

Evaluating MCI in AD Patients and the Effect of Symptomatic Drug Treatment

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Alzheimer's disease is a progressive brain disorder that causes a gradual and irreversible decline in memory and cognitive abilities. Until today the pharmacological therapy of AD is still limited to symptomatic temporary improvement or stabilization of cognitive performance and the reduction of neuropsychiatric symptoms of the disease. Five drugs are currently marketed for the treatment of AD including four cholinesterase inhibitors — tacrine, donepezil, galantamine, and rivastigmine — and one glutamate antagonist (memantine). However, owing to the extensive and multifocal nature of neurodegeneration in AD, the effects of transmitter modulators are modest. In recent years, a new therapeutic approach (disease modifying approach) has emerged. Unlike treatment that target symptoms, disease modifying therapies interact on the natural course of the disease by interrupting early pathologic events thus preventing underlying pathophysiologic processes. Although very promising, to date none disease modifying therapies have been clearly shown to be efficacious. In this context, the development of new drugs with symptomatic effect remains necessary.

The clinical development of drugs in Alzheimer's disease has been confronted with challenging methodological difficulties. Taking into account the financial stakes involved taking drug candidates to the phase III stage of development, and the risk of investing time and resources fruitlessly in the evaluation of poor candidate drugs, the crucial decision remains whether to proceed from phase II to phase III (Go/Nogo). The aim of phase II studies is to select a molecule likely to be effective in phase III, but also to eliminate candidate-drugs with an inadequate effect. No consensus currently exists on the best possible design of Phase II studies to inform the Go/Nogo decision optimally. At present time, neuropsychological-based tools are the most established and approved method of assessing outcomes in AD pharmacotherapy in part because they are widely available and do not require technological instrumentation. Because of the difficulties in demonstrating the efficacy of a candidate-drug using only clinical and cognitive tools, development of new assessment tools have become more important over the past few years [1].

Neuropsychological assessment

The Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) represent the most used cognitive scale to evaluate disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred as the core symptoms of AD. Several systematic reviews reported significant improvement in ADAS Cog score in MCI or AD subjects treated with donepezil, reflecting beneficial effects on cognitive status. In contrast, in healthy volunteers (HVT), donepezil induces a slight improvement in the retention of training on complex aviation tasks, verbal memory for semantically processed words and might improve long term visual memory. Moreover, two studies reported transient negative effects on episodic memory and no improvement in the Cambridge Neuropsychological Test Automated Battery (CANTAB), a computer-based cognitive assessment system consisting of a battery of neuropsychological tests.

EEG recording

It was recently reported that the electroencephalogram (EEG) could be a technique to predict the evolution of the Alzheimer disease [2]. **Resting-state EEG** is a suitable technique for monitoring the effects of pharmacological interventions because it is a highly reproducible condition that does not depend on task difficulty and subjects' anxiety and cooperation. Data available in the literature indicated that long- and short-term treatment with donepezil reduced significantly the deterioration of EEG spectral activity and REM sleep EEG disturbance observed in AD patients correlated with cognitive improvement rate on the ADAS-cog. In a small study, it has been demonstrated the ability of a **qEEG variance** combined with a delayed recognition memory task to

measure accurately treatment effects on patients with AD. In healthy elderly subjects, a single dose of memantine has been shown to compensate **diurnal vigilance** fluctuation measured by EEG recording.

Another EEG component, the P300 is of special interest as it is related to brain functions such as cognition and attention, which are severely impaired in patients with dementia. In AD patients performing auditory and visual oddball tasks, significant P300 latency changes were observed already during the first month of donepezil administration and were significantly correlated with various neuropsychologic tests scores changes. It has been suggested an effect of donepezil more evident, in the advanced stage of AD. EEG studies seems to confirm the validity of neurophysiological measurements as an additional instrument to evaluate the pharmacologic response to drug in patients affected by cognitive impairment since the effect of donepezil was rapidly and consistently evident. However there is a lack of data on healthy people.

Measurement of imaging markers

Neuroimaging techniques, which can reliably and noninvasively assess of neuroanatomy, chemistry, physiology and pathology, also hold promise as biomarkers. Neuroimaging is based on two different methods: MRI with different acquisition sequences; metabolic imaging by PET scan [3].

The clinical trials, using **structural MRI technique** to quantify the effect of drugs on brain structure volume changes, have confirmed that hippocampus was the most sensitive structure to change in AD patients exposed to donepezil or memantine treatment. These anatomical modifications have been shown to relate closely to neuropathologic and clinical data. Only one study failed to show alteration of hippocampal volume after 2 years of donepezil treatment in AD patients. Other anatomical structures such as white matter and whole brain, have also been studied but did not show any volume changes after donepezil therapy. These findings support the feasibility of using hippocampal atrophy detection by MRI as outcome measures in dementia treatment trials. However, shorter-term effect of these drugs has not yet been investigated in healthy subjects and AD patients.

Functional MRI is uniquely suited for evaluation of cognitive- enhancing agents. In 2 cognitive paradigms of visual memory, donepezil has been reported to produce activation in the ventrolateral prefrontal cortex and in the fusiform gyrus in patients with MCI or AD. In another study, donepezil has been shown to reverse the deficit of activation in fronto parietal region during a working memory task in patients with MCI. Furthermore, in a context of sleep deprivation-induced episodic memory deficit, donepezil enhanced activation of cerebral regions involved in attention and memory encoding processing during a semantic judgement task. Lastly, it has been observed during an auditory attention control task, a decreased of the prefrontal cortex and anterior cingulate cortex activation after memantine administration. Despite the limitations inherent to methodological problems and small sample size of these studies, results point to specific cortical substrates underlying the actions of donepezil and memantine, which can be tested in future studies. It appears as a sensitive imaging marker for very short-term therapy.

The **(18)F-fluorodeoxyglucose (FDG-PET)** technique was used in clinical trial to detect biochemical changes in tissue that precede anatomical changes. A study conducted in resting conditions have demonstrated that treatment with donepezil in AD patients may slow the decline in functional brain activity in right parietal lobe, left temporal lobe and right and left frontal lobes. In addition, it has been showed that the metabolic changes induced by donepezil, during a passive audio-visual stimulation, were limited to the right hippocampus and the left prefrontal cortex and independent of effects on cognitive performance. Finally, in patients treated with memantine for 52 weeks, it has been reported that glucose metabolism in all brain areas studied was preserved longer.

In conclusion, the physiological endpoints mentioned above might constitute a set of surrogate markers of cognitive-enhancing drug response. More sensitive neuropsychological tests or physiological endpoints like imaging and electrophysiological techniques could be relevant as biomarker of pharmacological intervention and could improve the selection of more efficient drug during the development of new compounds.

References

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