Perispinal Etanercept for Treatment of Alzheimer's Disease

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Abstract: Background: Increasing basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of Alzheimer's Disease. Excess TNF-alpha, a cytokine with pleotropic effects in the CNS, has been suggested to be involved in the pathogenesis of AD. In addition to its pro-inflammatory effects, TNF-alpha affects synaptic transmission; and glutamate, NMDA, and amyloid pathways. More specifically, TNF-alpha, produced by glia, has been shown to affect both synaptic strength and to mediate synaptic scaling, a homeostatic mechanism important to the control of neural networks. A recently published small, open-label pilot study suggested that inhibition of the inflammatory cytokine TNF-alpha utilizing the perispinal administration of etanercept may lead to sustained cognitive improvement for six months in patients with mild, moderate, and severe Alzheimer's disease. Results: Continued open-label clinical experience with this new treatment modality, now for more than two years, suggests that weekly maintenance treatment with perispinal etanercept may have a sustained positive effect. In addition, rapid clinical improvement, within minutes of dosing, has been observed on a repeated basis in multiple patients. Discussion: It is hypothesized that perispinal administration of etanercept may enable rapid delivery to the CNS via the cerebrospinal venous system, resulting in improvement in synaptic mechanisms which have been dysregulated by excess TNF-alpha. TNF-alpha modulation in Alzheimer's disease may also act by influencing glutamate, NMDA, amyloid and other inflammatory pathways. Methods of perispinal administration, as described in the pilot study, may prove useful for delivering other therapeutics, particularly large molecules, to the CNS. Further study in randomized, placebo-controlled clinical trials and in basic science studies is merited.

Keywords: TNF, etanercept, Alzheimer's, synaptic scaling, dementia, cytokines.

Increasing basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of Alzheimer's Disease (AD) [1, 2]. Recognizing that brain inflammation is a hallmark of AD, clinical trials for AD utilizing pharmacologic anti-inflammatory agents, including prednisone and non-steroidal anti-inflammatory drugs were attempted. Despite the fact that these initial trials were unsuccessful, it was still surmised that more successful methods to intervene in the inflammatory pathways of AD could be developed [3, 4]. The scientific community was aware that tumor necrosis factor-alpha (TNF) had been identified as the "master regulator" of the inflammatory response across multiple organ systems[5]. TNF, a pro-inflammatory cytokine, both initiates and amplifies the immune response. Using recombinant DNA technology selective and potent biologic antagonists of TNF were developed for human use. The biologic anti-TNF agents currently available for human use in the U.S. are etanercept, an anti-TNF fusion protein; infliximab, a chimeric anti-TNF monoclonal antibody; and adalimumab, an anti-TNF monoclonal antibody. Both etanercept and adalimumab are approved for subcutaneous use; infliximab is approved for intravenous dosing. Each of these anti-TNF biologics has been demonstrated to slow disease progression for their approved indications, which include rheumatoid arthritis. TNF had been implicated in the pathogenesis of RA.

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Increasing scientific evidence suggests that TNF is also centrally involved in the pathogenesis of AD. Excess TNF has been demonstrated in the cerebrospinal fluid, the serum, and the plasma in patients with AD [6-8]. There is substantial scientific evidence that amyloid, glutamate, and NMDA pathways are involved in AD pathogenesis. Increasing evidence suggests that TNF may interact with each of these pathways to increase neurotoxicity and neuronal damage in AD [9-19].

Recently an additional mechanism through which TNF may contribute to the pathogenesis of AD has been identified: interference with synaptic mechanisms. Synaptic dysfunction in AD is well-recognized, and it has previously been suggested that alterations in synaptic homeostatic mechanisms might contribute to memory impairment in AD [20]. TNF has been demonstrated to have synaptic effects, controlling synaptic strength and directly affecting glutamate transmission [21, 22]. In addition TNF has been demonstrated to mediate synaptic scaling, a homestatic mechanism for regulating synaptic connectivity that may have important implications for the maintenance and efficiency of neural networks [20, 23].

Excess TNF therefore represents a target for therapeutic intervention in AD, but there remained issues regarding the delivery of an anti-TNF biologic to the brain. Each of the three approved biologic TNF inhibitors is a large molecule, with a molecular weight in excess of 100,000 daltons. The blood-brain barrier characteristically prevents passage of molecules larger than approximately 500 MW [24].

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