the dose, he was able to lace his own shoes using his left and right hands together more easily than prior to the dose and improvement in his left facial droop was noted. At 1 month after the first dose, clinical improvement from baseline continued with no adverse effects noted.

Discussion

Prevailing conceptions regarding chronic ischaemic stroke would not predict that anti-

TNF intervention years after stroke would be effective.¹ [34,38,39] The surprising findings of rapid neurological improvement following perispinal etanercept administered years after acute stroke invite a re-examination of these prevailing conceptions. Expanding knowledge of the pleiotropic synaptic, gliotransmitter and vascular effects of TNF, recently reviewed, suggest a framework for re-consideration.^[19-21,24] The clinical effects of perispinal etanercept in these three patients provide pilot evidence that excess TNF is centrally involved in the pathogenesis of chronic neurological dysfunction following stroke.

The clinical findings reported are pilot, open-label results that require further characterization. Optimal dosing, dose intervals, duration of therapeutic response, patient selection and safety profile remain to be determined and will require further investigation. Assessment measures, such as the Barthel Index, Modified Rankin Scale, Functional Independent Measure and Fugl-Meyer Assessment, that are commonly employed in stroke trials and neuro-rehabilitation were not utilized and may impact the generalizability of these findings in the wider patient population. Although there are no formal control data, the patients treated were unselected and consecutive, and the neurological deficits in each patient had been constant and unvarying for months or years. In this sense, the stable neurological baseline of each patient constituted his or her own control data. Change from chronic baseline following stroke may facilitate identification of a therapeutic effect.

The observed pattern of clinical improvements in multiple domains (motor, sensory, speech, cognition and behaviour) in this small case series and a similar pattern of clinical improvement reported following perispinal etanercept in Alzheimer's dis-

ease (cognition, behaviour, speech and gait)^[19-21,23-25] suggest that chronic inflammatory TNF-mediated pathophysiology is common to both. One may speculate that the rapidity of the clinical response, i.e. discernible clinical improvement beginning within minutes following perispinal etanercept in both stroke and Alzheimer's disease, may be facilitated by the presence of TNF receptors on CSF-contacting neurons or other CSF-contacting cells, such as tanycytes, whose glial-neuronal signalling activity may be modulated by the presence of etanercept delivered into the CSF.^[21,22,40,41] Although recent pilot investigations have provided preliminary evidence to support this hypothesis and TNF receptor expression on CSF-contacting cells in the rat brain following inflammatory stimulation has been documented,² further research is needed.^[21,22,42] The recent studies documenting favourable effects of etanercept in a traumatic brain injury model and modulation of neurotransmitters in the brain paraventricular nucleus by etanercept delivered into the ventricular CSF provide further evidence of the involvement of TNF in brain physiology.^[17,43] The term 'TNF brain syndrome' may prove useful to denote a shared phenotype of brain dysfunction induced by excess TNF in brain disorders of diverse aetiology.^[16,17,21,44-54]

Arterial revascularization to restore perfusion for acute ischaemic stroke revolutionized the medical management of stroke. Recognition of the existence of the ischaemic penumbra as a potential therapeutic target challenged the then prevailing dogma that all stroke damage was irreversible within minutes.^[1,4] Just as identification of the ischaemic penumbra radically altered the possibility of therapeutic intervention in acute stroke, these pilot findings suggest that ongoing cerebral inflammatory pathology³ amenable to

1 For example, rapid improvement of gait years after stroke has not been reported. Initial walking function is impaired in the majority of patients with acute stroke, with recovery of function occurring mainly in the first 6 months.^[34,38,39] In a prospective study of 804 consecutive acute stroke patients, recovery of walking function within the first 11 weeks after stroke occurred in 95% of patients.^[38]

2 Evidence of expression of the gene encoding the p55 TNF receptor has been documented in the choroid plexus, ependymal cells, median eminence and paraventricular nucleus of the rat.^[42]

3 The rapid clinical response, beginning within minutes, suggests that the location of this inflammatory pathology may include not only the peri-infarct 'inflammatory penumbra' but also periventricular regions directly in contact with the CSF, such as the choroid plexus.^[21]

anti-TNF therapeutic intervention may be present months or years after the initial event. The magnitude of the unmet medical need of this population, and these novel clinical results, point to the importance of the rapid initiation of further research investigating excess TNF as a stroke therapeutic target.

Conclusions

Open-label administration of perispinal etanercept resulted in rapid neurological improvement in three consecutive patients with chronic neurological dysfunction due to strokes occurring 13–36 months earlier. These results suggest that stroke may result in chronic TNF-mediated pathophysiology that may be amenable to therapeutic intervention long after the acute event. Randomized clinical trials of perispinal etanercept for selected patients with chronic neurological dysfunction following stroke are indicated.

Acknowledgements

No sources of funding were used to study the use of etanercept in this series of patients, or to prepare this manuscript. The author has multiple issued and pending US and foreign patents detailing methods of use of etanercept for neurological indications, including perispinal etanercept for stroke, including, but not limited to, US patents 6419944, 6537549, 6982089, 7214658 and 7629311 and Australian patent 758523, all assigned to TACT IP, LLC. The author has received royalties from licensees to these patents.

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