MCI Clinical Trials Within the New Alzheimer´s Criteria

Mild cognitive impairment (MCI) aims to identify cognitive decline in its earliest stages. Episodic memory impairment is typically a common cognitive marker in those with MCI who progress to AD-dementia, and each year around 10 to 15 per cent of individuals with amnestic MCI are diagnosed with AD-dementia. Nowadays, there are no therapies that can prevent the conversion from MCI to AD-dementia. However, studies conducted with cholinesterase inhibitors have shown a modest cognitive improvement in MCI subjects (selected using the Petersen criteria) compared to placebo, but failed to prevent conversion from MCI to AD-dementia. In the Petersen study, donepezil was associated with a lower rate of progression to AD-dementia during the first year of treatment, but the rate of progression to AD-dementia was similar to placebo at the end of the three-year double-blind study. Rofecoxib, a selective COX-2 inhibitor, also failed in delaying progression to dementia. These trials, cumulatively, have involved more than 5000 MCI participants.

The MCI population is now requested for the majority of new studies due to drugs targeting beta amyloid in Phase II and III testing, failing in mild to moderate Alzheimer cases. The expectation is that positive results are more likely to be achieved with earlier treatment initiation for a potential disease modifying treatment (DMT), before the neuropathology has progressed to the advanced clinical dementia stage. So now the approach is to target early stages of the disease. In 2014 and beyond, there will be at least eight therapeutic interventional trials recruiting for prodromal AD-dementia, so this will be a highly competitive area. This approach is consistent with the strategy implemented for prodromal AD-dementia, so this will be a highly competitive area. Other chronic diseases, where it has been found that earlier is better.

The new NIA-AA research criteria for MCI require: 1) change in cognition recognised by the affected individual or observers; 2) objective impairment in one or more cognitive domains; 3) independence in functional activities; and 4) absence of dementia. And the diagnostic confidence for AD-dementia is enhanced by utilising biomarkers for amyloid-beta deposition and neuronal injury. The impairment in MCI patients is not always progressive, with a proportion of cases reverting to normal or remaining stable at follow-up. Longitudinal studies demonstrate the value of using biomarkers in the selection of subjects, with MCI more likely to progress in severity.

These pre-dementia trials are going to be large in patient numbers, and long (18 to 24 months), a great barrier to drug development, as well as bringing an increase in cost. It should be noted that MCI studies, despite global site involvement, would have relatively low recruitment rates (less than 0.40 patient/site/month, depending on the inclusion/exclusion criteria) and a high screen fail rate (over 60 per cent). For example, in the ongoing prodromal AD-dementia trial of Merck’s MK-8931 in early-stage patients (APecS Study), the inclusion/exclusion criteria are much more restrictive, requiring biomarker information as entry criteria: positive screening amyloid imaging PET scan using [18F]flutametamol tracer or positive screening CSF tau:amyloid-β42 (Aβ42) ratio. Also, it is to be noted that there are subjects with conflicting biomarker results. In a recent paper, Petersen et al. analysed biomarker distributions in the Mayo Clinic Study of Aging (population-based). 126 subjects met the clinical criteria for amnestic MCI, and had MRI, FDG PET and PiB PET scans at the time of diagnosis. 14 per cent of the subjects were biomarker negative and 28 per cent presented only with neurodegeneration and no amyloid.

In the majority of the cases, people with MCI are not yet patients and usually do not exist in electronic health records (EHR) as such. A search would have to piece together a number of disparate signs and symptoms, which even in configuration are neither sensitive, nor specific for MCI. Plus progression to AD may have happened by the time the subject is contacted. While some centres use the MCI diagnosis, the vast majority of eligible treatment-naive, never diagnosed, potential subjects would not be easily found in EHR systems. Concern about early cognitive change such as that experienced by people with MCI is often first expressed to general practitioners (GPs). Improved public awareness of AD-dementia is driving older adults who experience memory problems to seek help at an increasingly early stage. As a result, case finding in primary care and general practice clinics has been a topic of intense study. A way to create a network with primary care level and the community will be needed so that patients with MCI will be referred to potential clinical trial study centres.

Remaining questions that ongoing studies will hopefully provide answers to include: Will the new MCI studies show an effect of DMTs? Will patient biomarker-based selection into these studies be a critical factor for success? Will we get clinical and biomarker congruent results? How will the regulatory agencies worldwide react to the new data?

References

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