Impact of short-term administration of oral Minocycline, a repurposed anti-neuroinflammatory agent, on MR and neuropsychological biomarkers of MCI and AD

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Background: Reversal of neuroinflammation, broadly defined as hyperactivity of microglia, rather than removal of cerebral amyloid may become the new cornerstone of Alzheimer's disease prevention following a series of disappointing small animal and human studies in which 'clearance of amyloid' from the brain was successful but clinical improvement was lacking. With recent confirmation of glial hyper-activity in living brain of human MCI and AD [1], we anticipate appropriate agents will shortly enter clinical trials. This report describes a pilot study in which quantifiable MR biomarkers [1,2] and abbreviated neuropsychological test batteries were applied as outcome measures. Minocycline, a second generation tetracycline, with proven neuro-protective [3] and anti-neuroinflammatory [4] properties in small animals, has been used in clinical trials of Huntington's, Parkinson's, schizophrenia, bipolar disorder, HIV and stroke, but not to our knowledge in MCI or AD.

Design/Methods: Fourteen elderly (5 AD, one MCI and eight cognitively normal (NC) underwent a 6-month trial of minocycline 50mg twice daily. This was an open pilot study with no placebo controlled cohort. Each subject was monitored monthly with neuropsychological Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), hippocampal volume (vH/ICV) and posterior cingulate PRESS TE 35ms MRS to measure neuronal and glial biomarkers N-acetyl aspartate (NAA) and myo-inositol (mI), respectively expressed as NAA/mI (GE SAGE 1.5T). Initial diagnosis and drug response were defined by linear progression of [vH x NAA/mI x RBANS] $\pm$ SEM.

Results: Significantly different [vH x NAA/mI x RBANS] distinguished untreated NC, MCI and AD at the time of accrual ($P < 0.001$). Minocycline 50mg bd was well tolerated as were monthly neuropsychological and MR biomarkers examinations (1 AD did not complete MRS; 1 AD did not complete RBANS). Serial renal and hepatic function tests were negative. Differences remained significant at all time points during the administration of Minocycline. While no statistically significant effect on clinical or biomarker measures were encountered ($P > 0.1$), sporadic positive effects were observed. Most notably in MCI, mI/Cr improved 10 % over 6 months while in one AD, NAA/Cr increased 16% at four weeks. In untreated AD, vH and NAA/mI each deteriorated by 3% per annum in published studies.

Conclusions: (1) Minocycline, an FDA 'approved' surrogate for newer anti-neuroinflammatory drugs currently under development, showed modest benefit in MCI and AD without toxicity but was without statistical effect in this open label study (Clinical Trials NCT01463384). (2) Use of novel MR biomarker [vH x NAA/mI/RBANS] would power a placebo-controlled blind study with minocycline (or other drug) treatment for as few as 12 – 20 patients per group and at dramatically reduced cost.

		N	Correlation	Significance
Pair 1	%vH/ICV & NAA/mI	53	0.357	0.009
Pair 2	%vA/ICV & NAA/mI	52	0.438	0.001
Pair 3	RBANS & NAA/mI	47	0.584	< 0.001
Pair 4	RBANS & %vH/ICV	38	0.384	< 0.02
Pair 5	RBANS & %vA/ICV	37	0.576	< 0.001
Pair 5	RBANS & (%vH/ICV x NAA/mI)	37	0.524	0.001
Pair 6	RBANS & (%vA/ICV x NAA/mI)	36	0.651	< 0.001

vH = hippocampal volume; ICV = intracranial volume; vA = amygdala volume

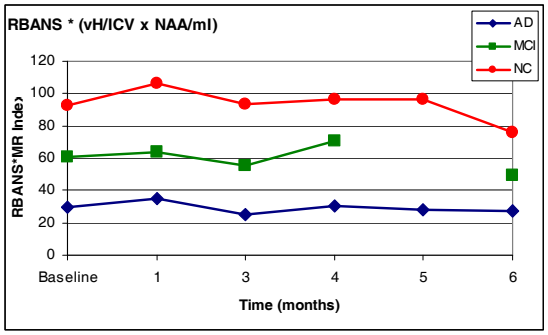

Figure 1. Combined indices distinguished controls from MCI and AD subjects at initial diagnosis, and throughout 6 month trial.

References: (1) Sailasuta et al. Neuropsychiat Dis Treat 2011; 7:495-499. (2) Brewer, J. Behav Neurol 2009; 21: 21-28. (3)Plane et al. Arch Neurol 2010; 67(12): 1442-1448. (4) Garwood et al. Frontiers in Psychiatry 2010; 1(136): 1-8.

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