

Authors' Reply to Whitlock: Perispinal Etanercept for Post-Stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence

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The authors of this article have each been involved, over the course of more than a decade, in the basic science and/or clinical investigation of tumor necrosis factor (TNF) mechanisms involving the brain, i.e. in neuroinflammation research [1–16]. One of the aims of our 2014 review was to bring together the increasing scientific evidence, from multiple fields of investigation and multiple academic centers that support a central role of neuroinflammation in the pathogenesis of post-stroke neurological dysfunction [17]. In 2014, neuroinflammation has emerged as an area of increased international research interest, with intense interest in Europe and a new neurology journal devoted to this specific field [18–20].

Novel scientific discoveries, synthesized with previous scientific evidence, provide a framework for the scientific rationale underlying the rapid effects of perispinal etanercept on brain pathology [9, 13, 16, 21–28]. This framework includes the discovery, in 2011, through the use of functional magnetic resonance imaging (fMRI), that within 24 h after neutralization of TNF by systemic intravenous administration of infliximab, nociceptive activity in the thalamus and somatosensory cortex, as well as activation of the limbic system, was blocked [22]. In 2013, a single systemic subcutaneous dose of another biologic TNF

inhibitor, certolizumab pegol, was found to produce a rapid decrease in disease-related fMRI brain activity in rheumatoid arthritis patients, which preceded both clinical and structural responses to the drug [28]. Just this week it was reported that a single dose of an antidepressant, the selective serotonin reuptake inhibitor escitalopram, dramatically alters functional connectivity throughout the whole brain in healthy subjects within 3 hours of the dose [23]. The rapid and profound effect that antidepressant drugs have on the production of TNF in the brain was first demonstrated by Ignatowski and Spengler in 1994 [29]. Antidepressant administration (desipramine) to rats prevented neuron-associated TNF production, as demonstrated by staining for TNF in the locus coeruleus and hippocampus [30]. This was demonstrated to occur within 24 h after drug administration [29, 30]. These findings, along with the scientific evidence previously considered in our 2014 review, demonstrate that rapid effects of perispinal etanercept are entirely compatible with brain physiology as it is understood today [9, 13, 14, 16, 17, 21, 23, 25–27, 31–37].

Whitlock has written a letter commenting on our 2014 review [38], which begins with a misconception regarding the well-known criteria that Sir Austin Bradford Hill originally developed to facilitate evaluation of causality [38, 39]. We utilized the Hill criteria in our 2014 review [17]. Contrary to the assertion of Whitlock, expert opinion supports use of the Bradford Hill criteria as one method to assist in the evaluation of the strength of evidence supporting therapeutic causality [40–43]. This modification of the Hill criteria for therapeutic evaluation was not the authors' invention; rather, this use of the Hill criteria was suggested by central figures in the evidence-based medicine paradigm (Howick and Glasziou) and others [40–44]. As Williams observed in 2001:

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The narrow definition of epidemiology is the study of the distribution of diseases in a population. The broader definition—an inductive science of biological inferences derived from observations—is more appropriate when relating EBM principals to clinical decision making The use of Bradford-Hill Criteria enhances evidence-based recommendations [42].

Explicit consideration of the Bradford Hill criteria may facilitate appreciation of the scientific rationale and evidence regarding pathophysiology underlying innovative therapeutic decision making [17, 40, 41, 43, 45].

Randomized clinical trial (RCT) evidence is essential for regulatory approval but RCTs that involve innovative methods of drug delivery may only be possible with direct involvement of the drug manufacturer [46]. A blind insistence that the RCT constitutes the only valid form of evidence, as Whitlock suggests, does a disservice to science and the public [40, 41, 43, 47–52]. The discovery of a new use of an existing drug often begins with an initial observation made in the course of clinical practice when utilizing the drug off-label [53, 54]. Evidence development commonly involves open-label observational studies; this was the case for the first approved indication of the biologic TNF inhibitors [55]. Rigorous observational studies, including case studies and case series, are a classical approach that may provide early evidence for therapeutic effectiveness before formal RCTs are conducted [40–44, 47–50, 53, 56–58]. It is not scientifically justifiable to ignore the valid evidence contained in observational studies when evaluating therapeutic interventions, particularly for emerging indications [41, 43–45, 47, 49–51, 56–60]. As multiple authors have stated:

Sometimes the effect of a medical intervention is so surprisingly strong, against the background knowledge of ‘usual prognosis’, that a case report or case series suffices to convince [57].

Case reports and case series have their own role in the progress of medical science. They permit discovery of new diseases and unexpected effects (adverse or beneficial) as well as the study of mechanisms, and they play an important role in medical education. Case reports and series have a high sensitivity for detecting novelty and therefore remain one of the cornerstones of medical progress; they provide many new ideas in medicine [58].

Given that randomized, controlled trials have not and often cannot be done for many clinical interventions, much of the clinical care provided in neurology (and all other specialties in medicine) would necessarily be considered unsubstantiated, if observational studies are discounted from consideration ... the popular

belief that randomized, controlled trials inherently produce gold standard results, and that all observational studies are inferior, does a disservice to patient care, clinical investigation, and education of health care professionals [49].

As recently restated in an opinion viewpoint published in *JAMA Neurology*, “... over-reliance on RCTs is similar to resting all of health care evidence on a one-legged stool” [41, 47]. The authors concluded:

“Most health care decisions, especially by clinicians and patients, are based on incomplete evidence. This process could be improved with better access to transparent, credible, and concise yet complete summaries of the available evidence and its strength, whether or not it is conclusive and whether or not it includes RCTs” [47].

Authorities in the field of evidence-based medicine have specifically addressed the fact that some treatments have effects that are “... so dramatic that randomised trials are unnecessary” [43]. Each of the authors has personally observed the unmistakable rapid neurological improvement produced by perispinal etanercept in patients with chronic, stable, baseline neurological dysfunction [8–10, 24, 26, 27, 32, 61]. The distinctive pattern of neurological improvement that often ensues following perispinal etanercept injection, documented in published digital video and written format, provides striking scientific evidence of a therapeutic effect [32, 62].¹ These results are supported by a diverse variety of additional clinical and basic science studies that have specifically utilized etanercept as a therapeutic agent [8–12, 14, 17, 21, 24–27, 32, 61, 63–78]. Our recent review presents a detailed overview of the scientific evidence that supports the mechanistic reasoning utilized [17, 45, 48]. There are no gaps in the pathophysiological mechanisms discussed; the inferential chain is complete [17, 48]. The published, peer-reviewed perispinal etanercept scientific literature provides more than a decade of scientific support that includes detailed case studies documenting rapid and sustained neurological improvement in patients with neurological dysfunction that had long been unchanged prior to perispinal etanercept administration [8–14, 16, 24–27, 32, 61, 74–76, 79–82].

These case reports are not isolated cases. Rather these results have been replicated, confirmed and extended [17, 25, 26, 32]. Four years of clinical experience with many additional patients with chronic brain dysfunction after stroke, intracerebral hemorrhage, and acquired brain injury has followed the documented pattern of statistically

¹ Further digital video documentation at <https://vimeo.com/user5534662/review/85796991/4385338257>; <https://vimeo.com/user5534662/review/85477199/2aa9b2c6f8> and <http://www.vimeo.com/18550399>.

significant improvements in motor impairment, cognition, psychological/behavioural function, aphasia and pain following perispinal etanercept injection reported in the 629-patient study of 2012 [17, 25, 26, 32]. Moreover, since publication of the 2012 study [26], the peer-reviewed medical literature has provided further basic science and clinical support for the scientific rationale [6, 7, 17, 21, 26, 31–37, 47, 59, 63, 65–67, 69, 71, 75, 83–120]. As Lei et. al. and Kathirvelu and Carmichael stated in 2013 and 2014, respectively:

Antagonism of pro-inflammatory cytokines by specific antibodies represents a compelling therapeutic strategy to improve neurological outcome in patients after intracerebral hemorrhage [107].

With direct blood extravasation into brain, secondary inflammation is a substantial feature. Drugs which reduce neuroinflammation enhance functional recovery [94].

As a noted authority in the field of TNF and brain dysfunction has written:

... the years-long interval between the stroke event and rapid clinical improvement described in these patients is consistent with experimental evidence that TNF generation persists in the CSF for very much longer (10 months plus) than in the serum (gone in 6 h)... In this report each patient's pre-treatment state provided an internal control. In practice, these individual pre-treatment comparisons are highly valid, since the likelihood of rapid spontaneous return of function is remote this long after the stroke event. Moreover, since no two stroke outcomes are the same, such internal controls allow precise before and after clinical comparison in a phenotypically heterogeneous condition [121].

There are now multiple, reported RCTs of etanercept for neurological indications that have shown etanercept to be superior to placebo [64–66, 69, 71]. The character, magnitude and reproducibility of patient recovery documented following perispinal etanercept for chronic post-stroke neurological dysfunction is unequivocal evidence of a therapeutic effect [8, 9, 12, 17, 24–27, 32, 74].

Whitlock further errs in his analogy comparing the effects of opiates and etanercept for neuropathic pain [38]. Exerting physiological effects that are distinct from those produced by opiates, TNF blockade using etanercept for treatment of neuropathic pain is a disease-modifying therapy that directly addresses a fundamental cause of the disorder, i.e. excess TNF [1, 63, 67, 68, 70, 72, 73, 77, 78, 84]. The authors each reported favorable effects of TNF blockade for the treatment of neuropathic pain, beginning more than a decade ago [1, 11, 12, 76]. To date, there are

four favorable double-blind, randomized controlled trials of etanercept for sciatica and other forms of spinal neuropathic pain that have been completed [64, 65, 69, 71]. In addition, the basic science evidence supporting a therapeutic, disease-modifying effect of etanercept for the treatment of neuropathic pain continues to increase [1, 63, 67, 68, 70, 72, 73, 77, 78, 84]. It is of significant interest that recent evidence suggests that the early analgesic effects of biologic TNF inhibitors in patients with rheumatoid arthritis may be directly mediated, not peripherally but rather by rapid brain effects of the biologic TNF inhibitor [22].

The rapid and dramatic neurological improvement repeatedly observed after perispinal etanercept administration in patients with chronic, post-stroke neurological dysfunction cannot be scientifically attributed to a placebo response, as Whitlock seems to suggest [1, 6, 8–10, 14, 16, 17, 21, 22, 24–27, 32, 36, 38, 41, 43, 44, 47, 56, 66, 75, 100, 118, 121–124]. In fact, a recent Cochrane review concluded:

There was no evidence that placebo interventions in general have clinically important effects [124].

Placebo effects do not produce the life-changing neurological improvements that have been documented and observed by each of the authors and others following perispinal etanercept injection [14, 25, 26, 32, 43]. In view of the distinctive character, quality and reproducibility of the clinical data, and the basic science evidence that supports the entire inferential chain, it would be a systematic error to deny the published, peer-reviewed evidence and characterize the reported clinical results of perispinal etanercept for post-stroke neurological dysfunction as anything less than a therapeutic breakthrough [8–12, 14, 17, 21, 24–27, 32, 48, 61, 63–78]. Those scientists who have recognized TNF antagonism for this indication as a “compelling therapeutic strategy” [107] are exactly in line with the guidance to “translate best neuroscience, including animal and human studies, into poststroke recovery research and clinical care” that is the published consensus recommendation of world stroke leaders [125].

Etanercept is providing billions of dollars of yearly income to its manufacturers. These drug manufacturers are the only entities that possess the combination of regulatory expertise and financial capability necessary to achieve regulatory approval for these essential novel therapeutic indications. The strength of the emerging evidence argues for joint industry–government–academic cooperation to facilitate overcoming the substantial translational barriers that exist for such an innovative therapeutic approach.

Acknowledgments and Conflict Disclosure Edward Tobinick has multiple issued and pending US and foreign patents, assigned to TACT

IP, LLC, which claim methods of use of etanercept for the treatment of neurological disorders, including, but not limited to, US patents 6419944, 6537549, 6982089, 7214658, 7629311, 8119127, 8236306 and 8349323, all assigned to TACT IP, LLC; and Australian patent 758523. Dr. Tobinick is the founder of the Institute of Neurological Recovery (INR), a group of medical practices that utilize perispinal etanercept as a therapeutic modality, and also train physicians; he is also the CEO of TACT IP, LLC. Tracey Ignatowski and Robert Spengler have been expert witnesses for the INR. Tracey Ignatowski and Robert Spengler's professional activities include their work as Co-Directors of Neuroscience at NanoAxis, LLC, a company formed to foster the commercial development of products and applications in the field of nanomedicine, which include novel methods of inhibiting TNF. This article represents the authors' own work in which NanoAxis, LLC, was not involved. No funding was received for this letter.

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