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Should persons with autosomal dominant AD be included in clinical trials?

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In a recent issue of Alzheimer's Research & Therapy, we read with great interest the discussion by Szigeti and Doody [1] of including early-onset Alzheimer’s disease (EOAD) (under age 65) in clinical trials. Successful enrollment is a challenge in most Alzheimer’s disease (AD) trials, and permitting the participation of these young motivated patients could aid recruitment. EOAD can be categorized as AD caused by autosomal dominant mutations (ADAD) in the amyloid precursor protein (APP), presenilin-1 (PSEN1), or presenilin-2 (PSEN2) genes and as AD in individuals not known or suspected to harbor such mutations, which we here refer to as sporadic AD (SAD).

We agree with the authors that SAD cases under age 65 should be included in AD trials. The literature describing these cases does not suggest that clinical or biological differences warrant exclusion. We take pause, however, with the recommendation of categorical enrollment of ADAD patients in trials. Inclusion of persons with ADAD should be dependent upon the nature of the causative mutation, the drug under investigation, and the study objectives. More than 200 AD-causing mutations are known, and predicting the impact of all disease-causing mutations on drug efficacy is difficult. APP mutations are most frequent in the β- and γ-secretase cleavage regions and result in increases in the levels of both Aβ42 and Aβ40, Aβ40 alone, or the ratio of Aβ42 to Aβ40 [2,3]. Aβ40 resultant from processing of mutated APP is resistant to degradation by neprilysin [4,5]. γ-Secretase inhibitors may lack efficacy in preventing APP cleavage by enzymes resultant from mutated PSEN genes [6,7]. On pathological examination, the brains of persons with ADAD can demonstrate atypical morphology, distribution, and composition of Aβ deposits [2]. Biological differences between ADAD and SAD might manifest similar differences in response or side-effect profile to a given intervention and thus should be considered carefully before patients with ADAD are enrolled in trials.

In phase I studies, biological differences between ADAD and SAD could translate to different dose requirements since younger patients with ADAD are likely to have a more rapid drug metabolism. Females may also be premenopausal, making teratogenicity a consideration. In phase II, differences in ADAD could have effects on outcomes and interpretation since ADAD participants might be overrepresented, given that the percentage of SAD patients who qualify for trials is low, ADAD patients have fewer barriers to participation, and trials are often conducted at academic centers where ADAD is studied. Alternatively, persons with ADAD might theoretically be enrolled in larger late-stage trials with a predefined plan to analyze efficacy and safety of this AD subtype separately. Acceptance of this approach by regulatory bodies and willingness of sponsors to risk an impact on the overall trial significance, however, are uncertain.

The Dominantly Inherited Alzheimer’s Network and the Alzheimer’s Prevention Initiative are preparing to conduct prevention clinical trials in ADAD, in part addressing the important need for clinical drug research in this population. These studies may not enroll persons already demented with ADAD. In accordance with the principle of beneficence, AD trial design should permit examination of efficacy in all possible disease-suffering populations. For every study, however, substantial consideration must be given to the issues of whether to include specific persons with ADAD and of how the data will be analyzed when the study is complete.

Abbreviations
AD, Alzheimer’s disease; ADAD, Alzheimer’s disease caused by autosomal dominant mutations; APP, amyloid precursor protein; EOAD, early-onset Alzheimer’s disease; PSEN, presenilin; SAD, sporadic Alzheimer’s disease.

Competing interests
JDG is the site investigator for clinical trials sponsored by Elan Corporation (Dublin, Ireland), Janssen-Cilag (a subsidiary of Johnson & Johnson, New Haven, CT), and Genentech (South San Francisco, CA). JMR is a consultant for Elan Corporation and Biogen Idec (Cambridge, MA). The other authors declare that they have no conflicts of interest.
Brunswick, NJ, USA), Bristol-Myers Squibb Company (Princeton, NJ, USA), Medivation (San Francisco, CA, USA), Pfizer Inc (New York, NY, USA), and the National Institute on Aging-sponsored Alzheimer’s Disease Cooperative Study. He is the principal investigator of a clinical trial sponsored by the John Douglas French Alzheimer’s Foundation (medical food generously supplied by Accera, Inc., Broomfield, CO, USA). He has received consultation fees from Avanir Pharmaceuticals (Aliso Viejo, CA, USA). JMR has received consultation fees from Takeda Pharmaceuticals Co. Ltd. (Osaka, Japan).

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