EFFECTS OF ANTI-TNF THERAPIES ON AMYLOID PATHOLOGY AND NEUROINFLAMMATION IN 12 MONTH OLD ARCAB MICE


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Background: Alzheimer's disease (AD) is a neurodegenerative disease associated with the accumulation of misfolded protein aggregates as well as, glia-mediated neuroinflammatory processes. The overexpression of tumor necrosis factor alpha (TNF), in particular, may promote amyloid plaque deposition and mediate Abeta-related synaptotoxicity. The use of anti-TNF therapies for the treatment of AD is therefore currently under preclinical and clinical investigation.

Aims: In this study we aimed to investigate the effects of anti-TNF immunotherapy in 12 month-old ArcAb mice, a recently published transgenic mouse model of AD.

Methods: Treatment design included intracerebroventricular infusion of Etanercept, Infliximab, Adalimumab and PBS for 28 days via using ALZET osmotic minipumps, and 4 weekly intraperitoneal injections of Etancercept, Infliximab, Adalimumab and PBS, with an additional 15 non-treated transgenic mice as a further control. All mice underwent general health and neurological examination, as well as, cognitive assessment before they were sacrificed for further biochemical (brain Aβ levels, brain cytokine panel) and histological analyses.

Results: Immunohistochemical analyses confirmed ventricular placement of the brain infusion cannula and the ubiquitous distribution of all biologics throughout the brain for both intracerebroventricular and intraperitoneal treated mice. Cognitive-behavioral assessment of mice demonstrated a treatment dependent improvement in cognitive performance in two hippocampus-dependent cognitive tests. Preliminary results from the biochemical analyses indicate that the improvement in cognition was not associated with changes in soluble brain Abeta levels or an overt shift in the neuroinflammatory profile.

Conclusion: Our preliminary results indicate that TNF-directed immunotherapy may successfully reverse Abeta-related cognitive deficits in a transgenic mouse model of AD. Further studies are underway to explore the role of neuroinflammatory mediators underlying these beneficial effects.