

Detection of Treatment Effects with ^1H MRS in Transgenic Mouse Model of Alzheimer's Disease

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Introduction

Drug development studies require sacrificing mice in order to histologically assess therapeutic efficacy. Histological assessment can only be performed once, at the end of the therapeutic study. Therefore histological assessment of therapeutic efficacy cannot evaluate change measures from baseline to treatment endpoint. In contrast, imaging enables the assessment of drug effect at baseline and at the end of treatment, or serially throughout treatment.

In this project, MRS was assessed as a non-invasive outcome measure capable of detecting metabolic alterations following passive immunization in a transgenic mouse model of Alzheimer's disease (AD). We employed two different anti-A β antibody treatment regimes that have previously been demonstrated to reduce amyloid plaque load in transgenic (APP-PS1) AD mice.

Methods

Eighty double transgenic APP-PS1 and sixteen B6SLJ wild-type mice were entered into a 4-month treatment study. APP-PS1 mice were randomly assigned to five treatment groups (1 mg/kg ponezumab, 3 mg/kg ponezumab, 10 mg/kg ponezumab, 10 mg/kg 2H6-D, control antibody). Treatment consisted of weekly intra-peritoneal injection of the antibodies supplied by Pfizer, Inc.

In vivo ^1H NMR spectra were obtained using a previously described LASER sequence (1). MR experiments were performed with a 9.4-T (31-cm horizontal bore) magnet equipped with Varian INOVA console to localize a 18 μL voxel placed in the cortex and the hippocampus. Each individual FID was stored separately and then frequency and phase corrected based on total creatine (tCr = creatine and phosphocreatine) signal at 3.03 ppm prior to summation. Small residual eddy currents effects were corrected using a reference water signal.

The obtained spectra were analyzed using LCModel with the spectra of eighteen metabolites and the experimentally measured spectrum of macromolecules included in the basis set. The quantification was obtained using tCr resonance as an internal standard.

Results and Discussion

Figure 1 illustrates a typical spectrum obtained in this study. We have shown previously that there is a dramatic increase in the concentration of mIns with age in APP-PS1 mice (2). This increase is attributed to the microglial activation in this mouse model of brain amyloid plaque deposition. The baseline-adjusted mIns results at 4 months are shown in Figure 2 and demonstrate three main findings: 1) a dramatic increase in mIns over time in vehicle treated APP-PS1 mice compared to WT mice ($p = 0.004$); 2) compared with untreated APP-PS1 mice, evidence of a dose-dependent response function for ponezumab; 3) the smallest increase in mIns in APP-PS1 mice is seen with 2H6-D antibody treatment ($p = 0.02$).

Treatment of transgenic AD mice with either of two anti-A β antibody regimes appears to slow the rate at which mIns normally increases in transgenic AD mice. ^1H MRS may provide an *in vivo* measure of anti-A β therapeutic efficacy in pre-clinical studies.

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References

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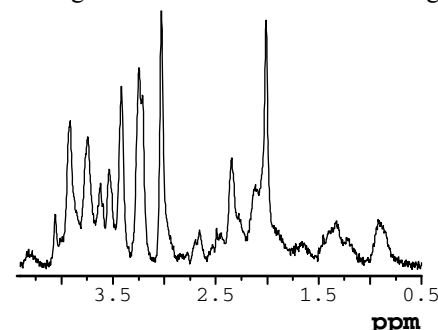


Figure 1. Quality of an average spectrum obtained during the study from 18 μL voxel placed in cortex and hippocampus with LASER sequence. $T_R = 4$ s, $T_E = 27$ ms, $N_{EX} = 384$, no line broadening.

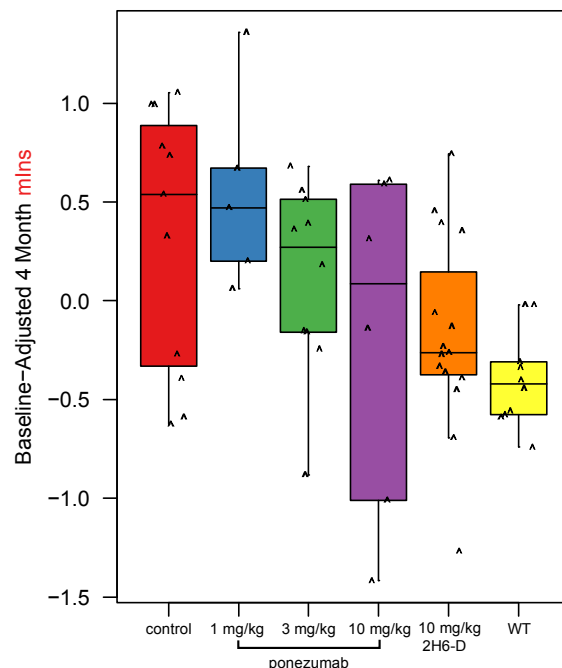


Figure 2. Analysis of covariance for mIns ($n = 57$).