Case report

**Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration**

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**Abstract**

Substantial basic science and clinical evidence suggests that excess tumor necrosis factor-alpha (TNF-alpha) is centrally involved in the pathogenesis of Alzheimer’s disease. In addition to its pro-inflammatory functions, TNF-alpha has recently been recognized to be a gliotransmitter that regulates synaptic function in neural networks. TNF-alpha has also recently been shown to mediate the disruption in synaptic memory mechanisms, which is caused by beta-amyloid and beta-amyloid oligomers. The efficacy of etanercept, a biologic antagonist of TNF-alpha, delivered by perispinal administration, for treatment of Alzheimer’s disease over a period of six months has been previously reported in a pilot study. This report details rapid cognitive improvement, beginning within minutes, using this same anti-TNF treatment modality, in a patient with late-onset Alzheimer’s disease. Rapid cognitive improvement following perispinal etanercept may be related to amelioration of the effects of excess TNF-alpha on synaptic mechanisms in Alzheimer’s disease and provides a promising area for additional investigation and therapeutic intervention.

**Background**

Neuroinflammation with overexpression of cytokines is a standard characteristic of the brain pathology present in Alzheimer's disease [1-4]. Involvement of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha) in the pathogenesis of Alzheimer's disease has long been suspected [5-9]. Increasing basic science, genetic, and clinical evidence now supports the concept that excess TNF-alpha plays a central role in Alzheimer’s disease [5-25].

In 1998 etanercept, a potent anti-TNF therapeutic, was approved for human use, with rheumatoid arthritis as the initial indication. Etanercept is a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two human p75 TNF-alpha receptors linked to the Fc fragment of human IgG1. Etanercept binds to TNF-alpha and blocks its interaction with cell surface TNF-alpha receptors, thereby reducing the biologic effect of excess TNF-alpha. The medical community now has more than 1 million patient-years of experience using etanercept for treatment of a variety of inflammatory disorders in which TNF-alpha has been postulated to play a role [26].

In 2006 the present authors published a pilot study which provided proof-of-concept that a novel method of administration of etanercept was efficacious for the treatment of Alzheimer’s disease [20]. This novel method, perispinal extrathecal administration in the posterior neck, was hypothesized to improve delivery of etanercept to the brain via the cerebrospinal venous system[21,27]. In an open-label study of 15 patients treated weekly for a period...