Strategies to reduce sample sizes in Alzheimer's disease primary and secondary prevention trials using longitudinal amyloid PET imaging

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Abstract:

Background: Detecting subtle-to-moderate biomarker changes such as those in amyloid PET imaging becomes increasingly relevant in the context of primary and secondary prevention of Alzheimer's disease (AD). This work aimed to determine if and when distribution volume ratio (DVR; derived from dynamic imaging) and regional quantitative values could improve statistical power in AD prevention trials.

Methods: Baseline and annualized % change in [11C]PIB SUVR and DVR were computed for a global (cortical) and regional (early) composite from scans of 237 cognitively unimpaired subjects from the OASIS-3 database (www.oasis-brains.org). Bland-Altman and correlation analyses were used to assess the relationship between SUVR and DVR. General linear models and linear mixed effects models were used to determine effects of age, sex, and APOE-ε4 carriership on baseline and longitudinal amyloid burden. Finally, differences in statistical power of SUVR and DVR (cortical or early composite) were assessed considering three anti-amyloid trial scenarios: secondary prevention trials including subjects with (1) intermediate-to-high (Centiloid > 20.1), or (2) intermediate (20.1 < Centiloid ≤ 49.4) amyloid burden, and (3) a primary prevention trial focusing on subjects with low amyloid burden (Centiloid ≤ 20.1). Trial scenarios were set to detect 20% reduction in accumulation rates across the whole population and in APOE-ε4 carriers only.

Results: Although highly correlated to DVR (ρ = .96), cortical SUVR overestimated DVR cross-sectionally and in annual % change. In secondary prevention trials, DVR required 143 subjects per arm, compared with 176 for SUVR. Both restricting inclusion to individuals with intermediate amyloid burden levels or to APOE-ε4 carriers alone further reduced sample sizes. For primary prevention, SUVR required less subjects per arm (n = 855) compared with DVR (n = 1508) and the early composite also provided considerable sample size reductions (n = 855 to n = 509 for SUVR, n = 1508 to n = 734 for DVR).

Conclusion: Sample sizes in AD secondary prevention trials can be reduced by the acquisition of dynamic PET scans and/or by restricting inclusion to subjects with intermediate amyloid burden or to APOE-ε4 carriers only. Using a targeted early composite only leads to reductions of sample size requirements in primary prevention trials. These findings support strategies to enable smaller Proof-of-Concept Phase II clinical trials to better streamline drug development.

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