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CHALLENGES IN THE CONDUCT OF DISEASE-MODIFYING TRIALS IN AD: PRACTICAL EXPERIENCE FROM A PHASE 2 TRIAL OF TAU-AGGREGATION INHIBITOR THERAPY

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What is a disease-modifying treatment?

It appears intuitively obvious that an approach which targets a basic pathophysiological mechanism of the disease ought in principle to delay disability. This arises from the epidemiological evidence for a correlation between pathology and disability or cognitive impairment.

It is important to understand the fundamental difference between clinical trial time and epidemiological clinico-pathological time. Clinical trial evidence has a maximum operational range of 1 – 2 years. Epidemiological evidence, particularly based on cross-sectional cohort approaches, has a much longer time perspective. Since it is not feasible in a clinical trial to study disease-retardation over the epidemiological time-span, a statement about underlying mechanism becomes a proxy or a link for validating an expectation about long-term retardation of disease process which is not in principle provable in normal clinical-trial time.

The burden of providing this critical evidential link, between clinical trial evidence and broader epidemiological expectation, is carried by the concept of the "well validated biomarker". However, it is doubtful whether any currently available biomarker is operationally fit to carry this evidential burden on proven empirical grounds. The FDA's concept of "a surrogate endpoint that appears 'reasonably likely' to predict clinical benefit" appears all that may be feasible (1).

There is of course the obvious absurdity of embedding a particular narrow mechanistic approach to the exclusion of others. For example, Cummings (2) believes that only an approach which targets some step in the APP pathway can be considered disease-modifying, everything else being merely "neuroprotective". This is no more than a statement of belief in a particular school of thought regarding the molecular pathophysiology of clinical dementia in AD. There are other possibilities.

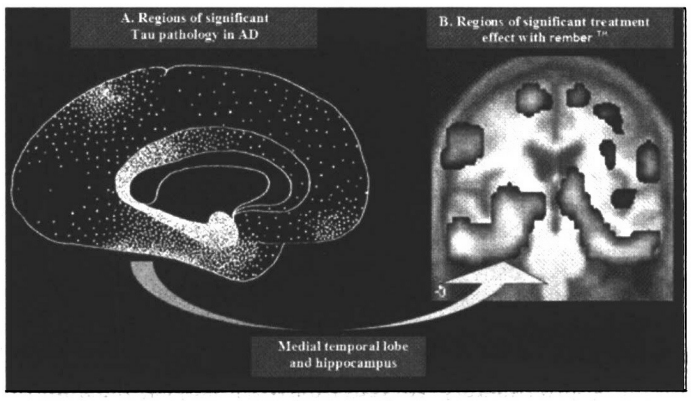
SPECT scan as indicator of cerebral metabolism and pathology

TAI (Tau Aggregation Inhibitor) therapy is directed towards inhibition of the Tau aggregation process which underlies the neurofibrillary degeneration of AD. The pathology of AD is highly correlated with the clinical deficit of AD. There is no technology for measuring the number and extent of neurofibrillary tangles in the brain *in vivo* directly. However, metabolic imaging techniques such as regional Cerebral Blood Flow (rCBF) Single Photon Emission Computed Tomography (SPECT) provide a technique for evaluating regional brain function. rCBF changes shown by SPECT have been shown to be correlated with Braak pathological stage by region and stage (3, 4). Several studies have shown that SPECT can be used to follow deterioration longitudinally (5, 6), a result which we have recently confirmed in our Phase 2 clinical trial. Finally, there is a strong body of evidence that the presence of the characteristic patterns seen on SPECT or PET scan at early clinical stages are predictive of future clinical deterioration (7-10).

Summary of Phase 2 molecular brain imaging results using SPECT

TauRx in its recent Phase 2 TAI therapy study found that both ROI (region of interest) and SPM (statistical parametric mapping) analyses of SPECT data (n = 135 subjects imaged twice) showed, as expected, that those receiving placebo had significant reduction in rCBF over a 24 weeks. Those treated with the drug showed no clinical decline over 24 weeks and the difference with respect to placebo was highly significant. The brain regions characterised by the most severe Tau aggregation pathology were the regions in which greatest treatment effect was demonstrated. This is illustrated in Figure 1.

Figure 1
Regions of Tau pathology (A) compared with regions of significant difference in subjects treated with MTC 60mg tds relative to placebo (B)



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We therefore believe that the EMEA criteria can be substantiated in the case of TAI therapy with rember™ (methylthioninium chloride, MTC). Specifically,

1) Molecular brain imaging outcomes show response to treatment.

2) There is correlation both between baseline severity and SPECT-scan deficits at baseline, and also correlation between response on brain scan and response on ADAS-cog following treatment.

3) Arguments can be advanced to support the proposition that changes in rCBF are compellingly related to an underlying pathophysiological process responsible for clinical dementia of the AD type.

The changes shown by functional brain scan provide a reasonable explanation both for the mechanism of action of MTC and for the clinical benefit seen with MTC treatment. The distribution of the MTC effects on SPECT and PET scans maps closely to the brain regions known to be severely affected by Tau aggregation pathology (Figure 1). These are also the brain regions where pathology is thought to explain the clinical deficits seen in AD (11, 12).

Choice of neuroimaging modality

According to Mani (13), "brain imaging modalities would, from a regulatory perspective, be considered surrogate markers if used as measures of efficacy in clinical trial" from an FDA perspective. For this purpose, it remains an open question whether the most appropriate approach is volumetric magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography or single-photon emission computerised tomography.

Volumetric approach

Although there is an intuitive appeal in volumetric approaches supporting disease-modifying treatment efficacy, there are no positive examples to date. As Aisen points out (14), volumetric outcomes may be influenced by fluid shifts or other factors including microinfarts in the hippocampus. Matsuda et al. (15) have compared directly the profiles of loss of grey matter and rCBF loss over 2 years and shown that volumetric changes occur much later than the deficits which can be shown by molecular imaging such as SPECT.

The explanation for the discrepancy may be found in the different time-courses of Tau aggregation pathology and neuronal destruction in different brain regions. Tau aggregation pathology can be measured in neocortical regions from Braak stage 2 onwards (16). By contrast, tangle-mediated neuronal destruction is much more restricted, becoming significant in the entorhinal cortex from Braak stage 3 onwards, in the hippocampus from Braak stage 4 onwards, and not appearing in neocortical regions until Braak stages 5 and 6 (17). Since the progression from one Braak stage to the next is very slow, taking approximately 10 years between stages, meaningful volumetric effects that are assumed to reflect neuronal destruction may not be measurable over a time-frame that is relevant to a clinical trial. Thus the intuitive appeal in the concept that a disease-modifying treatment should slow the rate of brain atrophy may be misleading in the setting of a confirmatory Phase 3 clinical trial.

SPECT vs PET functional neuroimaging

Although Dubois et al. (18) favour PET for diagnosis of prodromal AD and AD, the studies they quote are older studies using dated equipment. The Jagust paper (19) cited by Dubois was based on imaging data collected with a single headed gamma camera and assessed qualitatively. Recent studies using modern approaches such as Matsuda et al have demonstrated SPECT's ability to distinguish between very early AD and controls in a multicentre trial with a sensitivity >90% with a specificity of >80% (20). Similar studies have demonstrated the value of such quantitative methods in the analysis of rCBF data from modern SPECT systems (21, 22). The differential diagnosis between AD and non-AD dementia has also been investigated with advanced methods. Shimizu et al (23) found that SPECT had the ability to differentiate between LBD and AD (sensitivity, 85%; specificity, 85%), confirmed by Hanyu et al. (24). Nagao et al (25) found that SPECT had the ability to differentiate between FTLD and AD (sensitivity, 85.7%; specificity, 93.8%).

It is likely therefore that modern rCBF SPECT technology provides data of similar quality to that provided by PET. Although we support the general concept that molecular imaging approaches are extremely useful for supporting disease-modifying treatment approaches, there appears to be no particular reason for giving conceptual priority to PET over SPECT in clinical trials.

Conclusion

In summary, it is possible to provide reasonable objective biological support for disease-modifying efficacy of TAI therapy using molecular brain imaging as an indirect measure of neuronal function. There is also a reasonable level of conceptual validation of this approach from the prior literature. A case can therefore be made that it is feasible to support disease modifying claims using molecular brain imaging. Furthermore, it is also possible to demonstrate therapeutic efficacy at early disease stages that are confounded by cognitive reserve and other factors. A case could therefore be made that molecular brain imaging could provide a surrogate marker for disease modifying efficacy even at earlier disease stages when standard clinical outcome measures are operationally deficient.

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