Tau aggregation inhibitor therapy with rember™ changes molecular imaging in brain regions affected by tau pathology in mild and moderate Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is a major public health problem which has a serious impact on individuals, families, health care systems and society. Neurofibrillary degeneration is characterised by tau protein aggregation in tangles and neuritic plaques. This is a major pathological feature of AD that is correlated with clinical severity.

There is no currently available technology for directly measuring neurofibrillary degeneration in vivo. However, molecular imaging techniques, such as ^{99m}Tc hexamethyl propylene amine oxime single photon emission computed tomography (HMPAO SPECT) and ^{18}F-Fluorodeoxyglucose Positron Emission Tomogrphy (FDG PET) provide methods of evaluating brain pathophysiology.

In this study the effects of treatment with rember™, a Tau Aggregation Inhibitor (TAI), were examined in AD using HMPAO SPECT or FDG PET and a randomized, double blinded, placebo controlled, multicentre design.

Methods

The participants were subsets of a multi-centre randomized, double blinded, placebo-controlled trial of rember™ in AD. The primary objective of this trial was to investigate the effects of rember™ (30, 60 & 100mg) compared with placebo, on cognitive ability, measured by the AD Assessment Scale-cognitive subscale (ADAS-cog).

Eligible participants had a clinical diagnosis of dementia of the Alzheimer type (DSM-IV criteria), a diagnosis of probable Alzheimer's disease (NINCDS-ADRDA criteria), a Mini Mental State Examination (MMSE) score between 10 and 26 inclusive and Clinical Dementia Ratings (CDR) of either stage 1 or 2. Patients were excluded if they were taking either a cholinesterase inhibitor or memantine.

Subjects were assessed by ADAS-cog at baseline and at 6, 12, 18 and 24 weeks in the placebo controlled phase and at 37 and 50 weeks in an active extension.

HMPAO SPECT scans were carried out before randomisation and at between weeks 18 and 28 after the start of treatment. FDG PET was carried out at baseline and at 24 weeks after the start of treatment.

Data was analysed using a region of interest approach and statistical parametric mapping (SPM2 UCL, London, UK).

Results

126 patients completed the SPECT protocol and 19 the PET protocol. ROI changes in frontal, occipital, parietal and temporal lobes are shown in Figure 1 and indicate a general reduction in SPECT activity (rCBF) in the placebo group, as expected, and no significant change in the 60mg and 100 mg groups.

This finding was confirmed using the SPM approach. Figures 2, 3 and 4 show the significant locations of difference when change in rCBF in the placebo group is compared with change in rCBF in the active treatment groups.

The smaller FDG PET group indicated significant differences in the medical temporal lobes bilaterally when a similar analysis was performed (Figure 5).

Figure 6 shows the locations of significant correlation between the baseline ADAS cog score and baseline rCBF SPECT measurement.

Figure 7 shows the locations of significant correlation between the change in ADAS cog over 6 months and change in rCBF.

Discussion

The present study was designed to determine whether TAI treatment with rember™ has the capacity to impact on physiological progression of AD as determined by molecular imaging. The study shows that treatment with rember™ alters the decline of rCBF on HMPAO SPECT and FDG uptake on PET over 6 months in AD. There is striking resemblance of these rCBF SPECT results to the neuroanatomical pattern of tau aggregation in AD (Figure 8).

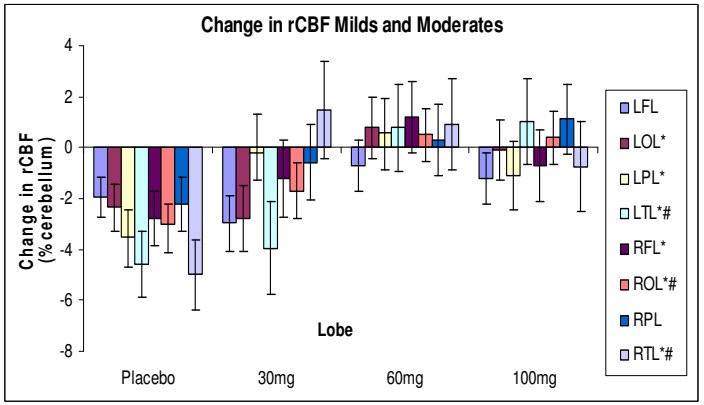

Figure 1: The region of interest changes in each patient group.
Key:
R – Right, L – Left. Lobes: TL – Temporal, PL – Parietal, OL – Occipital, FL – Frontal.
* p<.05 Placebo v rember™ 60mg comparison.
# p<.05 Placebo v rember™ 100mg comparison.

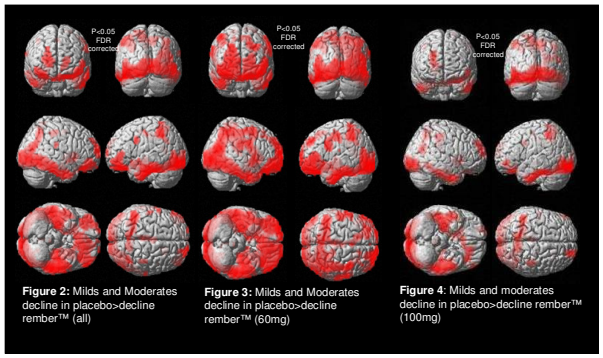

Figure 2: Milds and Moderates decline in placebo>decline rember™ (all)
Figure 3: Milds and Moderates decline in placebo>decline rember™ (60mg)
Figure 4: Milds and moderates decline in placebo>decline rember™ (100mg)

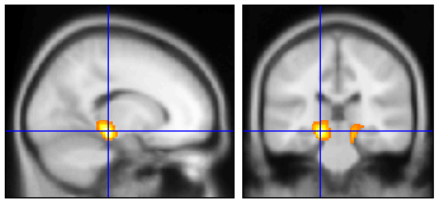

Figure 5. Areas of significance in the medial temporal lobes. Decline in placebo > change in rember™ treated groups, (p<0.05 cluster level corrected)

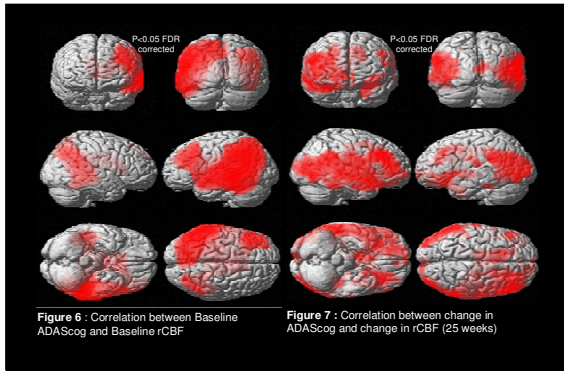

Figure 6 : Correlation between Baseline ADAScog and Baseline rCBF
Figure 7 : Correlation between change in ADAScog and change in rCBF (25 weeks)

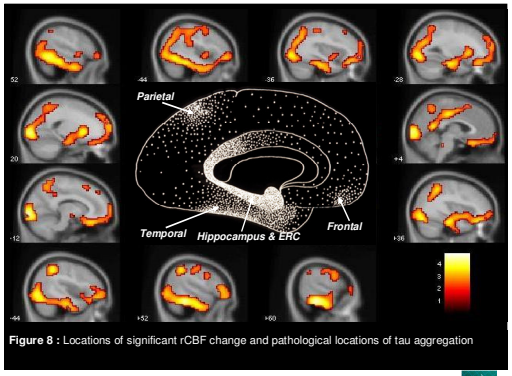

Figure 8 : Locations of significant rCBF change and pathological locations of tau aggregation

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