CTAD Task Force Paper

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What Have We Learned from Expedition III and EPOCH Trials? Perspective of the CTAD Task Force

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Abstract

Although the results were disappointing from two recent clinical trials of amyloid-targeting drugs in mild-to-moderate AD, the trials provided information that will be important for future studies, according to the EU-US CTAD Task Force, which met in November 2017 to discuss the EXPEDITION3 and EPOCH trials. These trials tested two of the predominant drug development strategies for AD: amyloid immunotherapy and BACE inhibition in populations largely composed of mild AD dementia patients. The results of these trials support the emerging consensus that effective amyloid-targeted treatment will require intervention in early, even pre-symptomatic stages of the disease. Further, the Task Force suggested that a refinement of the amyloid hypothesis may be needed and that other hypotheses should be more fully explored. In addition, they called for improved biomarkers and other outcome assessments to detect the earliest changes in the development of AD.

Key words: Alzheimer's disease, therapeutic trials.

Introduction

Two recent Phase 3 trials of amyloid-targeting drugs recently concluded with disappointing results, adding to the perception among many in the Alzheimer's disease (AD) community that failed trials indicate no progress in treating this devastating disease. However, at a meeting of the Clinical Trials in Alzheimer's Disease Task Force (EU-US CTAD Task Force) in November 2017, investigators from industry and academia agreed that there is a great deal to be learned from these studies that tested two of the major drug development strategies for AD: amyloid-β (Aβ) immunotherapy and beta-secretase (BACE) inhibition.

Expedition3

Expedition3 was the third major Phase 3 study of solanezumab, a humanized monoclonal antibody developed by Eli Lilly and Company to treat AD. Non-clinical studies suggested that the drug, which targets the mid-domain of the Aβ peptide, acutely reversed memory decline in transgenic mouse models but did not clear plaque deposits in the brain (1) after a single dose. Treatment with m266.2 (the murine analogue of solanezumab) for 5 months did slow the deposition of amyloid plaques in transgenic mice (2). One hypothesized potential mechanism of solanezumab was that the antibody provided a peripheral "sink" for toxic soluble forms of Aβ (3). Alternatively, approximately 0.1% of solanezumab (and most monoclonal antibodies) cross the blood brain barrier, and this small amount

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entering the central compartment suggests another potential mechanism for solanezumab. The transgenic mouse and other laboratory studies, and Phase 1 results, convinced the company to launch a Phase 2 trial, which was designed to assess safety and target engagement based on biomarkers. Subsequently two large Phase 3 trials, known as EXPEDITION and EXPEDITION2, in patients with mild-to-moderate AD, were initiated. Neither of these studies showed a significant signal in the primary outcome – a change from baseline on the Alzheimer's disease assessment scale-11 item cognitive subscale (ADAS-cog11) (4, 5) and the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) instrument (6) in EXPEDITION; and the ADAS-cog 14-item subscale (ADAS-cog14) in patients with mild dementia only in EXPEDITION2. However, post-hoc subgroup analyses of pooled data from the two studies suggested that there may have been some benefit in patients with mild AD, although a larger study would be needed to confirm this finding (7). These clinical results from EXPEDITION and EXPEDITION2 prompted the EXPEDITION3 trial in more than 2100 patients with mild AD and evidence of amyloid pathology.

The top-line results from EXPEDITION3 were presented at CTAD 2017. The overall conclusion was that patients treated with solanezumab did not show a statistically significant slowing of cognitive decline as determined by the ADAS-cog14 compared to those treated with placebo (8). Further analysis of these clinical results combined with extensive biomarker studies provided additional learnings. First, these data showed that the peripheral sink hypothesis does not appear to be a good framework to establish dose. An alternative method to assess central target engagement is by measuring cerebrospinal fluid (CSF) levels of Aβ1-40 and Aβ1-42 (either "total," the amount bound to antibody in addition to unbound Aβ, or "free," unbound Aβ alone). While modest amounts of target engagement based on CSF were demonstrated, these were not sufficient to produce the desired clinical benefits. Therefore, in future studies of solanezumab being conducted in preclinical AD, the dose will be quadrupled.

Another important insight drawn from magnetic resonance imaging (MRI) studies showed that smaller temporal lobe volumes at baseline indicating greater atrophy were predictive of more rapid progression. All patients showed declines in volumetric MRI measures over the course of the study, which likely represented a combination of age-related and AD-related decline. The confound of age-related volume loss could limit the potential of volumetric MRI to be used as a surrogate for clinical effect of an investigational drug.

Tau levels were determined both in CSF and by positron emission tomography (PET) scanning in a subset of patients. Surprisingly, these studies showed that although all study participants had Aβ pathology and mini-mental state exam (MMSE) scores between 20-26, some did not show evidence of tau pathology. The fact that younger people had relatively greater amounts of tau at baseline compared to older patients suggests that younger people with mild AD had more "pure" pathology while older participants had more mixed pathology. Elevated tau levels at baseline were also predictive of a greater rate of progression on the ADAS-cog (9), although the change in tau levels did not correlate with the change in cognitive scores. Some participants who had mild AD symptoms for 10 or more years had little or no tau. Since all patients in the trial were positive for amyloid plaques, the reasons for the lack of tau pathology in these individuals are not clear. Another problem that may have compromised the utility of tau measures was the use of different scanners and non-standardized white matter regions of interest.

EXPEDITION3 also provided interesting data relevant to the use of amyloid positivity as an inclusion criterion for a clinical trial. For inclusion, participants had to have a positive amyloid scan as determined by a visual read. When PET scans for these participants were quantified using the typical metric of whole brain cortical-to-cerebellar standardized uptake value ratio (SUVR), the mean was 1.51, whereas mild patients in EXPEDITION and EXPEDITION2 had mean SUVRs of only 1.31, suggesting that clinically mild patients in EXPEDITION3 may have had more advanced pathology than those in EXPEDITION and EXPEDITION2. This observation suggests that small differences in amyloid load at baseline may have a significant impact on a trial, and that more precise methods for establishing inclusion criteria may be needed.

The disappointing results in EXPEDITION3 also indicate a need for more sensitive readouts and theragnostic biomarkers in future studies (10, 11). However, Task Force participants agreed that solanezumab at the dose tested may have had a mild but not clinically meaningful effect in mild AD dementia. In contrast to the secondary analyses of EXPEDITION and EXPEDITION2, in EXPEDITION3 there was no evidence to indicate it reduced amyloid plaque load. Exploratory analyses did show an effect of treatment on temporal lobe atrophy that was nominally significant ($p=0.013$); however, this finding will require replication. While baseline flortaucipir PET severity did predict rate of cognitive decline, as seen in other observational studies (12), the lack of correlation between change in flortaucipir PET and change in cognition was disappointing. Further work with larger sample sizes and methods for PET analyses will be necessary to explore this topic further.

EPOCH

EPOCH was a Phase 2/3 trial in mild-to-moderate AD of the beta-secretase (BACE-1) inhibitor, verubecestat (MK-8931). Merck terminated EPOCH in February 2017 when the data monitoring committee concluded that

there was no clinical benefit to patients receiving the drug. The results of the study were presented at the full CTAD meeting on December 12.

Merck's decision to test verubecestat in a large pivotal study followed studies showing that the drug markedly reduced Aβ production in animal models and humans and was safe and well-tolerated in Phase 1 human studies (13). The doses tested in EPOCH were based on the phase 1 studies. While the clinical results of EPOCH were disappointing, the question facing the Task Force was whether this trial adequately tested the hypothesis that inhibiting BACE-1 would suppress Aβ production, leading to a slowing of progression. On this question, the answers were informative: There was clear evidence of target engagement, and the intended pharmacology (inhibition of BACE) was indeed present, with close to maximal suppression of Aβ production as measured in the CSF. In the subgroup of patients who had either CSF or PET studies performed at baseline, the large majority had changes consistent with and confirming the clinical diagnosis of AD, and the study was sufficiently large and long to have detected a treatment effect had one been present. The level of progression was sufficient to have detected an effect and rater performance was good. There was no evidence of off-target effects that would have affected cognition, and the drug appeared to be safe and tolerable despite some observed adverse effects. An amyloid PET sub-study with imaging at baseline and endpoint showed that there was a modest but consistent and dose-dependent change in SUVR, suggesting a reduction in amyloid plaques. Increase of hippocampal atrophy in the treated group have also to be carefully studied

The investigators concluded that amyloid production does not drive the ongoing disease process once patients have progressed to mild-moderate AD dementia. These results suggest that BACE inhibition is unlikely to be effective in patients who already have dementia. Indeed, animal data suggest that there is a critical window for BACE inhibition to rescue cognitive decline despite reductions in amyloid (14). While more biomarker data are needed to better characterize the critical window, the results of the EPOCH trial suggest that BACE inhibition should be tested at an earlier stage of disease.

A prodromal trial of verubecestat is fully enrolled. While the results of EPOCH suggest that the probability of success in this trial may be lower than originally believed, the rationale for looking at BACE inhibition at the prodromal stage of illness was that the disease might present a more tractable target for intervention when a lower burden of disease is present, and this remains an important hypothesis to test. Therefore, Merck plans to continue the study, with results expected early in 2019 .

Implications for the amyloid hypothesis

The results of these two studies have advanced understanding of the role of amyloid in AD and the potential for slowing or reversing the disease by targeting amyloid. In EXPEDITION3, solanezumab clearly showed some degree of central target engagement based on CSF and produced what could be construed as a small clinical signal yet did not provide meaningful clinical benefits. The nature of this small but possibly non-meaningful signal was similar to what was seen in previous mild subgroup analyses. Verubecestat also hit the intended target and reduced Aβ synthesis but yielded no clinical signal.

Could these results support a refinement of the amyloid cascade hypothesis (15)? Sperling and colleagues hypothesized an interaction of amyloid and tau in preclinical AD (16) where the gradual accumulation of tau with advancing age interacts with Aβ deposited via genetic or other age-related processes to accelerate the accumulation and spread of tau as well as synaptic dysfunction, glial activation, and neuronal loss. This hypothesis is supported by studies showing high levels of tau pathology in early symptomatic AD (17), and early results from the A4 study showing that cognitively normal, amyloid-positive individuals with higher tau levels have lower memory scores.

Both BACE inhibitors and anti-amyloid antibodies are being tested in presymptomatic AD in the A4, DIAN, and API trials. Even negative results in these trials may not necessarily indicate that the amyloid hypothesis is wrong, but could suggest that even the presymptomatic stage is too late if amyloid has begun to accumulate, or that a combination of drugs are needed at this stage, e.g., a BACE inhibitor to stop production combined with an anti-amyloid antibody to clear plaques, or combinations of drugs targeting amyloid and tau (18). Furthermore, the toxic species of Aβ – if indeed there are toxic species -- are still unknown so there remain mechanistic aspects of the amyloid hypothesis that still require investigation across the entire spectrum of disease. Higher dose have also to be considered

Alternative hypotheses remain open (19-21). From a therapeutics standpoint, reversing tauopathy may be more important than clearing amyloid, although there are concerns that once tau pathology is established and self-propagating, it may not be possible to stop or reverse disease progression. What is clear to Task Force participants is the need for additional biomarkers and more optimal use of existing biomarkers (22). But biomarkers alone will not enable effective treatment. Biomarkers provide a window into what is happening neuropathologically, but do not explain the disease in its totality. A more comprehensive understanding of genetic and molecular pathways altered at earlier stages of disease will be required. Basic neurobiological studies of AD thus must continue in parallel with efforts to

discover and develop better treatments for the disease.

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