Blood-Brain Barrier Penetrating Biologic TNF-α Inhibitor for Alzheimer's Disease.

Tumor necrosis factor alpha (TNF-α) driven processes are involved at multiple stages of Alzheimer's disease (AD) pathophysiology and disease progression. Biologic TNF-α inhibitors (TNFIs) are the most potent class of TNFIs but cannot be developed for AD since these macromolecules do not cross the blood-brain barrier (BBB). A BBB-penetrating TNFI was engineered by the fusion of the extracellular domain of the type II human TNF receptor (TNFR) to a chimeric monoclonal antibody (mAb) against the mouse transferrin receptor (TfR), designated as the cTfRMAb-TNFR fusion protein. The cTfRMAb domain functions as a molecular Trojan horse, binding to the mouse TfR and ferrying the biologic TNFI across the BBB via receptor-mediated transcytosis. The aim of the study was to examine the effect of this BBB-penetrating biologic TNFI in a mouse model of AD. Six-month-old APPswe, PSEN 1dE9 (APP/PS1) transgenic mice were treated with saline (n = 13), the cTfRMAb-TNFR fusion protein (n = 12), or etanercept (non-BBB-penetrating biologic TNFI; n = 11) 3 days per week intraperitoneally. After 12 weeks of treatment, recognition memory was assessed using the novel object recognition task, mice were sacrificed, and brains were assessed for amyloid beta (Aβ) load, neuroinflammation, BBB damage, and cerebral microhemorrhages. The cTfRMAb-TNFR fusion protein caused a significant reduction in brain Aβ burden (both Aβ peptide and plaque), neuroinflammatory marker ICAM-1, and a BBB disruption marker, parenchymal IgG, and improved recognition memory in the APP/PS1 mice. Fusion protein treatment resulted in low antidrug-antibody formation with no signs of either immune reaction or cerebral microhemorrhage development with chronic 12-week treatment. Chronic treatment with the cTfRMAb-TNFR fusion protein, a BBB-penetrating biologic TNFI, offers therapeutic benefits by targeting Aβ pathology, neuroinflammation, and BBB-disruption, overall improving recognition memory in a transgenic mouse model of AD.