

KEY PAPER EVALUATION



Randomized controlled trial validating the use of perispinal etanercept to reduce post-stroke disability has wide-ranging implications

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ABSTRACT

Developing effective drug treatments for neurodegenerative disorders has always been hamstrung by the accepted inability of large molecules (roughly those with a molecular weight greater than 600 Daltons) to cross the blood-brain barrier (BBB) in therapeutic quantities when administered systemically. The dogma has been that a simple, noninvasive way to accomplish this goal is not possible with many agents, including biologicals, because they are too large. Various novel technologies to breach the BBB have been attempted, but with little success. A randomized double-blind, placebo-controlled clinical trial (RCT) administering a widely used anti-tumor necrosis factor (TNF) biological, etanercept, given via perispinal injection, which bypasses the BBB, turns this dogma on its head. This new trial holds much promise for stroke survivors, as well as having implications for developing treatments based on other large molecules for this and other brain disorders.

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1. Relevance of TNF

The polypeptide tumor necrosis factor (TNF), first described in the mid 1970s, has proved to be an extremely pleiotropic cytokine that has a central role in physiology, pathology, and the innate immune system in organisms ranging from corals to humans. At physiological levels, it is an important and widespread signaling molecule. Once TNF had been appreciated to be generated and act in the brain as well as elsewhere, it proved to be a multifunction gliotransmitter that caused trouble if generated excessively.

2. The novel perispinal route of administration

The Key Paper discussed here [1] employs perispinal delivery of etanercept, a biological agent widely used to treat chronic systemic inflammatory disease, to address post-stroke syndromes. The outcome is discussed below. Etanercept acts through potently and specifically neutralizing TNF. Edward Tobinick, whose extensive collection of published observational studies over a decade this trial formally tests, published an extended review on perispinal etanercept delivery to the brain in Expert Review of Neurotherapeutics in 2010 [2] and an update elsewhere six years later [3]. Parenthetically, it should be noted that the term perispinal had sometimes been used in the 1970s as a regional anatomical term [4], which is quite different to its precise usage here [3]. With much attention being drawn to this cytokine's roles in chronic degenerative disease in the central nervous system, as well as its central involvement in disease pathogenesis generally (see [5,6] and [7] for reviews), any excess generation of it is an obvious therapeutic target. The challenge is how to get enough of these large TNF-neutralizing molecules through or past the BBB into the brain, where studies employing intracerebroventricular injections in mice over the years had demonstrated activity. Over

15 years ago Tobinick farsightedly addressed this challenge. Equipped with intimate knowledge of the anatomy and physiology of a long-forgotten venous system, he reasoned that it plausibly constituted a direct vascular route for drug delivery to the brain [8]. In this publication he used the term 'cerebrospinal venous system' (CSVS) to describe these vessels. In the same year (2006) Tobinick and colleagues reported the effects of perispinally injected etanercept followed by Trendelenburg positioning in a six-month open trial in Alzheimer's disease [9]. The results were very promising, but by 2008 both of the Big Pharmas who had earlier acquired the etanercept patent inexplicably refused to discuss furthering the perispinal approach or funding the trials needed to achieve regulatory approval.

Years earlier, during aviation medicine research into the effects of negative gravity in rabbits, Wen and coworkers had demonstrated that head-down positioning for a short period made the blood-cerebrospinal fluid (CSF) barrier permeable to plasma albumin [10]. Mindful of this, in 2009 Tobinick and colleagues from Stanford demonstrated, in a rat model, that perispinal injection of radiolabelled etanercept, followed by head-down (Trendelenburg positioning), enabled it to rapidly reach the choroid plexus and the CSF within the cerebral ventricles [11]. This was consistent with Wen's report with albumin, despite etanercept being a larger molecule (150,000 vs. 66,000 Daltons). Delivery of a labeled anti-TNF molecule via perispinal injection to the choroid plexus plus head-down positioning has recently been confirmed in an additional rat model [12].

In addition, collections of observational studies using this perispinal method of delivering etanercept to the brain, beginning in 2010, have reported impressive outcomes in treating post-stroke neurological dysfunction in many patients [13–17]. To summarize a recent text [12] that illustrates and quotes additional anatomical detail, perispinal injection followed by a short

Article highlights

- The blood-brain barrier has effectively excluded the brain from much of the biotech revolution. Much research has attempted to clear this roadblock, but without success to date.
- Perispinally injected etanercept, which involves injecting this anti-TNF biological into the cerebrospinal venous system before a short period of head-down tilt, has been commonly used by the originator of the technique since 2011 to treat post-stroke syndromes. Without witnessing the treatment, the Big Pharma owners of the patent for etanercept and the American Academy of Neurology have actively discouraged a trial.
- Funding from the Australia public has made possible the first formal controlled trial of perispinal etanercept on post-stroke patients. Within the goals set, the outcome was statistically significant, often markedly so.
- If confirmed in larger trials, this technique will likely have widespread usefulness in getting larger pharmaceuticals, particularly biologicals, into the brain in many different brain disease states, including cancer.

period of head-down positioning [10] may therefore be expected to enable etanercept to be delivered to the brain through the choroid plexus, the cerebral venous system, and the cerebrospinal fluid, thus bypassing the BBB. Such a route is consistent with the reported presence of labeled etanercept within the brain in experimental studies [11,12].

3. Unusual delay in an RTC testing perispinal etanercept

Unfortunately, a clinical trial of these promising observational studies continued to be delayed for over a decade. In the course of much favorable off-label treatment of post-stroke patients, many independent observers, from 2011 to the present, including non-neurological medical practitioners, nurses, speech pathologists, and neuroscientists, have witnessed this negligibly invasive treatment technique and its outcome in post-stroke patients. When faced with a striking mix of rapid onset, effectiveness, and persistence of outcome in an important circumstance where the usefulness of present treatments is very low, a common conclusion by these observers has been that this novel approach warrants an independent RCT. Nevertheless, the American Academy of Neurology (AAN), despite no member of its governing board having witnessed the treatment, or having addressed the science behind it, continues to display an on-line Clinical Advisory that explicitly discourages its members, and indeed any neurologist who reads it, from any association with this approach. In effect, the AAN fell in line behind the Big Pharma patent owners. Their position continues unchanged, despite the validity of the AAN's actions being questioned in an editorial some years ago in *Expert Review of Neurotherapeutics* [18] and the publication of additional supportive evidence [19,20]. Thus almost all neurologists, following the AAN's advice, have ignored invitations to observe or engage in this work, thereby establishing, for years, a quite unjustified barrier to clinical translation of the perispinal method, with its potential for wide application in disease and research.

4. Validation of perispinal etanercept technique in a randomized controlled trial

This bottleneck has now been overcome by a clinical trial outside the US funded by the community-based Stroke Recovery Trial Fund (<https://strokecoverytrialfund.org>), a national health promotion charity formed by Dr Coralie Graham in 2015 in Queensland, Australia, and funded by individual donations from the public, to compensate for AAN and Pharma intransigence. The first publication arising from the funding of this organization is a modestly-sized university-conducted randomized, placebo-controlled, double-blind trial of perispinal etanercept for chronic intractable central post-stroke pain [1]. This condition is notoriously difficult to treat and its unmet medical need is substantial. The trial subjects were selected for having had, among their symptoms, unrelenting central post-stroke pain for an average of more than 4 years. Approval of the study was obtained from the Griffith University Human Research Ethics committee (MSC/10/14/HREC).

Results were consistent with the previously published observational studies, in that shoulder flexion and pain attenuation demonstrated statistically significant improvements in study participants receiving perispinal etanercept compared to the placebo control. Indeed, in an appreciable percentage of those receiving perispinal etanercept, despite their history of years of daily intractable pain, there was rapid (within 30 minutes) and often nearly complete pain abatement, whereas no change occurred in the saline control group with the same pain. This outcome is remarkable, and quite unmatched by any present therapeutic approach for post-stroke pain. From the limited trial duration it was possible to fund, this relief lasted for at least 30 days. In addition, 90% of the etanercept group, but none of the placebo group, showed highly significant rapid enhancements in both active and passive shoulder flexion range of movement, indicating less spasticity of arm muscles. The effect was clear cut ($p = 0.003$) after the first treatment and more so ($p = 0.001$) after the second, 14 days later. A dose response such as this, Bradford-Hill's 'biological gradient', is one of the standard causation indicators.

Clearly, the larger trials necessary for regulatory approval are a pressing need. The rapidity and unprecedented nature of outcomes in patients achieved by perispinal delivery of etanercept in this initial trial is especially notable. This indicates a direct effect of etanercept on the brain following its perispinal injection, and is consistent with the location of labeled etanercept within the brain in animal models after perispinal delivery [11,12].

5. Wider ramifications of this RCT

Moreover, since this trial was the first RCT testing of perispinal administration of any agent, other therapeutics aspiring to access the brain might well benefit from its further validation. An example is the novel experimental anti-TNF therapeutic, XPro1595, an engineered dominant negative inhibitor of TNF [21]. Unfortunately, as with etanercept, its size greatly retards brain entry, with about one-thousandth of the concentration attained in the plasma after peripheral injection being detected in the cerebrospinal fluid [22]. Given the outcome of the present RCT, XPro1595 may be most effective in human

brain disease if also administered perispinally to bypass the BBB. Once proven safe and effective in humans, its unique characteristics [23] may give XPro1595 an advantage over etanercept, when frequent administration is required, of allowing the TNF-dependent innate immune system to keep latent *Mycobacterium tuberculosis* suppressed. Even so, regular testing for evidence of this organism has allowed regular subcutaneous etanercept to thrive as a treatment of rheumatoid arthritis, where the dose is much higher than was used in the RCT under discussion here. Much off-label experience indicates that only one or two doses of perispinal etanercept, and therefore predictably its biosimilars, are required to treat a number of acquired brain injury states, including stroke.

6. Five-year view

The tantalizing prospect now emerges of perispinal delivery revolutionizing the treatment of a range of brain disorders, including the neurodegenerative states, by enabling effective brain delivery of not only etanercept, but also other large molecules. This includes other biologicals, but the principle is open ended. Regulatory approval of perispinal etanercept will, through widely utilizing the perispinal route in science, broaden the research base of chronic neurodegenerative states, and other cerebral conditions, such as brain cancer.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

- Ralph SJ, Weissenberger A, Bonev V, et al. Phase I/II parallel double-blind randomized controlled clinical trial of perispinal etanercept for chronic stroke: improved mobility and pain alleviation. *Expert Opin Investig Drugs*. 2020;1–16. DOI: [10.1080/13543784.2020.1709822](https://doi.org/10.1080/13543784.2020.1709822)
- Tobinick E. Perispinal etanercept: a new therapeutic paradigm in neurology. *Expert Rev Neurother*. 2010;10(6):985–1002.
- Tobinick EL. Perispinal Delivery of CNS Drugs. *CNS Drugs*. 2016;30:469–480.
- Smythe H. Therapy of the spondyloarthropathies. *Clin Orthop Relat Res*. 1979;143:84–89.
- Clark IA. How TNF was recognized to be a key mechanism of disease. *Cytokine Growth Factor Rev*. 2007;18:335–343.
- Clark IA, Allewa LM, Vissel B. The roles of TNF in brain dysfunction and disease. *Pharmacol Ther*. 2010;128:519–548.
- Clark IA, Vissel B. Neurodegenerative disease treatments by direct TNF reduction, SB623 cells, maraviroc and irisin and MCC950, from an inflammatory perspective - a Commentary. *Expert Rev Neurother*. 2019;19(6):535–543.
- Tobinick E, Vega CP. The cerebrospinal venous system: anatomy, physiology, and clinical implications. *MedGenMed*. 2006;8(1):53.
- Tobinick EL, Gross H, Weinberger A, et al. TNF-alpha modulation for treatment of Alzheimer's disease: A 6-month pilot study. *Medscape Gen Med Neurol Neurosurg*. 2006;8(2):25.
- The first evidence that brain disorders could be dramatically influenced by anti-TNF biologicals.**
- Wen TS, Randall DC, Zolman JF. Protein accumulation in cerebrospinal fluid during -90 degrees head-down tilt in rabbit. *J Appl Physiol*. 1994;77(3):1081–1086.
- A vital early clue, from aviation medicine, in the process of constructing the perispinal route of administration by Tobinick.**
- Tobinick EL, Chen K, Chen X. Rapid intracerebroventricular delivery of Cu-DOTA-etanercept after peripheral administration demonstrated by PET imaging. *BMC Res Notes*. 2009;2:28.
- LaMacchia ZM, Spengler RN, Jaffari M, et al. Perispinal injection of a TNF blocker directed to the brain of rats alleviates the sensory and affective components of chronic constriction injury-induced neuropathic pain. *Brain Behav Immun*. 2019;82:93–105.
- The first negatively controlled evidence that etanercept enters the brain after perispinal administration.**
- Tobinick E. Rapid improvement of chronic stroke deficits after perispinal etanercept: three consecutive cases. *CNS Drugs*. 2011;25(2):145–155.
- The first evidence that post-stroke syndromes could be dramatically influenced by anti-TNF biologicals.**
- Tobinick E, Kim NM, Reyzin G, et al. Selective TNF inhibition for chronic stroke and traumatic brain injury: an observational study involving 629 consecutive patients treated with perispinal etanercept. *CNS Drugs*. 2012;26(12):1051–1070.
- Ignatowski TA, Spengler RN, Dhandapani KM, et al. Perispinal etanercept for post-stroke neurological and cognitive dysfunction: scientific rationale and current evidence. *CNS Drugs*. 2014;28:679–697.
- Ignatowski TA, Spengler RN, Tobinick E. Authors' reply to Whitlock: perispinal etanercept for post-stroke neurological and cognitive dysfunction: scientific rationale and current evidence. *CNS Drugs*. 2014;28(12):1207–1213.
- Tobinick E. Perispinal etanercept advances as a neurotherapeutic. *Expert Rev Neurother*. 2018;18(6):453–455.
- Clark IA. Editorial: an unsound AAN practice advisory on poststroke etanercept. *Expert Rev Neurother*. 2017;17(3):215–217.
- Tobinick E. Immediate resolution of hemispatial neglect and central post-stroke pain after perispinal etanercept: case report. *Clin Drug Investig*. 2020;40(1):93–97.
- Clark IA, Vissel B. A neurologist's guide to TNF biology and to the principles behind the therapeutic removal of excess TNF in disease. *Neural Plast*. 2015;358263.
- Steed PM, Tansey MG, Zalevsky J, et al. Inactivation of TNF signaling by rationally designed dominant-negative TNF variants. *Science*. 2003;301(5641):1895–1898.
- Barnum CJ, Chen X, Chung J, et al. Peripheral administration of the selective inhibitor of soluble tumor necrosis factor (TNF) XPro(R)1595 attenuates nigral cell loss and glial activation in 6-OHDA hemiparkinsonian rats. *J Parkinsons Dis*. 2014;4(3):349–360.
- Olleros ML, Vesin D, Lambou AF, et al. Dominant-negative tumor necrosis factor protects from *Mycobacterium bovis* Bacillus Calmette Guérin (BCG) and endotoxin-induced liver injury without compromising host immunity to BCG and *Mycobacterium tuberculosis*. *J Infect Dis*. 2009;199(7):1053–1063.