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Authors

Relkin, Norman R
Thomas, Ronald G
Rissman, Robert A
et al.

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A phase 3 trial of IV immunoglobulin for Alzheimer disease

Norman R. Relkin, MD, PhD
Ronald G. Thomas, PhD
Robert A. Rissman, PhD
James B. Brewer, MD, PhD
Michael S. Rafii, MD, PhD
Christopher H. van Dyck, MD
Clifford R. Jack, MD
Mary Sano, PhD
David S. Knopman, MD
Rema Raman, PhD
Paul Szabo, PhD
David M. Gelmont, MD
Sandor Fritsch, PhD
Paul S. Aisen, MD
For the Alzheimer's Disease Cooperative Study

Correspondence to Dr. Aisen: paisen@usc.edu

ABSTRACT

Objective: We tested biweekly infusions of IV immunoglobulin (IVIg) as a possible treatment for mild to moderate Alzheimer disease (AD) dementia.

Methods: In a phase 3, double-blind, placebo-controlled trial, we randomly assigned 390 participants with mild to moderate AD to receive placebo (low-dose albumin) or IVIg (Gammagard Liquid; Baxalta, Bannockburn, IL) administered IV at doses of 0.2 or 0.4 g/kg every 2 weeks for 18 months. The primary cognitive outcome was change from baseline to 18 months on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale; the primary functional outcome was 18-month change on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory. Safety and tolerability data, as well as serial MRIs and plasma samples, were collected throughout the study from all enrolled participants.

Results: No beneficial effects were observed in the dual primary outcome measures for the 2 IVIg doses tested. Significant decreases in plasma Aβ42 (but not Aβ40) levels were observed in IVIg-treated participants. Analysis of safety data showed no difference between IVIg and placebo in terms of the rate of occurrence of amyloid-related imaging abnormalities (brain edema or microhemorrhage). IVIg-treated participants had more systemic reactions (chills, rashes) but fewer respiratory infections than participants receiving placebo.

Conclusions: Participants with mild to moderate AD showed good tolerability of treatment with low-dose human IVIg for 18 months but did not show beneficial effects on cognition or function relative to participants who received placebo.

Clinicaltrials.gov identifier: NCT00818662.

Classification of evidence: This study provides Class II evidence that IVIg infusions performed every 2 weeks do not improve cognition or function at 18 months in patients with mild to moderate AD. *Neurology*® 2017;88:1768–1775

GLOSSARY

3MS = modified Mini-Mental State Examination; **Aβ** = β-amyloid; **AD** = Alzheimer disease; **ADAS-Cog** = cognitive subscale of the Alzheimer's Disease Assessment Scale; **ADCS-ADL** = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; **ADCS-CGIC** = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change; **CMH** = cerebral microhemorrhage; **IgG** = immunoglobulin G; **IRB** = institutional review board; **ITT** = intent-to-treat; **IVIg** = IV immunoglobulin; **mITT** = modified intent-to-treat; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; **PP** = per protocol; **QOL-AD** = Quality of Life in Alzheimer's Disease Scale.

Alzheimer disease (AD) is increasing in prevalence and progresses despite currently available treatments. The abnormal brain accumulation of β-amyloid (Aβ) is a ubiquitous and early event in AD pathogenesis, fueling interest in interventions that alter Aβ production or clearance, and various monoclonal anti-Aβ antibodies are under investigation as potential disease-slowing therapies.[1–3] Naturally occurring autoantibodies[4] include anti-Aβ antibodies; in contrast to humanized murine monoclonal antibodies, blood-derived human anti-Aβ immunoglobulin G (IgG) are polyclonal, have lower avidity for single Aβ molecules, and bind preferentially to a broader range of epitopes, including those in Aβ oligomers and fibrils.[5,6] One group reported

Supplemental data at Neurology.org

From Weill Cornell Medicine (N.R.R., P.S.), New York, NY; University of California (R.G.T., R.A.R., J.B.B.), San Diego; University of Southern California (M.S.R., R.R., P.S.A.), Los Angeles; Yale University (C.H.v.D.), New Haven, CT; Mayo Clinic (C.R.J., D.S.K.), Rochester, MN; Mount Sinai School of Medicine (M.S.), New York, NY; and Baxalta (D.M.G., S.F.), Bannockburn, IL.

Coinvestigators are listed at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

the presence of natural anti-Aβ antibodies in IV immunoglobulin (IVIg) and proposed IVIg as a potential AD treatment. IVIg is derived from plasma of healthy donors and contains a majority of the IgG-type antibodies in the human repertoire. IVIg's established safety record and known immunomodulatory and anti-inflammatory properties were considered favorable for testing as a potential AD treatment.[7] Administration of IVIg in murine models of AD resulted in minimal plaque clearance without microhemorrhage or vasogenic edema and promoted neurogenesis.[8] Prior human studies involved small numbers of participants but showed good safety and tolerability, though were underpowered to detect efficacy.[9–14] We report the results of a phase 3 trial testing the safety and efficacy of 2 doses of IVIg in mild to moderate AD dementia.

METHODS

The primary research question of this study was whether IVIg infusions performed every 2 weeks improve cognition or function at 18 months in patients with mild to moderate AD. The study was designed to provide Class I evidence.

Study sites and participants. This was a randomized, parallel-group, placebo-controlled trial in which the blinded study medication was administered to individuals taking stable doses of approved AD medications. The study was conducted at 41 sites in the United States and 4 sites in Canada between December 2008 and February 2013.

Eligible participants were community-dwelling, medically stable adults, aged 50–89 years, clinically diagnosed with probable AD dementia according to the criteria of the National Institute of Neurologic and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association[15] of mild to moderate severity, with an available study partner to report their status throughout the trial. Participants had Mini-Mental State Examination[16] (MMSE) scores between 16 and 26 inclusive. Participants with untreated hypercholesterolemia, immunoglobulin A deficiency, or renal insufficiency were excluded owing to increased risks of IVIg treatment. Treatment with a cholinesterase inhibitor (donepezil or rivastigmine or galantamine), an NMDA antagonist (memantine), or both was allowed if dosing was stable for at least 12 weeks prior to screening. MRI brain scan consistent with AD was required for inclusion; participants with contraindications to MRI were excluded, as were those found to have 2 or more cerebral microhemorrhages, brain infarctions greater than 1 cm^3, or space-occupying brain lesions. Participants were excluded if they showed evidence of other causes of dementia, unstable general medical conditions, or untreated major psychiatric disorders, or were taking other investigational AD medications.

Standard protocol approvals, registrations, and patient consents. This study was approved by the University of California San Diego and each individual site's institutional review boards (IRBs). Written informed consent was obtained from all participants. The study was registered on ClinicalTrials.gov; the registry number is NCT00818662.

Study oversight. The study was approved by the IRB at each participating site. Participants or legally authorized representatives consented for participation. The study was designed by the academic investigators and revised in collaboration with the investigational new drug sponsor (Baxalta, Bannockburn, IL; formerly Baxter Healthcare Corporation). The results represent the consensus of independent analyses performed by the academic investigators and Baxalta.

Study design and treatment. The study evaluated whether 0.4 or 0.2 g/kg IVIg administered every 2 weeks (the 2 most promising regimens in earlier studies) was safe and more effective than placebo in slowing cognitive and functional decline as measured by change from baseline to 18 months on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale[17] (ADAS-Cog) and on the 23-item Alzheimer's Disease Cooperative Study Activities of Daily Living Scale[18] (ADCS-ADL). Secondary objectives included effects on the ADAS-Cog and ADCS-ADL at 9 months and additional measures of behavior, cognition, and caregiver burden at 18 months. Biomarker outcomes included MRI measurement of change in ventricular volume, hippocampal volume, and total brain volume from baseline to 18 months, and change in serum immunoglobulin, plasma Aβ-40 and Aβ-42 levels, and anti-Aβ antibodies from baseline to 18 months. Substudies assessed change in cerebral Aβ burden by ^{18}F-florbetapir PET and CSF analysis of tau, phospho-tau, Aβ-42, and anti-Aβ levels.

The study had 80% power at an α level of 0.05 to detect a mean difference of 3.25 points on the ADAS-Cog and a 4.52-point mean difference on the ADCS-ADL between the 0.4 g/kg IVIg treatment arm and placebo control over 18 months. Participants were assigned (1:1:1) to IVIg 0.4 g/kg, IVIg 0.2 g/kg, or placebo. A stratified (site, MMSE [≤20, >20], and *APOE* ε4 carriage), permuted-block randomization procedure was used.

Study participants and study partners, site personnel including clinicians and raters, and study team leadership remained blinded to treatment assignments until after locking of the study dataset.

Outcome measures. The ADAS-Cog was assessed at baseline and every 3 months through month 18. The ADCS-ADL was administered at baseline, 9 months, and 18 months. Additional cognitive measures including the modified MMSE[19] (3MS) and select neuropsychological tests were administered at baseline and 9 and 18 months. The Neuropsychiatric Inventory[20] (NPI), the Quality of Life in Alzheimer's Disease Scale (QOL-AD),[21] and the Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change (ADCS-CGIC)[22] scales were also assessed.

Volumetric measures were made using 3D T1-weighted sequences and analyzed longitudinally. NeuroQuant (CorTechs Labs, Inc., San Diego, CA) was used to segment images, and Quarc, an inverse-consistent nonlinear registration method,[23] was used to assess regional deformation between baseline and each follow-up time point. The change in lateral ventricular volume from baseline to 18 months was the preplanned primary volumetric imaging outcome, supplemented by change in whole brain and hippocampal volume from baseline to 18 months.

Blood samples were obtained to determine *APOE* genotype and monitor hematology and chemistry safety parameters. In addition, serum and plasma samples were drawn to determine total immunoglobulin and levels of Aβ-40 and Aβ-42. Aβ assays used the Meso Scale Discovery (Rockville, MD) platform. CSF anti-monomer and anti-oligomer anti-Aβ assays were performed at Weill Cornell Medical College by a validated ELISA previously reported.[5]

Populations. The modified intent-to-treat (mITT) population consisted of all participants who were randomized and completed at least one postbaseline outcome evaluation. The safety population consisted of all participants who received at least one dose of study medication. The per protocol (PP) population comprised those who completed 90% of the prescribed infusions and the planned evaluation at month 18.

For subgroup analyses, all participants who underwent 2 ^{18}F-florbetapir PET scans at baseline and 18 months were included in the brain Aβ analyses. Participants who had ^{18}F-fluorodeoxyglucose PET scans at baseline and 9 months were included in the cerebral metabolism analyses. The CSF substudy group included all participants who underwent a successful lumbar puncture at baseline and at least one other time point at 9 or 18 months.

Safety and tolerability monitoring. Safety was assessed on the basis of adverse events, which were recorded at each visit based on history, examinations, and laboratory tests. The study was monitored by an independent Data and Safety Monitoring Board whose members were aware of the arm assignments and reviewed the safety data every 3 months as well as data from a single interim futility analysis.

Statistical analysis. For the primary and secondary analyses of efficacy, analysis of covariance models were employed to assess change in the intent-to-treat (ITT) population from baseline to 18 months on the ADAS-Cog and ADCS-ADL scales. The dependent variable was change in score from baseline to 18 months. Study assignment (IVIg 0.2 g/kg, IVIg 0.4 g/kg, placebo) and *APOE* ε4 carriage were treated as fixed effects (independent variables) in the model. Continuous covariates included the baseline scores, baseline age, and years of education. The multiple imputation method was employed to account for missing data at 18 months. The analysis plan required positive outcomes in both of the co-primary measures to establish efficacy, and dose effects were tested in a hierarchical fashion with primacy given to the comparison of the 0.4 g/kg dose to placebo.

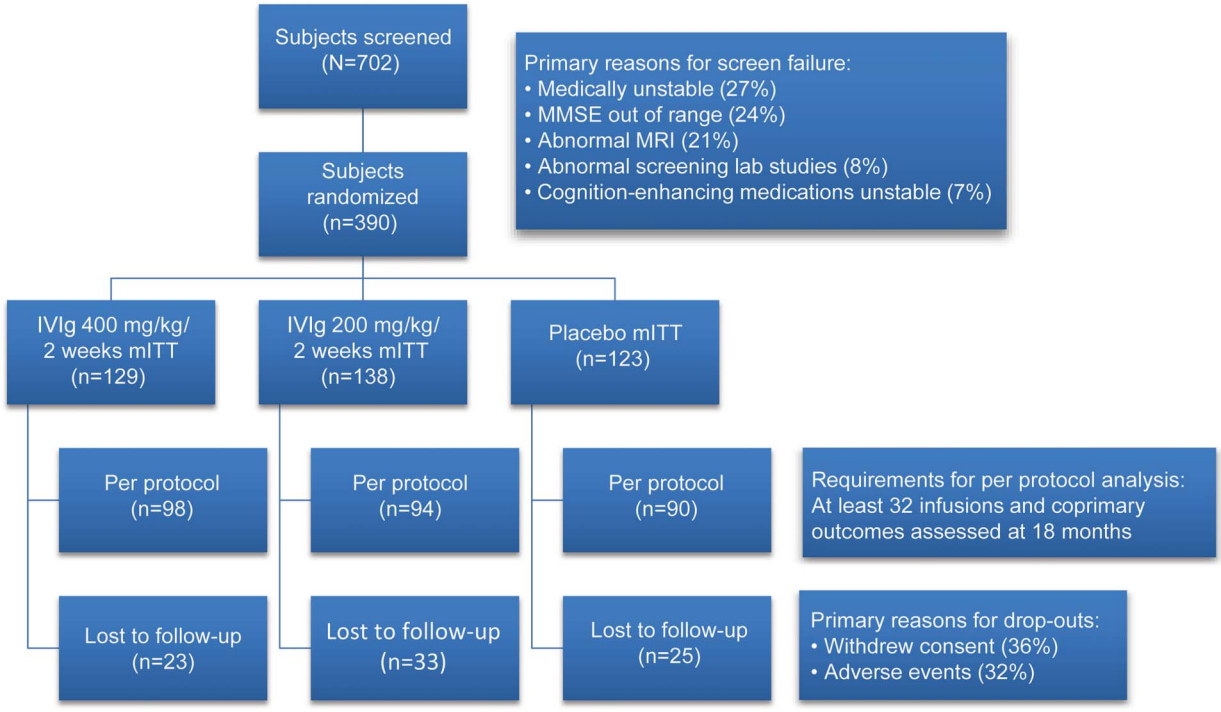
The primary study outcomes were assessed in the mITT population; secondary analyses were also performed on the PP population. Secondary efficacy outcome measures included change from baseline at 9 months in ADAS-Cog, ADCS-ADL, ADCS-CGIC, NPI, and QOL-AD. Preplanned secondary analyses included a comparison of the effects of IVIg and placebo on the PP population stratified by *APOE* ε4 carrier status and level of cognitive impairment (defined as mild for participants with a baseline MMSE score of 21–26 and moderate for those with baseline MMSE scores from 16 to 20).

RESULTS

Participant disposition. The disposition of enrolled participants is shown in figure 1. The number of participants randomized to receive 0.2 g/kg IVIg was 138, for 0.4 g/kg IVIg arm 129, and for placebo arm 123. The PP population represented 72.3% of those randomized, including 75.9% of participants randomized to 0.4 g/kg IVIg, 68.1% to 0.2 g/kg IVIg, and 73.2% to placebo.

A total of 81 participants discontinued from the study after randomization, representing a 20.8% attrition rate. The rate of attrition was 17.8% from the 0.4 g/kg IVIg arm, 23.9% from the 0.2 g/kg arm, and 20.3% from the placebo arm. Reasons for discontinuation that occurred in at least 2 or more participants included adverse events (n = 26), withdrawn consent or inability to participate (n = 29), study partner dropout (n = 7), death (n = 4), and

Figure 1 Participant flow



IVIg = IV immunoglobulin; mITT = modified intent to treat; MMSE = Mini-Mental State Examination.

Table 1 Demographic characteristics (intent-to-treat dataset)

Characteristics	IVIg 0.4 g/kg (n = 129)	IVIg 0.2 g/kg (n = 138)	Placebo, all doses (n = 123)	Total (n = 390)
Age, y	70.6 ± 9.7	70.1 ± 8.3	70.2 ± 9.9	70.3 ± 9.3
Female	70 (54.3)	77 (55.8)	66 (53.7)	213 (54.6)
White race	128 (99.2)	133 (96.4)	120 (97.6)	381 (97.7)
Education, y	15.3 ± 2.9	15.7 ± 3.2	15.4 ± 3.0	15.5 ± 3.0
MMSE total score	21.3 ± 3.2	21.5 (3.1)	21.1 (3.2)	21.3 (3.2)
AD duration, y	5.4 ± 2.6	4.9 ± 2.5	5.1 ± 2.2	5.1 ± 2.4
AD mild stage (MMSE 21–26)	83 (64.3)	83 (60.1)	68 (55.3)	234 (60.0)
AD moderate stage (MMSE 16–20)	46 (35.7)	55 (39.9)	55 (44.7)	156 (40.0)
APOE ε4 carrier	87 (67.4)	94 (68.1)	85 (69.1)	266 (68.2)
APOE ε4 heterozygote	64 (49.61)	70 (50.73)	63 (51.22)	197 (50.5)
APOE ε4 homozygote	23 (17.83)	24 (17.39)	22 (17.89)	69 (17.70)

Abbreviations: AD = Alzheimer disease; IVIg = IV immunoglobulin; MMSE = Mini-Mental State Examination.
Values are n (%) or mean ± SD.

protocol violations (n = 2). An additional 13 discontinuations occurred for other reasons.

The demographic characteristics of the ITT population are presented in table 1. Randomization was stratified based on *APOE* ε4 carrier status and disease stage. As a consequence, the 3 study arms were closely matched with respect to these parameters as well as other baseline characteristics.

The mean (29.9, 30.5) number of infusions received was similar across treatment and placebo groups, respectively. There were a total of 34 infusions where the actual dose was at least 50% less than the planned volume, with a mean (SD) number of infusions per participant of 1.3 (0.87) in the 0.4 g/kg dose group, 1.1 (0.38) in the 0.2 g/kg dose group, and 1.2 (0.44) in the placebo dose group.

Efficacy. No differences were observed among the groups receiving IVIg and placebo on the 2 primary outcome measures, the ADAS-Cog and the ADCS-ADL, at 18 months (figure 2, A and B). The mean changes in ADAS-Cog from baseline to month 18 were 7.42, 8.94, and 8.43 for the 400 mg/kg, 200 mg/kg, and placebo dose groups, respectively. The mean changes in ADCS-ADL from baseline to month 18 were −11.4, −12.4, and −11.4 for the 400 mg/kg, 200 mg/kg, and placebo dose groups, respectively. Likewise, no differences were observed among the IVIg and placebo treatment groups on the secondary outcomes including the ADCS-CGIC, 3MS, NPI, QOL-AD, and supplemental neuropsychological tests in either the ITT (table 1) or the PP populations (not shown).

Preplanned secondary analyses compared the effects of IVIg to placebo on the PP population stratified by *APOE* ε4 carrier status and level of impairment. Less decline at 18 months on the 3MS (100-point scale with lower scores indicating greater impairment) were observed among *APOE* ε4 carriers treated with the 0.4 g/kg IVIg dose (change from baseline −10.6 points) compared to placebo (change from baseline −14.9 points) (p = 0.012, unadjusted). No differences from placebo were observed in analyses using the prespecified MMSE cutoff point or for 0.2 g/kg IVIg dose on any of the measures administered.

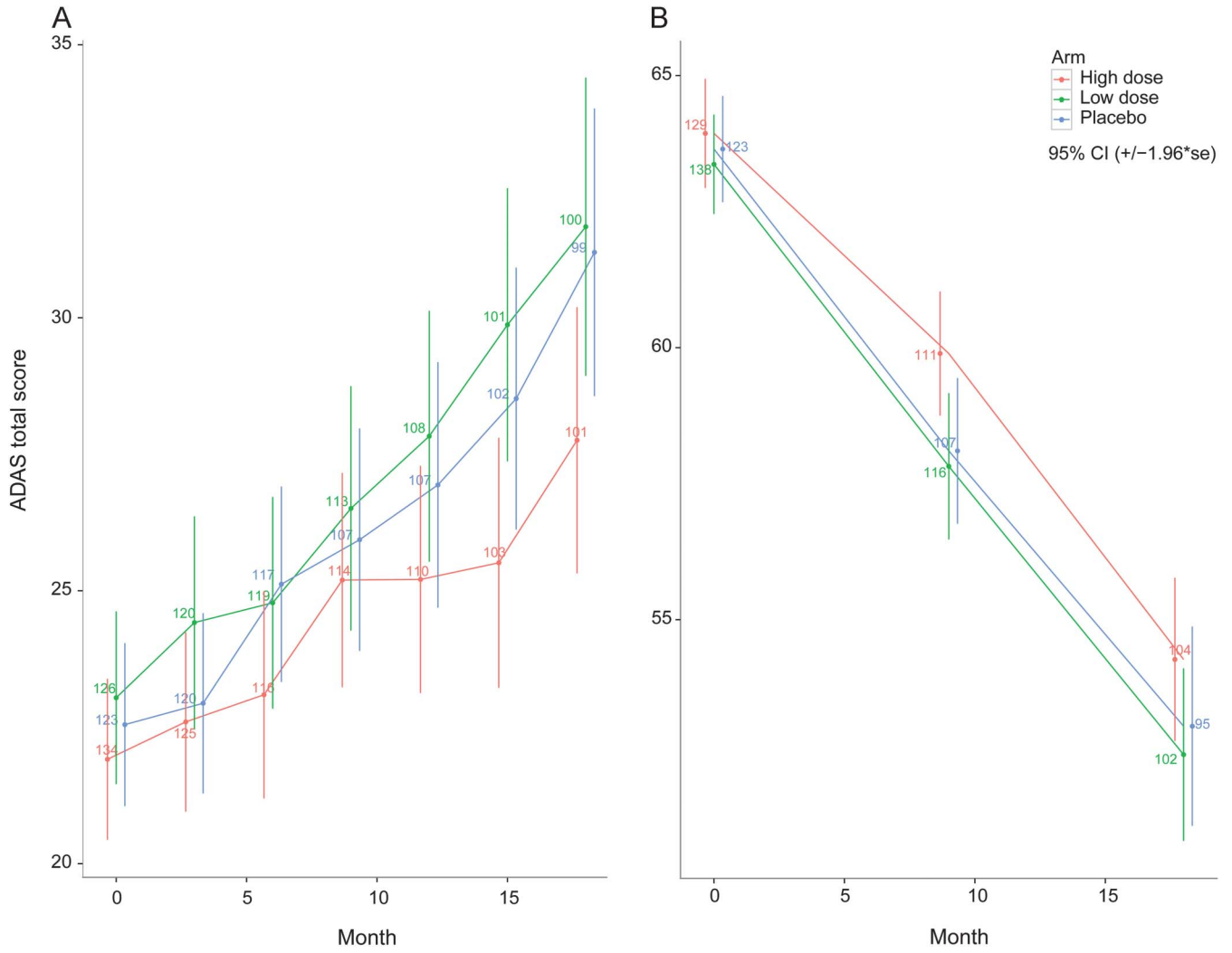
Key biomarker outcomes. At 18 months, mean serum IgG nearly doubled to 17.2 g/L in the 0.4 g/kg IVIg treatment arm (δ = 7.31 g/L, range 8.58–25.9, n = 100), increased by 37% to 13.64 g/L in the 0.2 g/kg arm (δ = 3.37 g/L, range 7.17–20.8, n = 99), and was essentially unchanged at 9.59 g/L in the placebo-treated group (δ = 0.07 g/L, n = 93). Parallel increases in CSF IgG levels were detected in IVIg-treated participants at 9 and 18 months; however, only 35 participants had evaluable CSF data at 18 months.

No changes in plasma Aβ-40 levels were observed in any of the treatment groups. In contrast, at 18 months plasma Aβ-42 levels declined by 7.91 ng/mL in the 0.4 g/kg IVIg arm, 3.51 ng/kg in the 0.2 g/kg arm, and 1.35 in the placebo group (figures e-1 and e-2 at Neurology.org). The differences from baseline in plasma Aβ-42 levels were significant for the 0.4 g/kg (p = 0.001) and 0.2 g/kg (p = 0.001) IVIg doses but not for placebo.

Mean change from baseline to month 18 in ventricular volume (the prespecified primary MRI outcome) was not different among the 0.4 g/kg, 0.2 g/kg, and placebo dose groups. Likewise, there were no differences in rate of change of hippocampal or whole brain volume over 18 months in the IVIg-treated participants compared to those who received placebo (figure e-3).

Analysis of CSF biomarkers in a subset of participants, including Aβ species, tau, and phospho-tau,

Figure 2 **Primary outcomes**



(A) Estimated mean change from baseline to 18 months on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS) (scores ranging from 0 to 70 and higher scores indicating impairment) for the modified intent-to-treat population based on analysis of covariance analysis. No significant differences were observed. (B) Estimated mean change from baseline on the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (scores ranging from 0 to 78 and higher scores indicate less functional impairment). Error bars indicate estimated standard errors. No significant differences were observed. Numbers indicate participants contributing to the analysis at each timepoint. CI = confidence interval.

did not show any treatment effect (figure e-4). A numerical increase in CSF anti-Aβ oligomer antibodies (but not anti-Aβ monomer) was observed with high-dose treatment, but this was not different from the other groups (figures e-5 and e-6).

An exploratory PET substudy measured cerebral Aβ burden using the radioligand ^{18}F-AV-45 (Florbetapir; Eli Lilly and Company, Indianapolis, IN). Mean changes from baseline to month 18 were −0.062, −0.047, and −0.013 for the 0.4 g/kg, 0.2 g/kg, and placebo dose groups, respectively. With a total of 61 participants with evaluable ^{18}F-AV-45 at 18 months, the differences were not significant.

Safety. Safety outcomes from the study are summarized in tables 2 and 3. IVIg treatment was not associated with death or serious morbidity. Nonserious adverse events reported with greater frequency in IVIg-treated participants included rash requiring treatment and decreases in hemoglobin levels. Rashes tended to be maculopapular in nature, a kind previously associated with IVIg therapy. Decreases in hemoglobin levels were detected by surveillance laboratory tests and were not associated with symptoms of anemia. Other adverse occurrences associated with IVIg treatment included infusion-related events such as chills, arthralgia, vomiting, epistaxis, and eczema, which occurred only rarely. Fewer upper respiratory infections were seen in IVIg-treated than placebo-treated participants.

The rate of occurrence of cerebral microhemorrhages (CMH) was similar in the IVIg-treated participants and the placebo groups (10, 8, and 9 treatment-emergent microhemorrhages in for the

Table 2 Results of secondary clinical outcome analyses in the modified intent-to-treat population

Study assessment	Change from baseline (95% CI)			Difference in LSM change 0.4 g/kg vs placebo	Difference in LSM change 0.2 g/kg vs placebo
	0.4 g/kg (n = 129)	0.2 g/kg (n = 138)	Placebo (n = 123)		
Change at month 9 in ADAS-Cog (LSM)	3.1 (1.9 to 4.3)	4.6 (3.4 to 5.8)	3.6 (2.4 to 4.9)	−0.5 (−2.2 to 1.2), $p = 0.586$	1.0 (−0.7 to 2.7), $p = 0.237$
Change at month 9 in ADCS-ADL (LSM)	−5.4 (−7.2 to −3.6)	−5.7 (−7.6 to −3.9)	−5.6 (−7.5 to −3.7)	0.2 (−2.4 to 2.8), $p = 0.878$	−0.1 (−2.7 to 2.4), $p = 0.912$
ADCS-CGIC (LSM)	5.2 (5.0 to 5.3)	5.3 (5.1 to 5.4)	5.2 (5.0 to 5.4)	−0.1 (−0.3 to 0.2), $p = 0.660$	0.0 (−0.2 to 0.3), $p = 0.766$
NPI (mean)	3.7 (1.2 to 6.3)	4.9 (2.3 to 7.5)	2.4 (0.2 to 4.6)	0.7 (−2.1 to 3.4), $p = 0.640$	2.5 (−0.3 to 5.3), $p = 0.075$
Logsdon QOL-AD (subject) (mean)	−0.5 (−1.5 to 0.6)	−0.7 (−1.6 to 0.2)	−1.5 (−2.6 to −0.4)	1.1 (−0.2 to 2.3), $p = 0.093$	1.1 (−0.2 to 2.3), $p = 0.094$
Logsdon QOL-AD (caregiver) (mean)	−3.0 (−4.0 to −2.0)	−2.5 (−3.5 to −1.5)	−1.6 (−2.7 to −0.6)	−1.1 (−2.3 to 0.2), $p = 0.096$	−1.0 (−2.2 to 0.3), $p = 0.123$

Abbreviations: ADAS-Cog = cognitive subscale of the Alzheimer's Disease Assessment Scale; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change; CI = confidence interval; LSM = least squares method; NPI = Neuropsychiatric Inventory; QOL-AD = Quality of Life in Alzheimer's Disease Scale.

0.4 g/kg, 0.2 g/kg, and placebo dose groups, respectively). One participant treated with 0.4 g/kg IVIg who was homozygous for the *APOE* ε4 allele developed asymptomatic vasogenic edema that was detected on a surveillance MRI performed 5 weeks after initiation of IVIg infusions. Subsequent MRI studies showed resolution of vasogenic edema and development of a microhemorrhage at the location of the initial edema.

DISCUSSION In an adequately powered, randomized, placebo-controlled clinical trial that enrolled patients with mild to moderate AD dementia, we found no differences between 2 doses of IVIg and a placebo on the coprimary (ADAS-Cog and ADCS-ADL) or secondary clinical endpoints (NPI, 3MS, and QOL-AD). We found elevated IgG levels in CSF samples from IVIg-treated participants, as well as a numerical increase in anti-Aβ-oligomer antibodies in the high-dose arm that was not different from other arms, suggesting that potentially therapeutic autoantibodies administered IV were able to reach the CNS. The dose-related reduction by IVIg of plasma Aβ42 but not Aβ40 levels may reflect preferential sequestration of self-assembling Aβ42 molecules by confirmation-selective anti-amyloid antibodies in IVIg and plasma.[5] A selective interference effect on the Aβ42 assay is possible[24] but seems less likely.

The tolerability of IVIg in patients with AD was acceptable, as was safety, consistent with profiles that have emerged from studies of IVIg's various indications. Decreased hemoglobin levels in association with IVIg treatment occurred with greater frequency than in controls. Hemoglobin decreases from IVIg treatment were generally mild and self-limiting, not requiring discontinuation of treatment; the cause did not appear to be hemolysis. Maculopapular rash necessitated discontinuation of the study medication in cases in which the rash was particularly extensive or recurrent despite treatment.

IVIg showed no predilection to cause CMH in the present study. Vasogenic edema sometimes occurs as part of the natural history of AD,[25] so the relatedness of the single observed event to IVIg is uncertain.

There was no indication in the present study that mildly impaired patients with AD dementia benefited more from IVIg than those with moderate impairment. This is noteworthy because there is an emerging belief that anti-Aβ agents might be more effective

Table 3 Serious adverse events

Event	IVIg 0.4 g/kg (n = 127), n (%)	IVIg 0.2 g/kg (n = 135), n (%)	Placebo (n = 121), n (%)
Deaths during or after treatment	1 (0.8)	3 (2.2)	2 (1.7)
Hospitalization due to an adverse event	19 (15.0)	26 (19.3)	24 (19.8)
Rash requiring therapy	19 (15.0)	16 (11.9)	8 (6.6)
Renal failure	2 (1.6)	1 (0.7)	2 (1.7)
Venous thromboembolic events	2 (1.6)	3 (2.2)	6 (5.0)
Arterial thrombosis (myocardial infarction, stroke)	1 (0.8)	0 (0.0)	1 (0.8)
Upper respiratory infections	16 (12.6)	24 (17.8)	28 (23.1)

Abbreviation: IVIg = IV immunoglobulin.

in very early stages when AD pathology is primarily Aβ-related compared to later stages in which other collateral pathology is present.[26] In the preplanned secondary analysis stratified by disease severity, the ADAS-Cog and 3MS results numerically favored patients in moderate stage over mild (but were not different), the opposite pattern of response to what might be expected for a purely anti-Aβ treatment.

The lack of clinical efficacy of IVIg in the current study diverges from encouraging reports in some earlier phase investigations[9,10]; the previous studies were too small to determine efficacy. The rationale for studying low doses of IVIg was partially pharmacoeconomic, since IVIg is in short supply and relatively expensive. IVIg use in other neurologic disorders generally involves a higher dose, up to 2 g/kg infusion. The doses tested here were commensurate with those used for antibody replacement therapy rather than anti-inflammatory effects; to target inflammation in AD, higher doses may be necessary. It is also plausible that anti-amyloid immunotherapy must be administered earlier in the disease process for optimal efficacy.[26] However, the results of this trial do not lend support for the use of IVIg to treat AD. Other anti-amyloid immunotherapy strategies, particularly with monoclonal antibodies specific for amyloid peptide epitopes or conformation, provide greater promise for disease-modifying therapy in AD.

AUTHOR CONTRIBUTIONS

Dr. Relkin: study concept and design, interpretation of data, drafting of manuscript. Dr. Thomas: statistical design and analysis. Dr. Rissman: study design, analysis and interpretation. Dr. Brewer: study design, analysis and interpretation. Dr. Rafii: study design, analysis and interpretation. Dr. van Dyck: data acquisition and interpretation. Dr. Jack: study design, analysis and interpretation. Dr. Sano: study design, analysis and interpretation. Dr. Knopman: interpretation of data. Dr. Raman: study design and statistical analysis. Dr. Szabo: study design and analysis. Dr. Gelmont: study design and interpretation. Dr. Fritsch: statistical analysis. Dr. Aisen: study concept and design, analysis and interpretation of data, revision of manuscript.

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DISCLOSURE

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