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EDITORIAL

Prescribing anti-amyloid immunotherapies to treat Alzheimer's disease: Fully informing patient decisions

The objective of this editorial is to advocate for minoritized individuals, as well as other demographic groups who were under-represented in clinical trials of anti-amyloid immunotherapies, to ensure that they are able to make fully informed choices in considering whether to undergo treatment with these drugs.

The Alzheimer's disease (AD) research and drug development field has entered a new, and arguably very exciting era. In the past 2 years, the Food and Drug Administration (FDA) in the United States has deliberated on three therapeutic agents that target disease modification for AD: one currently with full approval,[1] one granted accelerated approval,[2] and a third expected to have a decision in late 2023.[3] For the first time, we are discussing clinical data and concepts of clinical meaningfulness with respect to disease-modifying treatments for AD. There is little question that rapid expansion of disease knowledge and mechanisms can be anticipated in ways that until recently could only have been wildly speculated. However, there are critical issues and limitations to these data that require serious consideration. While controversies certainly exist and broad consensus is far from having been achieved, the reality is that these drugs are being approved as delivering sufficient efficacy with acceptable risk. It is not the purpose of this editorial to take a position on these regulatory decisions. Rather, the goal is to discuss the serious consequences that may result from expanding the use of these disease-modifying treatments from carefully controlled clinical trial cohorts to the general population. Much remains ahead for the field to understand and resolve as we move toward safely treating AD and related dementias (ADRD), including whether any of these agents will ultimately become part of a precision-oriented combination therapy, and for whom efficacy and sufficient safety can be adequately demonstrated. And, of course, when and how these clarifying studies will be performed.

Health disparities are well known to exist among identifiable demographic populations, due to deep-rooted and long-standing social determinants, systemic inequities, structural racism, and discrimination (e.g., see ref. 6). Co-pathologies, co-morbidities, biomarkers, risks, and cognitive/functional outcomes have been shown to differ for ADRD among races, ethnicities, sexes, and genders. Racial biases have been identified in cognitive assessment batteries that were developed by and created for the majority White population. Biomarkers differ to varying degrees among racial groups including amyloid deposition, as does the impact of carrying the major genetic risk for AD —*APOE* ε4. These differences impact our understanding of ADRD, as well as emerging disease-modifying treatments, yet they remain ignored and/or neglected in most studies.[7] As stated in a concise editorial review of efficacy and safety results of these anti-amyloid immunotherapy trials,[8] "A major limitation of the (donanemab) trial[3] is the lack of racial and ethnic diversity.… This continues a poor track record of inclusion and representation in AD clinical trials and raises ethical concerns as well as questions about the generalizability of results to populations at high risk for AD and dementia."

As noted by Manly and Deters,[9] minoritized groups are typically diagnosed at later stages of disease, with structural inequalities (e.g., differential distribution of socioeconomic resources, years and quality of education, income, occupational prestige, and less access to health care), that lead to higher prevalence of vascular co-morbidities among people racialized as Black. This had the effect of reducing the proportion of this population who met the inclusion criteria of the donanemab Trailblazer-ALZ 2 phase 3 trial. Moreover, aging into the seventh decade of life (and beyond) is the most common risk factor associated with AD, and 96% of Medicare beneficiaries with an AD diagnosis have at least one additional chronic condition.[10] Yet, none of the clinical trials enrolled significant numbers of older adults (≥ 75 years), nor those with multiple chronic conditions. Thus, the exquisitely controlled enrollment criteria in clinical trials result in participant cohorts that do not generalize to the far more diverse general population, particularly because the exclusion rate of Black and Hispanic individuals has been noted to be significantly higher than the overwhelming representation of White participants in clinical trials.[11] The obvious impact of these issues is that outcomes have been defined based on data from a largely homogeneous White population, and will likely differ to varying degrees among other participant groups that remain to be studied. Thus, these studies potentially hinder our understanding of other factors that contribute to the disease across populations.[11]

Furthermore, amyloid-related imaging abnormalities (ARIA-E and ARIA-H) comprise the most common and potentially serious adverse side effects of these drugs, yet data on ARIA generally come from trial data, and racially heterogeneous populations have not been included in trials to sufficient degree to determine group differences in its prevalence. A systematic review of ARIA and amyloid beta–targeting

therapies did not report findings based on race/ethnicity.[12] Examination of the individual papers included in that analysis revealed that the cohorts comprised 95% or more non-Hispanic White participants. It may be anticipated that risk of ARIA due to the exposure to anti-amyloid immunotherapies may be elevated in individuals with elevated vascular burden. But despite the accelerated or full approvals by the FDA of two (perhaps soon to be three) anti-amyloid immunotherapies, and recognition as stated on the FDA website that "African American and Hispanic/Latino populations are disproportionately affected" by ADRD (https://www.fda.gov/consumers/minority-health-and-health-equity-resources/alzheimers-disease), we simply do not know at this time whether ARIA risk differs among those with greater vascular burden and those at greatest risk for AD/ADRD.

These issues may be mitigated in part by the Centers for Medicare and Medicaid Services (CMS) having confirmed a coverage requirement for traditionally approved anti-amyloid immunotherapies to be contingent on physicians entering treatment and outcome data into an approved patient registry. On the positive side, this approach will lead over time to the accumulation of efficacy and safety data in populations that are far more diverse than those studied in the clinical trials. However, it should be recognized that this makes primary care a fundamental extension to the clinical research program for the approved drugs, albeit with an important nuance. Instead of full costs being covered by the drug sponsor as in a clinical trial, these critical (essentially phase 4) research studies will be paid for in part through the co-pays from patients and their families required for CMS coverage (unless they carry extended health coverage), as well as taxpayers and payers of Medicare premiums. Together, this pushes significant costs for determining efficacy and safety, including in populations at highest risk for disease, to the individuals being exposed to the drugs outside of the controlled and highly monitored clinical trial setting. Moreover, these processes will be profitable for the drug sponsors by virtue of drug sales, and beneficial for the clinical/imaging/infusion centers due to cost accruals for billable procedures.

As noted by Ramanan and Day,[13] "… the findings from CLARITY-AD (lecanemab) and TRAILBLAZER-ALZ 2 (donanemab) emphasize that emerging therapies for AD will require judicious selection of appropriate patients for treatment (with the goal of maximizing benefit and minimizing harm), individualized counseling regarding potential risks and burdens of treatment, and robust pathways for monitoring safety and clinical response." Moreover, formidable resources will need to be integrated, and substantial challenges overcome, to provide access to these drugs (e.g., see refs. 13–15). This is particularly important given the unknown impacts across populations with varying degrees of social and structural determinants of health and health access, including racial and gender minorities as well as urban versus rural populations. An equitable public health assessment in clinical trials includes those who are affected by a disease. Because there was inadequate representation of minoritized groups in the clinical trials, there is an ethical responsibility on the part of health-care providers across the spectrum of specialties to inform patients of these realities. These health-care providers will need to participate in the safe implementation of these treatments and provide this information to minoritized patients when discussing whether they wish to choose to take these drugs and acknowledge that their benefit-to-risk ratio is unknown.

We are therefore advocating that broadly across health-care systems, candid and objective information is provided to practitioners and to patients and their families regarding these trial outcomes. Educational materials should be developed for practitioners to enable them to effectively communicate the current state of the science with patients and their families. Clear information needs to be made available on how disease endophenotypes, genetic risk, and pathophysiology over the disease course may be associated with individual differences in racial background, lifestyle, socioeconomic status, sex, age, etc.; differences that may, in turn, lead to unforeseen risks for certain demographic groups that have not been studied in the trials. These individuals (who will be essentially contributing to the next phase of the clinical research program with their own finances and well-being at stake), must be able to comprehend these complexities sufficiently so that they can make a *fully informed choice* about whether they wish to accept the balance of the risks and burdens inherent to undergoing exposure to these drugs versus the possible benefits. Specifically, this information should explain in very clear and concise terms: (1) the very small number of minoritized participants included in these trials, (2) the small number of people older than 75 years of age included in these trials, (3) the fact that people with multiple chronic conditions were excluded from these trials, (4) the potential risks and benefits from taking the drugs; and (5) the fact that the burdens (e.g., regular infusions, serial magnetic resonance imaging, *APOE* genotyping, financial and lifestyle challenges) and risks of adverse events (e.g., ARIA-E, ARIA-H—some of which may be severe) will be left to the patients and their health-care practitioners to manage rather than meticulously monitored by trialists. These points should be clarified and fully understood before treatment is initiated, including the possibilities of emergent changes in health status that may lead to risk of serious adverse events if therapeutic treatments are required that are contraindicated in combination with anti-amyloid immunotherapies.

We are not advocating for or against the approval of these drugs. Strong arguments have been raised in both directions, and it is not the purpose of this editorial to mediate these differences of opinion. Rather, we accept that approved use of these drugs is part of our current reality, that individuals may benefit from these treatments who were not represented in the trials and deserve access to these drugs if they qualify. We also believe that benefits may be expected for some individuals that exceed those of the average cognitive and functional changes observed in the outcomes of the treatment versus placebo arms of the clinical trials. Of course, similar statements can be made about the potential risks. Thus, in this reality, we acknowledge the limitations of our knowledge resulting from a lack of representation in clinical studies, and at the individual level, advocate strongly for *fully informed choice*.

As noted by Liu et al.,[16] "Besides race and ethnicity, it would also be important to ensure that the eventual product labelling of an approved drug aligns with trials' participant inclusion and exclusion criteria." Consistent with this position, we further advocate for

modifying the labeling for these drugs to acknowledge and reflect these limitations, until such time as the efficacy and safety have been far more broadly investigated and understood. Specifically, the drug label should include verbiage indicating that based on the low numbers of many demographic groups of participants in the clinical trials, the efficacy and safety of anti-amyloid antibodies (or the specific antibody name) remain unclear at this time for many individuals; therefore, patients seeking these treatments whose demographic groups were not adequately studied in the clinical trials should be provided with this information so that they and their families can make an informed choice about initiating treatment.

We as a field are witnessing profound accomplishments that are worthy of applause, but remain less than fully understood. We, as a responsibly objective data-driven research field have much work to do now and in the future toward building an inclusive science on AD. We look forward to progress from this work that can lead to the ultimate aim of treating all individuals who will benefit from therapeutic interventions for progressive dementia at its earliest stages, in an ethical, inclusive, and safe manner.

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CONFLICT OF INTEREST STATEMENT

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