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EDITORIAL

One step forward to personalized medicine?

On June 7, 2021, Aduhelm (aducanumab) received an accelerated approval by the Food and Drug Administration (FDA) as the first disease-modifying agent for the treatment of patients with early Alzheimer's disease (AD). Despite its public health significance, the approval came with significant controversy over the drug's benefit-risk profile. In particular, there has been substantial criticism of the perceived low efficacy of Aduhelm as measured by the primary endpoint of two pivotal Phase III trials, the Clinical Dementia Rating-Sum of Boxes (CDR-SB). In the EMERGE trial (NCT02484547), at the population-level the average benefit in CDR-SB at 78 weeks for patients receiving high dose Aduhelm was 0.39 point. Many have argued that a benefit at this magnitude may not be clinically "meaningful".[1] The same criticism has also been leveled at other therapeutic monoclonal antibodies targeting amyloid-beta, including Leqembi (lecanemab), which received conventional approval by the FDA in July, 2023. In the pivotal trial CLARITY-AD (NCT 03887455), patients receiving Leqembi had at the population-level an average 0.45-point slower worsening in CDR-SB at 18 months compared to patients on placebo.

Some of the criticism of Aduhelm and Leqembi results from a potentially false assumption and misunderstanding that every patient will derive the same (or similar) degree of benefit from a therapeutic agent. In other words, the therapeutic agents have a "homogeneous treatment effect". The study by Pang et al.[2] published in Alzheimer's & Dementia (doi:10.1002/alz.13431), demonstrated that this assumption is unlikely to hold for Aduhelm in the treatment of AD, which could have implications for other anti-amyloid beta monoclonal antibodies in this regard as well. Specifically, Pang et al. found that there is statistically significant evidence that patients in the high-dose arm of the EMERGE trial varied in their benefit in slowing CDR-SB worsening, and there may exist patients who derived benefit of 1 point in CDR-SB or even more. As such, the average benefit of 0.39 point in CDR-SB is an overly simplistic characterization of the efficacy profile of Aduhelm, failing to capture the heterogeneity of response with some patients deriving significantly more benefit. The work of Pang et al. builds upon previous precision medicine methodology that constructs an individual treatment response (ITR) numerical score using multi-modal baseline information on a training set to reveal covariates-treatment interactions.[3] The study highlights the complexity of defining clinically meaningful efficacy solely from averaged population-level outcomes. Indeed, readily implementable methodologies can now also be applied that more comprehensively measure a drug's efficacy profile, including the ability to account for nuanced individual-level heterogeneity in treatment effect.

In addition to the benefits, we know the risks of drugs also vary from patient to patient. In the case of anti-amyloid drugs, these risks include amyloid-related imaging abnormalities (ARIA) which are generally asymptomatic but can sometimes, albeit rarely, result in serious adverse events.[4] In this context, a benefit:risk ratio that combines the assessments of efficacy and adverse events can be heterogeneous on both sides of the equation. The extension of the concept of heterogeneity to benefit:risk ratio again underscores the over-simplification of existing population-level methods that treat benefit:risk ratio as a static measure universally applied to any and all patients. To properly characterize a therapeutic agent's benefit:risk profile, we need to use recently developed precision medicine approaches that are designed to detect and measure heterogeneity in both efficacy and safety outcomes and subsequently construct prediction models for individual-level treatment benefit ***and*** risk. It should be acknowledged that the traditional approach to drug development that follows a "one-size-fits-all" axiom and targeting an "average treatment effect" at the population-level may lower the probability of success and increase cost and time burdens for clinical trials in neurodegenerative dementias where individual-level neuropathological heterogeneity is much more common than not. The work of Pang et al. is a good example of a situation echoing the *Pareto Principle*, where 20% of patients may potentially explain 80% of the observed average treatment effect at the population-level.

Population-based efficacy outcomes may be appropriate for regulatory and public health officers and economic forecasters tasked with protecting and improving the health of populations and society, but they provide little guidance for the health care provider sitting with their patient, deciding whether to prescribe a new drug. While the roots of personalized medicine date back as far as 5000 years B.C. with the Ayuverdic system[5] and later with Hippocrates of Kos (c. 460 B.C.–c. 370 B.C.),[6] it is only with modern and emerging statistical techniques such as counterfactual prognostic models[3] and machine learning[7,8] that we can now try to generate reliable individual-level predictions for hitherto unpredictable diseases and to conceive a path for truly "individualized" drug development and patient management in "heterogeneous" disorders.

As AD is itself a complex and pathologically heterogeneous disease, it is unrealistic to expect a single agent targeting a single molecular

pathway to benefit every patient equally. Further research is warranted to improve performance accuracy at the individual level which then can better evaluate the generalizability of the approach in diverse cohorts.[9] ITR models, when appropriately applied, may optimize the safe and effective personalized use of monoclonal antibodies targeting amyloid beta in people living with AD. The findings by Pang et al. serve as a compelling proof-of-concept, setting a valuable precedent for the analytical approaches employed in AD clinical trials and should be taken into consideration in the reporting of results in future trials.

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CONSENT STATEMENT

We confirm that human subject consent was not necessary for the provided work.

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SUPPORTING INFORMATION

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