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Continuing Progress in Alzheimer's Disease Trials: Cause for Optimism

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The Alzheimer's disease (AD) community has been shaken by disappointing clinical trials for treatments created to slow or stop disease progression, including the recent failure of the Lilly Expedition 3 trial of solanezumab in mild AD dementia to meet its primary endpoint and the early halt to the Merck verubecestat study in mild to moderate AD. Nonetheless, there remain reasons for optimism based on an improved understanding of the pathophysiology and course of the disease and increasing collaboration among industry, academia, and regulatory stakeholders. Success is expected as the field adopts trial designs and endpoints appropriate for trials targeting early stage illness.

Cognitive change is the most relevant indicator of disease progression, represents the essential manifestation of the disease, predicts functional change, and can be measured using relatively inexpensive tools. However, since the cognitive decline that characterizes AD progresses slowly over decades, detecting a slowing of decline is challenging, particularly in the early stages. Optimizing drug dose thus typically requires lengthy and expensive trials; yet due to the enormous unmet need for AD treatments, pharmaceutical companies have taken the risk of initiating pivotal phase 3 trials even in the absence of adequate dose optimization studies. Consequently, there remains the possibility that treatment trials have failed due to inadequate dosing.

The slow progression of disease, in combination with substantial variability among individuals, creates additional problems for clinical trial design. Cognition represents a clinically meaningful outcome across all stages of disease and thus provides a powerful approach to drug development by potentially enabling trials conducted across different phases of disease to be submitted together for regulatory approval for a single disease. However, too many trials for AD treatments continue to use time-to-endpoint designs, with the endpoint being a clinical diagnosis of mild cognitive impairment (MCI) or AD. While clinical endpoints are clearly meaningful, they reduce the information gathered over time into one step, essentially throwing away information about gradual progression of cognitive impairment. As a result, this type of design results in a two- to three-fold loss of statistical power in comparison to using a continuous measure, such as cognitive performance, as an endpoint (1).

In recent years, drug development for AD has been revitalized by an emerging consensus on the need to share data and experience so that the field can maximize lessons from every trial. The Collaboration for Alzheimer's Prevention (CAP) is a good example of this paradigm (2). Through their involvement with CAP, investigators involved in the leading prevention studies currently underway or in the planning stages have agreed to a set of principles to ensure that data and biological samples are shared in a timely manner: screening and prerandomization baseline data within 12 months of enrollment completion and postrandomization data within 18 months of the completion or termination of a trial.

Increased lessons from ongoing trials will also be enhanced by the development and incorporation into studies of many non-cognitive biomarkers, including amyloid and tau positron emission tomography (PET) imaging. There has also been increased investment in initiatives aimed at improving trial efficiency through innovative recruitment strategies (3), creation of a standing network of clinical trial sites (4), and utilization of a centralized institutional review board (IRB).

Novel and potentially very effective drugs are in the pipeline. Although the failure of drugs that target amyloid has raised concern about the validity of the amyloid hypothesis, there remains substantial agreement among AD researchers that amyloid drives the AD process in the early stages, and thus that targeting amyloid in the preclinical or prodromal stages is most likely to have an impact in halting disease progression. There are also many other pathways that contribute to the development of AD and that may be modifiable with drug therapy, including tau, inflammation, insulin resistance, and metabolism. Drugs designed to enhance neurogenesis or neuroprotection may be useful; and it may turn out that combination therapy will be needed to fully arrest the disease.

With the drugs that are currently available to remove aggregated amyloid or stop the overproduction of amyloid, two studies can and should be done immediately. These drugs, such as the anti-amyloid monoclonal antibody aducanumab (5) and the BACE1-inhibitor verubecestat (6), among others, offer the

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potential to stop disease progression before there has been significant neurodegeneration.

In the first of these two proposed studies, an anti-fibrillar amyloid antibody should be tested in a 3- to 4-year trial in clinically normal, preclinical AD participants selected on the basis of amyloid PET or CSF Aβ assessment. In a small pilot study, aducanumab showed that one-year of treatment in patients with prodromal or mild AD reduced the accumulation of amyloid and slowed cognitive decline in a dose- and time dependent manner. The primary outcome for a preclinical-stage trial would be a cognitive composite, with multiple secondary outcomes including patient- and informant-reports of function, computerized cognitive measures, amyloid PET, and tau PET.

The second proposed trial would demonstrate the feasibility of curing preclinical AD by normalizing amyloid generation in participants with autosomal dominant AD (ADAD) mutations by lowering the production of Aβ42 at least 15 years prior to the expected onset of symptoms. A BACE1 inhibitor or gamma-secretase modulator could be utilized in this study. While the study would take many years to complete, ADAD families have demonstrated a high degree of enthusiasm for such trials and a willingness to accept manageable risks.

These studies are possible now because of the collaborations and partnerships that have been built in recent years, and they are necessary to address the urgent need to address the AD crisis worldwide. The field is close to finding an effective treatment and must continue vigorous, creative efforts to achieve success.

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References

1. Donohue MC, Gamst AC, Thomas RG, Xu R, Beckett L, Petersen RC, et al. The relative efficiency of time-to-threshold and rate of change in longitudinal data. Contemp Clin Trials. 2011;32(5):685-93.
2. Weninger S, Carrillo MC, Dunn B, Aisen PS, Bateman RJ, Kotz JD, et al. Collaboration for Alzheimer's Prevention: Principles to guide data and sample sharing in preclinical Alzheimer's disease trials. Alzheimers Dement. 2016;12(5):631-2.
3. Sperling R, Cummings J, Donohue M, Aisen P. Global Alzheimer's platform trial ready cohorts for the prevention of Alzheimer's dementia J Prev Alz Dis. 2016;3(4):185-7.
4. Cummings J, Aisen P, Barton R, Bork J, Doody R, Dwyer J, et al. Re-engineering Alzheimer clinical trials: Global Alzheimer's Platform Network. J Prev Alz Dis. 2016;3(2):114-20.
5. Sevigny J, Chiao P, Bussiere T, Weinreb PH, Williams L, Maier M, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature. 2016;537(7618):50-6.
6. Kennedy ME, Stamford AW, Chen X, Cox K, Cumming JN, Dockendorf MF, et al. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS beta-amyloid in animal models and in Alzheimer's disease patients. Sci Transl Med. 2016;8(363):363ra150.