The Role of Amyloid Biomarkers in Accelerating Alzheimer's Disease Drug Development

PEER REVIEWED

Shortly after the last issue of CNS Watch (Volume 3 Issue 1) which reviewed the recent FDA guidance on biomarker and patient reported outcome qualification, the European Medicines Evaluation Agency (EMEA) released its first Qualification Opinion of Alzheimer's Disease Novel Methodologies/biomarkers for BMS-708163 for public opinion. This opinion addresses whether the use of two cerebral spinal fluids (CSF) related biomarkers (AB1-42 and total tau) are qualified in selecting subjects for trials in early Alzheimer's disease (AD). This CNS watch will summarise this opinion, as well as the utility of amyloid targeting drugs and biomarkers in AD drug development, including the possible use of amyloid-based surrogate biomarkers as primary efficacy variables to accelerate AD drug development.

The EMEA biomarker qualification team carefully considered whether the positive signature of CSF biomarkers was qualified to predict the evolution to dementia in patients diagnosed with Mild Cognitive Impairment (MCI) by reviewing publically available data submitted by Bristol Myers Squibb. Analyses were restricted to prospective longitudinal studies that evaluated the sensitivity and specificity of these CSF biomarkers over a long term (>1 year) period. Despite variable entry criteria, all of the prospective longitudinal studies that informed the accuracy of CSF biomarkers were performed in populations defined by the Petersen criteria (which are less specific than the more recent Dubois criteria, as the latter are based on a very specific episodic memory measure). BMS expressly requested qualification of these amyloid biomarkers as related to the application of the Dubois criteria for prodromal AD[1,2].

The qualification team concluded that overall studies were supportive of the concept that a positive CSF signature predicts the evolution to dementia, and the Committee for Medicinal Products for Human Use (CHMP) qualification opinion stated that "In patients with MCI a positive CSF biomarker signature based on a low AB1-42 and a high T-tau is predictive of evolution to AD-dementia type. This is based on the results of a meta-analysis which showed that the sensitivity of the combination AB1-42+total tau to predict AD type dementia was 0.87, 95% CI 0.80-0.95, the specificity 0.70, 95% CI 0.57-0.83 and the positive predictive value of 0.65, 95% CI 0.53-0.77. Overall the accuracy is considered sufficient to provide the desirable population enrichment of patients at risk of developing AD dementia. In fact the biomarker signature of low AB1-42 and high Tau has a relatively high sensitivity that allows the exclusion of subjects with a low likelihood of developing dementia when it is not present." (www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2011/02/WC500102018.pdf).

This is the first opinion released by either the EMEA or the FDA on biomarker qualification. Representing a major step forward in the quest for relevant biomarkers for use in AD clinical trials, it may even assist the pursuit of a claim for disease modification (DM) in AD. The main focus of this qualification was to provide a valid and reliable technique to enable accurate categorisation or selection of patients in the prodromal stages of AD. As such it would be seen largely as a predictive biomarker rather than a pharmacodynamic biomarker to be used as a surrogate for efficacy. Having a qualified biomarker may enable more accurate evaluation of AD drugs that were developed to inhibit the production or aggregation of beta amyloid or to enhance its clearance, ultimately increasing the chances of marketing approval. Unfortunately, to date the numerous drugs and vaccines (>20) developed targeting amyloid (to treat symptoms of AD or modify the course of AD based on the amyloid cascade hypothesis) have largely failed, causing some researchers to question even the validity of the approach.

These failed trials along with various amyloid-based approaches to AD drug treatment were recently reviewed at the 7th annual scientific meeting of the International Society of CNS Clinical Trials and Methodology (ISCTM) in Washington DC http://www.isctm.org/. Although somewhat debatable, it was generally agreed upon that most amyloid-targeting drugs/vaccines have mechanistically been able to impact their intended targets in the predicted manner, they have not proven to be clinically efficacious, and in some cases are even deleterious. This may be

due to a variety of methodological and design flaws which include underpowering, poorly chosen outcome measures, short timeframes, and inappropriate subgroup analyses. However, the most salient factor contributing to these failed trials has been subject inclusion criteria, as it was determined that these various amyloid-based interventions may have all been administered much too late in the course of AD illness. The general sentiment was that some good drug candidates were simply applied at the wrong stage of illness. Therefore, investigating amyloid agents in patients who are in the prodromal or even "pre-prodomal" phases of illness would be more advantageous when assessing efficacy. While it was also suggested that the presence of a measurable biomarker implied that it was far too late to significantly improve the disease state, nevertheless it is accepted that having qualified biomarkers in the arsenal of CNS drug development tools is beneficial.

The session also summarised the circumstances under which a biomarker/unvalidated surrogate measure could be adopted as a primary efficacy variable, with accounts provided from representatives of both US and EU regulatory agencies. These represented personal views and not those of their respective agencies. A "surrogate marker" can be defined as "...a laboratory

measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy"[3]. The FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials, establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. They may also grant approval on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity [4]. Obviously, there is no accepted definition or clear threshold of evidence supporting the term "reasonably likely" which is subjective and open to interpretation.

As such, surrogate markers remain insufficiently understood, and none to date are validated for use as sole primary measures of effectiveness in definitive trials of CNS investigational drugs. Surrogates are sought after as they have the potential to significantly decrease both the duration and size of studies, shorten development timelines, save money, and accelerate approval. Surrogates are also particularly useful when the clinical benefit of the drug is likely to be well in the future and when there are no other therapies. Surrogates may be less useful when clinical effects are easily measured in a reasonable timeframe. Therefore surrogates are often proposed as a more realistic way to support a claim for slowing down disease progression in AD[5] which remains an ambitious goal for any CNS drug development company.

US regulatory authorities have implied that the disappointing AD trial results to date fail to lend credence to the utility of amyloid-targeted surrogates in AD trials, suggesting that the preferable but as yet undefined indication for testing an amyloid-based unvalidated surrogate would be in the setting of the very early stage of AD. In this case subjects would be included in trials ,even though they are essentially asymptomatic, but may be at high risk of AD at a later time, based on some combination of risk factors, including, but not limited to, family history, apolipoprotein E, genotype status, medical history, etc. In this trial setting, the assessment of traditional AD outcome measures such as the ADAS-Cog or CGIC/CBIC would be impossible, or at best irrelevant. Instead, a correlation between the effects on a surrogate marker and an appropriate clinical outcome (such as cognition either as a single scale or domain) could be considered for a disease modification claim in AD, in which a slowing of progression, not prevention, is evidenced. In these very early patient populations a defined change in a biomarker and cognition, even with no global measure provided, may be adequate for approval, pending an advisory meeting to support the validation of the biomarker[5].

European regulators also identified the need for a link or plausible correlation between a biomarker (such as a PET ligand that labels beta amyloid plaque in the brain) and a desired clinical outcome. To facilitate this, they have essentially proposed a two-step approach which shows a delay of progression based on initial signs and symptoms and followed by a correlation with biomarker data to support a disease modification claim in AD[6]. Because a "disease modifying effect cannot be established conclusively based on clinical outcome data alone, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. As this is difficult to achieve without an adequately qualified and validated biomarker, a two-step approach may be more suitable. If in a first step, delay in the natural course of disease progression can be established based on clinical signs and symptoms of the dementia condition, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a convincing package of biological and/or neuroimaging data, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered" (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003562.pdf).

Of note, on January 20th, the FDA's Peripheral and Central Nervous System Advisory committee failed to recommend approval of florbetapir, a PET ligand-targeting B-amyloid, but unofficially sanctioned florbetapir if the company (Avid, purchased by Lilly) were to step up educational initiatives for training programmes to ensure accuracy and consistency of imaging readers, bringing this two-stage approach closer to realisation (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM244441.pdf).

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