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Editorial

Change on Clinical Trial Outcome Assessments: The Search for Meaningfulness

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What constitutes meaningful benefit as measured by commonly used clinical trial instruments and who determines "meaningfulness"? These are key questions of importance to sponsors of drug development programs, trial participants and their care partners, regulators, and payers (1).

Determination of mean differences in change from baseline in the treatment group compared to the placebo group is the gold standard for determining efficacy of an agent in a clinical trial. This approach provides a summary measure of what happened across all patients in the trial but does not afford insight into the number (percent) of patients on active treatment who responded to the intervention by exhibiting a delay in decline. Analytic approaches that provide this within-patient information are needed. Lansdall and colleagues (2) performed an analysis of the data from the Alzheimer's Disease Cooperative Study (ADCS) clinical trial evaluating the effects of vitamin E or donepezil compared to placebo on progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia. Using best practices as defined by the Food and Drug administration (FDA) they developed an anchor-driven approach to determine what changes on target instruments corresponded to mild or moderate worsening as determined by clinicians using global rating scales (3). Two anchors were used in the assessment; the retrospectively applied MCI-Clinical Global Impression of Change (MCI-CGIC) and the prospectively derived Global Deterioration Scale (GDS). The target measures whose range of change corresponding to one- and two-point progressions on the seven-point scales of each of the anchor assessments included the Clinical Dementia Rating - Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), and Mini-Mental State Examination (MMSE). These scales are commonly used in clinical trials and are familiar to trialists and clinicians.

Using this anchor-driven approach, minimal decline on the MCI-CGIC corresponded to a 0.50-to-0.64-point worsening, and moderate decline corresponded to a 2.00-to-2.35-point worsening. On the GDS, a one-point decline (minimal) corresponded to a 1.00-to-1.08-point worsening on the CDR-SB and a two-point (moderate) decline corresponded to a 2.75-to-3.39-point change. Minimal decline on the MCI-CGIC corresponded to a two-point change on the ADAS-cog 13, and moderate decline corresponded to a 4-to-5-point change on the ADAS-cog 13. The MMSE was more difficult to interpret in this dataset and 36-month data were used rather than 12-month data. Minimal worsening on the GDS corresponded to a 2-to-3-point MMSE decline over 36 months and moderate worsening corresponded to a decline of 6 to 7 points.

These data will be very helpful in terms of interpreting the outcomes of clinical trials. The percent of patients who had mild or moderate worsening on placebo compared to active treatment (responders are those that do not progress) as determined by the ranges established for the CDR-SB and ADAS-cog will inform patient and care partner discussions regarding the likelihood and magnitude of benefit associated with one year of treatment. These thresholds could be used in time-to-event analyses to assess delay in reaching mild or moderate levels of decline with treatment. Drug-placebo differences are expected to increase over time in patients receiving disease modifying therapies and analyzing observed data or modeling the expected longitudinal within-patient differences will further inform patient and care partner discussions (1).

In current trials, anti-amyloid monoclonal antibodies that are associated with marked plaque reduction on amyloid positron emission tomography reduce the rate of disease progression as measured on the CDR-SB by approximately 30%. Translating this information into more patient-relevant outcomes will help clinicians, patients, and care partners understand the meaning of this effect. Performing the analyses of the type explored by Lansdall et al will be an important step towards facilitating understanding of within-patient treatment effects.

Several limitations of this study may affect the analysis and interpretations. All trial patients were included in the analyses including those in the donepezil and vitamin E treatment arms. In the original trial, patients on donepezil were observed to progress more slowly in the first 12 months of this trial --- the data set from which most of the

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conclusions were derived (4). The trial had an unusually high attrition rate of 40% over the three-year period and this may have compromised some of the conclusions that can be drawn from outcome measures. The study was conducted prior to the routine use of biological confirmation of the diagnosis of AD, and it is likely that non-AD patients were included in the trial. This is reflected in the lower percentage of apolipoprotein E e-4 gene carriers included in the study --- 55% in this early ADCS trial compared to the 65-70% in a contemporary biologically confirmed population (5). Only patients with MCI were included in the trial and this population may progress more slowly than the MCI/mild AD dementia populations included in many current early AD trials. These trial design features and analytic choices may have resulted in analyzing a population whose progression differs from that of populations included in current trials. The MCI-CGIC and GDS are clinician rated scales. The relationship of the change thresholds developed in this analysis to meaningful benefit as seen by patients and their care partners warrants study. Conducting analyses of the type done by Lansdall and colleagues on other trial sets --- particularly those derived from trials including early AD populations with biological confirmation --- will be informative and will extend our ability to apply this approach to emerging trial data.

This analysis adds to our ability to interpret the disease course changes observed in treatment arms of clinical trial populations. Responder analyses of this type will not influence conclusions drawn from the primary outcome measures regarding the treatment efficacy in the overall population. This approach provides insight into how to evaluate treatment benefits expected by patients in trials of disease modifying agents. Clinical trial sponsors are encouraged to perform analyses of the type presented in the Lansdall et al paper.

Conflict of interest: JC has provided consultation to Acadia, Actinogen, Alkahest, AlphaCognition, AriBio, Biogen, BioVie, Cassava, Cerecin, Corium, Cortexyme, Diadem, EIP Pharma, Eisai, GemVax, Genentech, Green Valley, GAP Innovations, Grifols, Janssen, Karuna, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, PRODEO, Prothena, ReMYND, Resverlogix, Roche, Sage Therapeutics, Signant Health, Simcere, Sunbird Bio, Suven, TrueBinding, and Vaxxinity pharmaceutical, assessment, and investment companies. JC is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; NIA grant P20AG068053; NIA grant P30AG072959; NIA grant R35AG71476; Alzheimer's Disease Drug Discovery Foundation (ADDF); Ted and Maria Quirk Endowment; and the Joy Chambers-Grundy Endowment.

References

1. Assuncao SS, Sperling RA, Ritchie C, Kerwin DR, Aisen PS, Lansdall C, et al. Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. Alzheimers Res Ther. 2022;14(1):54; 10.1186/s13195-022-00984-y.
2. Lansdall CJ, McDougall F, Butler L, Delmar P, Pross N, Qin S, et al. Establishing clinically meaningful change on outcome assessments frequently used in trials of mild cognitive impairment due to Alzheimer's disease. J Prev Alz Dis 2023;1(10):9-18; Doi: http://dx.doi.org/10.14283/jpad.2022.102
3. Food and Drug Administration (FDA). Patient-focused drug development public workshop: incorporating clinical outcome assessments into endpoints for regulatory decision-making. December 6, 2019. https://www.fda.gov/media/132505/download (accessed August 22, 2022).
4. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005;352(23):2379-2388; 10.1056/NEJMoa050151.
5. Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019;380(15):1408-1420; 10.1056/NEJMoa1812840.

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