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EDITORIAL

Perispinal etanercept advances as a neurotherapeutic

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1. The pivotal role of tumor necrosis factor (TNF) in modulating neuronal function

TNF is a signaling molecule whose study and characterization have transformed modern medicine [1]. Drugs bioengineered to selectively reduce TNF's biological activity have proven effective for a variety of inflammatory disorders that could not be adequately controlled with conventional therapeutics [1]. During the past two decades, there has been increasing scientific recognition that TNF plays a pivotal role in the nervous system, modulating both synaptic transmission and neuronal network function [2–7]. To describe TNF as simply a pro-inflammatory cytokine omits the fundamental role that TNF plays in regulating neuronal function [2–9].

TNF, in fact, is an essential neuromodulator. TNF is produced by both glia and neurons and participates in the normal physiology of the tripartite synapse [2–7]. When in excess, TNF interferes with neurotransmission, perturbs brain function, and mediates neuropathic pain [2–9]. Excess TNF is centrally involved in the initiation and maintenance of neuroinflammation, an area of accelerating interest in the field of neurology [1–20]. Bioengineered TNF inhibitors are natural candidates for study in clinical trials of neuroinflammatory disorders [1–21].

2. Perispinal etanercept (PSE) off-label indications expand to chronic stroke and traumatic brain injury (TBI)

The bioengineered TNF inhibitors include etanercept, FDA-approved in 1998 to treat rheumatoid arthritis [1]. Etanercept, because of its anti-inflammatory efficacy and excellent safety profile, is widely used around the world for a number of chronic inflammatory disorders, including several forms of arthritis and psoriasis, an inflammatory skin disorder [1]. The rapid improvement in neuropathic pain seen in patients treated with etanercept in 1999, given by perispinal administration (discussed in more detail below), was the first clinical evidence of the therapeutic promise of bioengineered TNF inhibitors in neurology [2]. This was followed by the favorable results of a small 6 month open-label clinical trial of PSE for Alzheimer's disease (AD), published in 2006 [2]. The science underlying the use of PSE in neurology was the subject of an invited review in this journal in 2010 [2]. What has happened since?

The most significant development may have been the novel observation, in 2010, that PSE was capable of producing unprecedented rapid neurological improvement in patients with chronic neurological dysfunction after stroke or TBI [22–24]. The reproducibility of the initial observations has since been confirmed and expanded by the clinical experience of multiple physicians, who have together treated a total of more than 2000 patients with chronic neurological dysfunction after stroke using PSE off-label [22,23]. Many of these patients were treated years or decades after the acute injury [22,23]. Neurological improvements in these patients have included favorable changes in gait, spasticity, mental function, aphasia, sensation, and chronic poststroke pain and a host of less common, but no less important improvements, including improvements in special senses, bladder function, etc [20,22,23]. Since 2010, the scientific rationale has been strengthened by at least six favorable studies of etanercept in stroke models and three favorable randomized clinical trials of etanercept for spinal neuropathic pain (cited in [21]); see also [2,6–10,12–15,18,20,24,25].

3. Excess TNF is a 'circuit breaker' that impairs brain connectivity

Accumulating evidence, together with the fact that TNF controls both synaptic strength and synaptic scaling, supports the conclusion that one may regard excess TNF as a reversible 'circuit breaker' in the nervous system [2,3,6,7,20,22–27]. Etanercept's known ability to neutralize excess TNF and reduce microglial activation, and thereby address neuroinflammation, is likely responsible for the rapid (within minutes) and prolonged neurological improvement repeatedly observed after PSE administration [2–7,9,20–27]. PSE, through its effects on neurotransmission and brain connectivity, may thus be conceptualized as flipping a switch that reactivates clinically relevant brain circuits made dormant by neuroinflammation [2–7,20–27].

Other recent developments have also been significant. There is increasing recognition in the scientific community of the role of excess TNF in the pathophysiology of neuroinflammation, with hundreds of citations to scientific publications involving PSE treatment for spinal pain, AD, stroke, and TBI [1–8,11–27]. A Google Scholar search of 'PSE' currently yields 680

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results, one measure of the scholarly interest that these scientific publications have generated. For space considerations, we cannot do justice to the extensive supportive scientific evidence that preceded and has followed our 2010 review, which for decades has had the potential to alter the course of neurodegenerative disease research [2,3,6,7,16]. Much of this evidence can readily be discovered by an online search of the medical literature with search terms including 'neuroinflammation,' 'TNF,' and 'microglial activation.'

4. Perispinal administration facilitates CNS drug delivery

The vascular route through which PSE travels has become more familiar to the scientific community since 2010 [6,20,21,28–30]. Prior to a 2006 review, the anatomy and physiology of this route, the cerebrospinal venous system (CSVS), had fallen into obscurity for decades [2,20,21,28,29]. The words of Oscar Batson, a professor of anatomy at the University of Pennsylvania in the middle of the last century who did seminal research establishing the anatomy and physiology of the CSVS, are still relevant today: 'It seems incredible that a great functional complex of veins would escape recognition as a system' [28]. Perispinal injection of a drug in solution posterior to the spine, whether superficial or deep, will invariably lead to absorption of that drug into the CSVS, because the CSVS, through its external vertebral venous plexus division, drains the anatomic region posterior to the spine [2,20,21,28]. Drugs reaching the external vertebral venous plexus will then invariably drain into the internal vertebral venous plexus (IVVP), a constituent of the CSVS [20,21,28]. Once a drug reaches the valveless IVVP, it is capable of being distributed into the cerebral venous system, including the choroid plexus [2,20,21,23,24,28–30]. The flow in the IVVP is bidirectional [2,6,20–25,28,30]. The clinical significance of the anatomy and physiology of the CSVS merits its inclusion as a standard part of medical training, from which it has been largely omitted for decades [20,21,24,27–30].

The clinical advantages of perispinal administration are considerable. There is no need to drill burr holes in the skull or insert needles into the parenchyma of the brain [2,20,21,24,27]. Likewise, there is no need to use a long needle, as is required for epidural or intrathecal injection [2,20,21,24,27]. Thus, this therapeutic method is distinct from neuraxial (epidural or intrathecal) administration, as there is no risk of needle injury to the spinal cord or the epidural veins with perispinal administration superficial to the ligamentum flavum [2,20,21,24,27].

Unfamiliarity with CSVS anatomy and physiology has been a barrier to widespread recognition of perispinal administration as a viable method for CNS drug delivery, but this barrier is being overcome through education and the publications of independent scientists [2,6,7,12,15,17,20,21,24,27,29,30]. As one example of this progress, in 2015 PSE off-label for chronic poststroke neurological dysfunction was recognized by a judicial and state medical board decision to be within the medical standard of care [17]. Supportive scientific data continues to accumulate [1–30]. The success of PSE suggests that efforts to develop potent TNF inhibitors that cross the blood-brain barrier after oral or systemic administration may be warranted, but specific challenges to these delivery methods for CNS indications exist [7].

5. The promise of PSE in neurology

The clinical results achieved with PSE have expanded our understanding of human physiology and pathophysiology, particularly in the field of neurology. PSE provided the first favorable clinical data regarding TNF inhibition for the following neuroinflammatory disorders (date of first observation indicated):

(1) Chronic spinal pain due to intervertebral disc herniation (**1999**) [2];
(2) Radicular sensory dysfunction (anesthesia and paresthesia) associated with intervertebral disc herniation (**2000**) [2];
(3) Radicular motor dysfunction (muscle weakness) due to intervertebral disc herniation (**2000**) [2];
(4) Spinal pain due to cancer metastasis to bone (**2001**) [2]; see also [19];
(5) Cognitive dysfunction in AD (**2004**) [2];
(6) Behavioral dysfunction in AD (**2004**) [2];
(7) Chronic motor impairment and spasticity due to TBI (**2010**) [23,24];
(8) Chronic motor impairment, spasticity, sensory dysfunction, cognitive dysfunction, psychological/behavioral dysfunction, aphasia, and pain after stroke (**2010**) [22,23];
(9) Chronic dysfunction of taste, smell, vision, and bladder function after stroke (**2011**) [22,23].

With two clinical trials of PSE for treatment of chronic poststroke neurological dysfunction currently in development at academic centers, one in Australia and the second in Europe, there is room for optimism that regulatory approval and reimbursement in about 5 years' time may be achievable. The opportunity to alleviate suffering and disability on a more widespread basis is substantial. The future is bright indeed.

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Declaration of interest

E Tobinick holds multiple U.S., European and Australian patents claiming methods of use of etanercept for treatment of neurological disorders, including perispinal administration, and receives royalties pursuant to those patents. Dr. Tobinick is the Director of the Institute of Neurological Recovery, a private medical practice that utilizes PSE for treatment of neuroinflammatory disorders. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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