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TASK FORCE ON ALZHEIMER'S DISEASE TRIAL METHODOLOGY: RECRUITMENT AND RETENTION, DATA MANAGEMENT AND ANALYSIS. THE USE OF IMAGING IN RECRUITMENT: MAINTENANCE AND METHODOLOGICAL ISSUES IN ALZHEIMER'S TRIALS

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Abstract: Imaging has been used in clinical trials for decades and has proven a useful biomarker in many disease states. Although imaging is not widely used in clinical practice for AD patient care, many pharmaceutical and biotech companies have relied on this technique for eligibility, safety and efficacy roles in their trials. In this overview, issues with standardization, validation and regulations will be discussed in order to gain a better understanding of the benefits, risks and impact on study conduct of adding imaging to Alzheimer's disease clinical trials.

Key words: Alzheimer's disease, imaging, MRI, PET.

Practical aspects of imaging in clinical trials

Imaging is already widely used in AD clinical trials and that experience has provided a good understanding of the issues that can arise. The most widely used imaging method is magnetic resonance imaging (MRI). One of the primary advantages of MRI is that it does not use ionizing radiation, which increases patient acceptance and simplifies the ethics committee approval. However, claustrophobia remains a problem due to the confined space of the scanner. The MRI scan is not physically or mentally demanding; the subject simply needs to lie still during the examination. However experience has shown this can be difficult in the AD population. Compliance will improve with prodromal AD patients. The other imaging technique used in AD trials is positron emission tomography (PET). PET exposes patients to radiation, thus there are extra considerations to be taken for IRB approval. PET acquisition costs are higher than MRI plus there are the tracer costs . The FDA announced in August this year the availability of a draft guidance for industry entitled ''Standards for Clinical Trial Imaging Endpoints.'' The purpose of this draft guidance is to assist sponsors in the use of imaging endpoints in clinical trials of therapeutic drugs and biological products.

Low Hippocampus volume used at screening for enriching patient population

A proven and objective method of targeting patients with Alzheimer's disease (AD), before the appearance of overt clinical symptoms, is an important goal for effective treatment and even prevention or prolongation of the time to development of AD. Low hippocampus volume has been shown in numerous studies to be reliable predictor of progression from mild cognitive impairment to AD dementia in a time frame of 2-3 years (1). Thus, hippocampus volume can help target the right patients for prodromal AD studies.

Recently, the Critical Path Institute Coalition against Major Diseases (C-Path CAMD) Biomarker Working Group received a positive response from the European Medicines Agency (EMA) via a Qualification Opinion of low hippocampus volume (atrophy) by MRI for use in Regulatory Clinical Trials in Pre-dementia stage of Alzheimer's disease. This is a significant first step toward the broad use of low hippocampus volume for patient selection in clinical trials, but several scientific, methodological and operational issues remain leaving much work to be done. One of the biggest challenges will be standardization and validation of the measurement and development of normative data to set the objective and optimal threshold for 'low' hippocampus volume. One facet of this is already being addressed by the hippocampus consensual definition, a harmonized protocol project (2, 3). The likelihood for success seems high as similar markers have been used in other diseases. A classic example is bone mineral density (BMD) in osteoporosis trials. Low BMD is an indication of compromised bone strength and increased risk of future fracture, with fracture being the primary endpoint of Phase 3 registration trials in this indication. Standardized methods (4) and large normative databases have been developed (5). This, combined with the WHO definition of osteoporosis (6), provides a widely accepted and universally used criterion for patient selection.

There may also be implications to be considered for the drug label after approval as well as for sites to perform methods locally. If patients were selected by their hippocampus volume for entry into a trial, it is possible that this may end up on the drug label and treating physicians would have to be able to measure a patient's hippocampus volume prior to prescribing the drug. Some tools exist for this purpose (7, 8) but more work remains to make them more user friendly and widely available. While diagnostic criteria are simple and comparatively easy to develop and use for dichotomous assessments, this is a challenge when the parameter is a continuous variable which

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represents a gradient of risk. Careful investigation will be necessary to find the optimal cut point that maximizes sensitivity and specificity as well as positive predictive value (9). However, being that all patients must obtain a pre-study MRI scan for safety screening purposes for anti-amyloid therapies, and with the challenges associated with CSF biomarker collection and standardization, hippocampus atrophy by MRI may turn out to be a strong biomarker for patient selection and enrichment.

Harmonization of protocols for the manual tracing of the hippocampus: An EADC-ADNI joint effort

For hippocampus volume to have broad acceptance and become a relevant and useful biomarker of AD, there must exist a universally accepted definition of the hippocampus, as depicted by MRI. The project of Frisoni and colleagues (2, 3) will develop a harmonized protocol for the estimation of hippocampus volume with manual tracing on MRI The preliminary results were presented during the AAICAD meeting in Paris (10) with plans to finish defining the harmonized protocol by end of 2011. This will accomplish a major milestone towards the effort of standardization of the hippocampus volume. From there is some work to implement this approach at central reading centers for clinical trials. Before this can bring value in the clinic, software tools will need to be developed. These software tools will need to delineate this harmonized protocol either via a fully automated method or one that combines an automated step followed by manual editing. A mechanism by which these tools are validated will be required.

FDA advice letter on screening and monitoring patients for anti-amyloid therapies

FDA has suggested that clinical trials using anti-amyloidal therapies screen and monitor patients for amyloid related imaging abnormalities ARIA-E and ARIA-H (11). This is now being done at screening for safety purposes and patients enrolled into these types of trials undergo this type of evaluation. This will surely have an impact on patient recruitment as candidates with abnormal findings on baseline examinations will be excluded from participation. However, subjects with a clear scan can enter trials with more confidence in their health status and baseline condition. This can help with patient retention as patients likely to experience adverse events associated with treatment are now being excluded and those that are recruited will be carefully monitored. Regulations in different countries call for an additional layer of scrutiny and thus local regulations must also be considered.

The FDA criteria concern AD trials of longer than 3 months in duration with compounds targeting A-beta in the brain. Patients must have an MRI at screening to screen for greater than 4 cerebral micro hemorrhages, or a single area of superficial siderosis, or evidence of a prior macrohemorrhage. The microhemorrhage cutoff is relatively generous, excluding a low percentage of patients. There are additional recommendations regarding minimum frequency of MRI monitoring and discontinuation criteria. This stems from the need to monitor patients for treatment side effects such as vasogenic edema or ARIA- E. These additional MRI exams can impose an additional burden on patients and impact on retention. However the rigorous monitoring for treatment related adverse events addresses safety concerns of patients, investigators and ethics committees, ultimately broadening the appeal of such trials and making them possible to conduct.

PET scans

Since the discovery of 11C PiB amyloid imaging tracer, several 18F tracers have been developed including: Avid Radiopharmaceutical's florbetapir, GE's flutemetamol and Bayer's florbetaben (12). Currently florbetapir is awaiting decision from the FDA on their phase III registration trial. In the meantime, trials have been using some of these experimental imaging agents to demonstrate that the therapeutic agent may be able to move this biomarker in the brain. Additionally, amyloid positivity is now being considered as an inclusion criterion for prodromal AD trials. This has some challenges and limitations which include the availability of the tracer, PET scanner access for all sites and radiation exposure for the entire patient population compared to just within a PET sub-study as has been historically done for efficacy measures. On the other hand, a positive amyloid PET scan may be a more attractive option than an atrophic MRI due to its higher specificity for AD. The literature has shown strong conversion data from MCI to AD as well as normals to AD, with the presence of a positive amyloid scan (13). The possibility that this technique may soon be approved by the FDA and ultimately insurance coverage also makes it an attractive biomarker for use in clinical trials. There are minimal changes seen longitudinally for amyloid but the screening potential could be just as good if not better than other biomarkers. Similar to hippocampus volume based on MRI, development and validation of the assessment guideline for amyloid positive scan needs to be established. Issues previously mentioned apply regarding patient consent and retention due to the added radiation exposure.

In addition to amyloid PET, trials have also looked at cerebral metabolic rate of glucose in the brain by 18F FDG PET scans, although FDG has not been used very often as a screening tool for AD in trials.. 18F FDG is easier to incorporate as it is widely available and even correlates longitudinally with cognitive measures (14). As the 18F FDG tracer is much more widely available, there could be better patient retention associated with the ability to use almost any PET facility, as opposed to amyloid where careful selection of the PET facility is needed to ensure proximity to the tracer.

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