MedGenMed Neurology & Neurosurgery

TNF-alpha Modulation for Treatment of Alzheimer's Disease: A 6-Month Pilot Study

Edward Tobinick, MD; Hyman Gross, MD; Alan Weinberger, MD; Hart Cohen, MD, FRCPC

Medscape General Medicine. 2006;8(2):25.
Posted

Abstract and Introduction

Abstract

Context: Current pharmacologic treatments for Alzheimer's disease (AD) do not prevent long-term clinical deterioration. Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD.
Objective: To investigate the use of a biologic TNF-alpha inhibitor, etanercept was given by perispinal extrathecal administration for the treatment of AD.
Methods: This was a prospective, single-center, open-label, pilot (proof-of-concept) study, in which 15 patients with mild-to-severe AD were treated for 6 months. We administered etanercept, 25-50 mg, once weekly by perispinal administration. Main outcome measures included the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Severe Impairment Battery (SIB).
Results: The average age of our patient population was 76.7. The mean baseline MMSE was 18.2 (n = 15); the mean baseline ADAS-Cog was 20.8 (n = 11); and the mean baseline SIB was 62.5 (n = 5). There was significant improvement with treatment, as measured by all of the primary efficacy variables, through 6 months: MMSE increased by 2.13 ± 2.23, ADAS-Cog improved (decreased) by 5.48 ± 5.08, and SIB increased by 16.6 ± 14.52.
Conclusion: Increasing amounts of basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of AD. This small, open-label pilot study suggests that inhibition of the inflammatory cytokine TNF-alpha may hold promise as a potential approach to AD treatment. Further study in randomized, placebo-controlled clinical trials is merited.

Introduction

Inflammatory immune mechanisms play a central role in the causation of Alzheimer's disease (AD).[1-5] Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, the "master regulator" of the immune response, is the key initiator of immune-mediated inflammation in multiple organ systems, including the brain.[6] Scientific evidence identifying TNF-alpha involvement in the pathogenesis of AD began accumulating a decade ago in experimental models. In vitro, with use of a human monocytic cell line, beta amyloid was found to stimulate secretion of TNF-alpha.[7] TNF-alpha plus gamma-interferon was found to induce beta-amyloid production.[8] Beta amyloid was shown to stimulate microglial inflammatory pathways, resulting in neurotoxicity mediated by TNF-alpha generated by reactive microglia and monocytes.[9] Clinical evidence followed, with a central place for TNF-alpha in AD pathogenesis suggested by demonstration of 25-fold elevated levels of TNF-alpha in the cerebrospinal fluid of patients with AD,[10] and the finding that increased cerebrospinal fluid TNF-alpha levels correlated with clinical deterioration.[11] In 2005, the evidence supporting TNF-alpha involvement in AD accelerated, including identification of a greater risk for AD in an Australian population associated with a polymorphism in the promoter region of the TNF gene.[12]

Increasing amounts of laboratory evidence implicate TNF-alpha in inflammatory molecular mechanisms producing neurotoxicity, neuronal death, or neuronal dysfunction involving both TNF-glutamate[13-17] or TNF-amyloid