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MRI Substudy Participation in Alzheimer Disease (AD) Clinical Trials: Baseline Comparability of a Substudy Sample to Entire Study Population

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Abstract

Objective—To determine if a self-selected group of participants who enroll in an imaging substudy of Alzheimer disease (AD) clinical trials is representative of the overall study sample.

Methods—Baseline data from 2 ongoing AD clinical trials with 402 and 313 randomized participants were analyzed. Magnetic resonance imaging substudy enrollers (166 participants in trial 1 and 161 participants in trial 2) and nonenrollers were compared on baseline demographic, medical and clinical characteristics separately for the 2 trials.

Results—In both trials, enrollers were statistically similar to nonenrollers on most demographic and clinical measures. One study sample showed that enrollers had lower cognitive scores at baseline when compared with nonenrollers: lower Mini Mental State Examination scores (20.15±3.6 vs. 21.04 ±3.6, *P*=0.02), and higher Alzheimer's Disease Assessment Scale-cognitive domain scores (24.99 ±8.5 vs. 23.03±9.3, *P*=0.03); however, the difference was not considered clinically important and was not observed in the second trial.

Conclusions—The groups of individuals who agreed to participate in the imaging substudies of AD trials were remarkably comparable to the comparison groups at baseline on a wide range of demographic and clinical measures; there seems to be a minimal effect of self-selection bias. The results indicate that it may be reasonable to generalize findings in an imaging substudy to the complete the study population.

Keywords

AD; MRI; randomized clinical trials

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The inclusion of magnetic resonance imaging (MRI)-derived rates of brain atrophy as an outcome measure in Alzheimer's disease (AD) clinical trials are an increasingly common practice, as feasibility in multicenter trials has improved. Primary outcome measures in AD trials are typically clinical measures, including psychometric and functional assessment scores. Atrophy rates are usually secondary measures, included for the purpose of distinguishing "symptomatic" from "neuroprotectant" therapeutic effects. Due in part to cost, imaging studies are often completed on a self-selected subgroup of subjects rather than the entire cohort. The few published clinical trials, which have included MRI-derived rates of brain atrophy in subgroups[1–3] have not consistently examined how representative the MRI subgroups are compared with the total study population. Biases could be introduced by self-selection or refusal in imaging substudies. In randomized, controlled studies, self-selection can decrease the generalizability of the subgroup findings if the subgroups differ from the full study population in characteristics associated with disease progression rate or intervention effects. The consequence of these biases in the interpretation of study results could be important.

To determine the effect of such self-selection in AD clinical trials, we analyzed the screening and baseline data from 2 fully enrolled, ongoing, randomized intervention trials. With these data, we were able to determine whether participants who enrolled in MRI substudies and those who did not were comparable with respect to the baseline characteristics, particularly those anticipated to be associated with disease progression.

METHODS

Study Design and Participants

The 2 clinical trials are being coordinated by the Alzheimer's Disease Cooperative Study (ADCS). Participants in both trials were approached to participate in an MRI substudy, and enrollment into the substudy was entirely voluntary and self-selected. The primary endpoints for the MRI substudies are the rate of brain atrophy as measured by the following: hippocampal atrophy, whole brain atrophy, ventricular enlargement, and temporal horn enlargement.

Clinical Trial 1

The docosahexanoic acid (DHA) trial is an ongoing double-blind, multicenter, randomized, placebo controlled clinical trial of DHA supplementation for the treatment of AD. Fifty-one ADCS sites in the United States are participating in the trial after obtaining approval from their local institutional review boards. Patients were recruited between February 16, 2007 and November 1, 2007. All participants provided written informed consent. Written informed consent was obtained from participants and/or legally authorized representatives, according to local guidelines. Participants were not given any extra compensation for their participation in the MRI substudy of the trial. The coprimary endpoints are the rate of change in Alzheimer's Disease Assessment Scale-cognitive domain (ADAS-Cog) 11[4] and the Clinical Dementia Rating-Sum of Boxes (CDR-SOB)5 over 18 months.

Subjects were diagnosed with AD according to NINDS-ADRDA criteria and were in the mild-moderate range of severity on the basis of screening MMSE score between 14 and 26. Subjects were permitted to be on stable doses of cholinesterase inhibitors and memantine. Other psychotropic medications and unstable medical conditions were reasons for exclusion. Dietary consumption of DHA was limited to 200 mg per day at baseline. The imaging substudy had no additional exclusion criteria other than contraindications to MRI. The trial is fully enrolled with 402 randomized participants. Among those randomized in the study, 166 (41%) had a baseline MRI scan and were considered MRI substudy enrollers.

Clinical Trial 2

The Valproate neuroprotection trial is an ongoing randomized, placebo-controlled, double-blind, multicenter 2 year trial of low-dose (10 mg/kg/d) sodium valproate therapy in outpatients with mild-to-moderate AD who lacked agitation and psychosis at baseline. Patients from 43 ADCS sites were recruited between October 2003 and January 2007 after obtaining approval from their local institutional review boards. Written informed consent was obtained from participants and/or legally authorized representatives, according to local guidelines. Participants were not given any extra compensation for their participation in the MRI substudy of the trial. The primary outcome is the emergence of agitation and/or psychosis.

Subject selection criteria for this trial included participants with a diagnosis of probable AD age 50 years or older, weighing at least 40 kg, and residing in the community at baseline. Additionally, patients had to have a MMSE score of 10 to 20 inclusive, not experience agitation or psychosis as the onset of their illness and not require treatment with psychotropic medications with the exception of antidepressants and limited use of sedatives for sleep. The imaging substudy had no additional exclusion criteria other than contraindications to MRI. This trial is fully enrolled with 313 randomized participants, of whom 161 (51%) were MRI substudy enrollers.

Group Definitions

Enrollers are defined as participants who have an MRI scan at baseline

Measures

For all randomized patients in these studies, information on demographic and clinical characteristics was collected at screening/baseline.

Demographic—Age, years of education, sex, race, ethnicity, martial status, primary language, and years since AD onset, smoking, and alcohol history.

Medical—Medical history and vital signs.

Clinical—Screening MMSE score, Screening Modified Hachinski. Baseline CDR-SOB, baseline Global Clinical Dementia Rating (CDR), baseline Neuropsychiatric Inventory score, baseline DHA and eicosapentaenoic acid levels, baseline quality of life (QOL)-partner, baseline quality of life (QOL)-subject, baseline Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), and ADAS-Cog11 scores.[6–10]

Statistical Analysis

Unadjusted comparisons between enrollers and nonenrollers with respect to screening and baseline characteristics were performed using χ^2 tests (or Fisher exact tests when appropriate) for categorical variables and 2-sample *t*-tests for continuous variables. Ordinal logistic regression models were fit to compare the groups on the ordinal CDR.

To assess the differences between the groups for those clinical outcome variables that do not show a statistical significance, 95% confidence intervals are used instead of post hoc power calculations.[11] Results are described and reported separately for the 2 trials. All analyses were carried out using the statistical software R 2.1.1 (www.R-project.org). A 2-tailed $P<0.05$ was considered an indication of statistical significance.

RESULTS

Table 1 presents study characteristics between the MRI substudy enrollers and nonenrollers in the 2 trials. The groups did not differ significantly on demographic and medical measures, with 2 exceptions. Enrollers reported less history of ear, nose, and throat complaints (55% vs. 67%, P=0.011) and were slightly taller (167.7±9.7 cm vs. 165.1±10.7 cm, P=0.01) than nonenrollers in trial 1, whereas enrollers had slightly lower diastolic blood pressure (73.2±9.8 vs. 76.9±9.1; P<0.001) than nonenrollers in trial 2; the differences are not considered clinically important.

In terms of clinical measures, there were some statistically significant but relatively small differences between the 2 groups of participants. In trial 1, enrollers had lower screening MMSE scores (20.15±3.6 vs. 21.04±3.6; P=0.02), lower screening Modified Hachinski scores (0.62±0.7 vs. 0.88±0.8; P<0.001) and higher baseline ADAS-cog scores (25.0±8.5 vs. 23.0 ±9.3; P=0.03) than the nonenrollers, whereas, in trial 2, enrollers had lower Neuropsychiatric Inventory score (2.52±2.7 vs. 3.17±2.5; P=0.03). The groups did not differ significantly on baseline CDR-SOB, global CDR, QOL, or Alzheimer's Disease Cooperative Study-Activities of Daily Living.

Table 2 presents the difference in mean scores between the 2 groups with the corresponding 95% confidence interval around these differences. None of the confidence intervals include effects that are considered to be clinically important, although a few were statistically significant.

DISCUSSION

Current clinical trials in AD frequently include imaging substudies that compare rates of change (between baseline and study end) in cerebral volume between treatment groups. Patients who participate in these imaging substudies are self-selected and hence raise questions of selection bias and generalizability of observed treatment effects on the imaging measures.

In this self-selected sample from 2 ongoing trials conducted by the ADCS, we found that imaging substudy enrollers are very similar to those participants who chose not to enroll in the substudy. Baseline comparisons revealed no differences in terms of age, sex, comorbidities, or clinical characteristics, with the exception of lower mean Hachinski score in enrollers in trial 1. Although this could reflect some under-representation of subjects with vascular risk factors in the MRI enroller group, the magnitude of the difference in Hachinski scores (0.26 points) is probably too modest to be considered clinically important. Differences between enrollers and nonenrollers on cognitive and behavioral measures were also not considered to be clinically important (for example, mean difference on MMSE= −0.89 points in trial 1 and 0.24 in trial 2, mean difference on ADAS-cog of 1.96 in trial 1 and −1.23 in trial 2). The relationship between enrollers and nonenrollers on these measures were reversed between the 2 trials (enrollers are more impaired than nonenrollers in trial 1 and less impaired in trial 2) reinforcing the impression that these modest differences are not indicative of systemic bias in substudy selection.

There are certain limitations to this study that must be considered. First, the analyses included data from 2 ongoing clinical trials in AD conducted through 1 coordinating center; and these findings may not generalize to other AD trials with different baseline study populations. However, as there were no specific exclusion criteria for the MRI substudy in both cases, we hypothesize that other trials, including industry sponsored trials will probably show similar results if there are no additional exclusion criterion for substudy participation. This would be consistent with our overall hypothesis that willingness to participate in an imaging trial component does not introduce important bias. However, this is a hypothesis that still needs to be confirmed more widely.

Second, comparisons did not include follow-up data and so did not compare the groups in terms of rate of change in cognition, behavioral or other efficacy measures. Future analyses are planned that include additional trials conducted by the ADCS and analysis of follow-up data.

In summary, the sample of participants who volunteered to enroll in the imaging substudy of these clinical trials had very similar baseline demographic, medical and clinical characteristics compared to the rest of the study sample. This suggests that it may be possible to recruit a representative sample for a longitudinal imaging substudy in AD. We believe that possible reasons for this finding include the lack of specific exclusion criteria for the MRI substudy and the absence of inducements such as financial remuneration. Further research is underway to confirm these results in other AD clinical trials.

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TABLE 1

Comparison of Enrollers and Nonenrollers in the Magnetic Resonance Imaging Substudy at Baseline: Demographic, Medical, and Clinical Outcome Characteristics in the Docosahexanoic Acid Trial

	AD Clinical Trial 1*			AD Clinical Trial 2		
	Enrollers (N = 166)	**Nonenrollers (N = 236)**	***P*†**	**Enrollers (N = 161)**	**Nonenrollers (N = 152)**	***P*†**
Demographics						
Age (years)	75.4 ± 8.9	76.7 ± 8.5	0.16	74.9 ± 8.3	76.7 ± 7.3	**0.035**
Women, no (%)	81 (49)	129 (55)	0.29	97 (60)	87 (57)	0.67
Education (years)	14.1 ± 2.6	14.4 ± 2.9	0.39	13.8 ± 3.2	13.8 ± 3.4	0.92
White race, No (%)	151 (91)	217 (92)	0.87	148 (92)	141 (93)	0.95
AD onset (years since)	4.4 ± 2.5	4.0 ± 2.4	0.11	6.8 ± 2.6	6.9 ± 2.6	0.66
Alcohol abuse, no (%)	7 (4)	4 (2)	0.21	9 (6)	3 (2)	0.14
Smoking, no (%)	38 (23)	56 (24)	0.94	47 (29)	39 (26)	0.57
Weight (kg)	73.6 ± 14.2	71.7 ± 14.2	0.19	70.9 ± 14.3	71.4 ± 13.4	0.74
Height (cms)	167.7 ± 9.7	165.1 ± 10.7	**0.01**	164.6 ± 10.6	165.6 ± 10.6	0.38
Diastolic BP	72.9 ± 10.3	72.9 ± 9.8	0.99	73.2 ± 9.8	76.9 ± 9.1	<**0.001**
Systolic BP	133.4 ± 18.6	132.3 ± 17.8	0.58	136.7 ± 18.4	136.6 ± 16.7	0.99
Total DHA levels	90.0 ± 56.2	88.3 ± 51.0	0.75	—	—	
Total EPA levels	55.1 ± 40.9	53.0 ± 34.2	0.59	—	—	
Cognitive, Behavioral						
MMSE	20.15 ± 3.6	21.04 ± 3.6	**0.02**	17.03 ± 2.9	16.8 ± 2.9	0.48
CDR-SOB	5.74 ± 2.7	5.62 ± 2.6	0.65	7.14 ± 2.9	7.48 ± 2.9	0.30
CDR (treated as continuous)	0.95 ± 0.5	0.97 ± 0.5	0.61	1.17 ± 0.6	1.27 ± 0.5	0.12
CDR			0.56			0.071
0.5	60 (36)	78 (33)		26 (16)	18 (12)	
1	85 (51)	127 (54)		97 (60)	84 (55)	
2	21 (13)	30 (13)		35 (22)	50 (33)	
3	0 (0)	1(0)		3 (2)	0 (0)	
Modified Hachinski	0.62 ± 0.72	0.88 ± 0.81	<0.0001	—	—	
NPI	9.48 ± 10.9	8.69 ± 10.3	0.47	2.52 ± 2.7	3.20 ± 2.6	**0.022**
QOL subject rating	40.64 ± 4.8	39.81 ± 5.2	0.11	40.28 ± 6.0	39.77 ± 5.1	0.42

	AD Clinical Trial 1*			AD Clinical Trial 2		
	Enrollers (N = 166)	**Nonenrollers (N = 236)**	***P*†**	**Enrollers (N = 161)**	**Nonenrollers (N = 152)**	***P*†**
QOL partner rating	36.62 ± 6.1	36.68 ± 5.8	0.92	36.97 ± 6.2	37.57 ± 5.6	0.37
ADCS-ADL	59.17 ± 12.8	60.50 ± 12.4	0.30	54.35 ± 13.5	52.41 ± 13.3	0.20
ADASCog11	24.99 ± 8.5	23.03 ± 9.3	**0.03**	29.27 ± 8.8	30.50 ± 10.0	0.25

Bold values indicates $P<0.05$.

Data were expressed as means±SD for continuous variables and number (%) for categorical variables

*Two individuals had unreadable scans, one owing to poor quality of motion and the other owing to the participant noncompliance and were not considered enrollers.

†From χ^2 (proportions) or *t* test (means); ordinal CDR compared using ordinal logistic regression.

AD indicates Alzheimer disease; ADASCog11, Alzheimer's Disease Cooperative Study 11 item Cognitive scale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; BP, blood pressure; CDR, Clinical Dementia Rating; CDR-SOB, Clinical Dementia Rating Scale-Sum of Boxes; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Exam; NPI, Neuropsychiatric Inventory; QOL, quality of life.

TABLE 2

Comparison of Enrollers and Nonenrollers in the Magnetic Resonance Imaging Substudy at Baseline: Mean Difference and 95% Confidence Intervals Between Groups

	AD Clinical Trial 1		AD Clinical Trial 2	
	Mean Difference	**95% CI**	**Mean Difference**	**95% CI**
Demographics				
Age (years)	− 1.25	− 2.99 0.50	− 1.87	− 3.61, − 0.14
Education (years)	− 0.24	− 0.79, 0.31	− 0.04	− 0.77, 0.70
AD Onset (years since)	0.4	− 0.09, 0.90	− 0.13	− 0.71, 0.45
Weight (kg)	1.87	− 0.96, 4.71	− 0.51	− 3.60, 2.58
Height (cms)	2.54	0.52, 4.56	− 1.06	− 3.42, 1.31
Diastolic BP	− 0.01	− 2.03, 2.01	− 3.74	− 5.84, − 1.63
Systolic BP	1.02	− 2.63, 4.67	0.02	− 3.89, 3.93
Total DHA levels	1.76	− 9.02, 12.54	—	—
Total EPA levels	2.1	− 5.53,9.73	—	—
Cognitive, Behavioral				
MMSE	− 0.89	− 1.61, − 0.17	0.24	− 0.42, 0.89
CDR-SOB	0.12	− 0.40, 0.65	− 0.34	− 0.98, 0.3
Global CDR	− 0.02	− 0.12, 0.07	− 0.10	− 0.22, 0.03
Modified Hachinski	− 0.26	− 0.41, − 0.11	—	—
NPI	0.79	− 1.34, 2.91	−0.68	− 1.26, − 0.10
QOL subject rating	0.83	− 0.20, 1.86	0.51	− 0.74, 1.76
QOL partner rating	− 0.06	− 1.30, 1.17	−0.60	− 1.92, 0.72
ADCS-ADL	− 1.33	− 3.84, 1.19	1.94	− 1.04, 4.92
ADASCog11	1.96	0.19, 3.72	− 1.23	− 3.35, 0.89

AD indicates Alzheimer disease; ADASCog11, Alzheimer's Disease Cooperative Study 11 item Cognitive scale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; BP, blood pressure; CDR-SOB, Clinical Dementia Rating Scale-Sum of Boxes; CI, confidence interval; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; MMSE, Mini Mental State Exam; NPI, Neuropsychiatric Inventory; QOL, quality of life.