Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial

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Summary

Background Three small trials suggest that intravenous immunoglobulin can affect biomarkers and symptoms of mild-to-moderate Alzheimer's disease. We tested the safety, effective dose, and infusion interval of intravenous immunoglobulin in such patients.

Methods We did a multicentre, placebo-controlled phase 2 trial at seven sites in the USA and five in Germany. Participants with probable Alzheimer's disease aged 50–85 years were randomly assigned (by a computer-generated randomisation sequence, with block sizes of eight) to infusions every 4 weeks (0·2, 0·5, or 0·8 g intravenous immunoglobulin per kg bodyweight, or placebo) or infusions every 2 weeks (0·1, 0·25, or 0·4 g/kg, or placebo). Patients, caregivers, investigators assessing outcomes, and staff at imaging facilities and the clinical research organisation were masked to treatment allocation, but dispensing pharmacists, the statistician, and the person responsible for final PET analyses were not. Treatment was masked with opaque pouches and infusion lines. The primary endpoint was median area under the curve (AUC) of plasma amyloid β ($Aβ_{1–40}$) between the last infusion and the final visit (2 weeks or 4 weeks depending on infusion interval) in the intention-to-treat population. The trial is registered at ClinicalTrials.gov (NCT00812565) and controlled-trials.com (ISRCTN64846759).

Findings 89 patients were assessed for eligibility, of whom 58 were enrolled and 55 included in the primary analysis. Median AUC of plasma $Aβ_{1–40}$ was not significantly different for intravenous immunoglobulin compared with placebo for five of the six intervention groups (–18·0 [range –1347·0 to 1068·5] for 0·2 g/kg, –364·3 [–5834·5 to 1953·5] for 0·5 g/kg, and –351·8 [–1084·0 to 936·5] for 0·8 g/kg every 4 weeks *vs* –116·3 [–1379·0 to 5266·0] for placebo; and –13·8 [–1729·0 to 307·0] for 0·1 g/kg, and –32·5 [–1102·5 to 451·5] for 0·25 g/kg every 2 weeks *vs* 159·5 [51·5 to 303·0] for placebo; p>0·05 for all). The difference in median AUC of plasma $Aβ_{1–40}$ between the 0·4 g/kg every 2 weeks group (47·0 [range –341·0 to 72·5]) and the placebo group was significant (p=0·0216). 25 of 42 (60%) patients in the intervention group versus nine of 14 (64%) receiving placebo had an adverse event. Four of 42 (10%) patients in the intravenous immunoglobulin group versus four of 14 (29%) receiving placebo had a serious adverse event, including one stroke in the intervention group.

Interpretation Intravenous immunoglobulin may have an acceptable safety profile. Our results did not accord with those from previous studies. Longer trials with greater power are needed to assess the cognitive and functional effects of intravenous immunoglobulin in patients with Alzheimer's disease.

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Introduction

Alzheimer's disease is the most common form of dementia in elderly people and available symptomatic treatments have little effectiveness.[1] Intravenous immunoglobulin might have beneficial effects on the pathogenic processes of Alzheimer's disease (as assessed by biomarkers) and might improve symptoms in patients with the illness.[2–5] Intravenous immunoglobulin is a fractionated blood product used to treat several medical conditions.[6] The rationale for using it to treat Alzheimer's disease is based on the existence of naturally occurring antibodies directed against amyloid β (Aβ); these antibodies might interfere with metabolism of Aβ and seem to be reduced in patients with Alzheimer's disease.[3,7]

Three small clinical trials have tested the efficacy of intravenous immunoglobulin for mild-to-moderate Alzheimer's disease. In an initial uncontrolled trial,[2] five patients received 1·2 g/kg intravenous immunoglobulin every 4 weeks for 6 months. The concentration of total Aβ decreased in CSF and increased in blood compared with baseline. The patients had no cognitive deterioration. These results were independently reproduced in an uncontrolled trial[5] with eight patients (given 0·4–2·0 g/kg per month for 6 months). Finally, a placebo-controlled (saline) multiple dose study[8] of 24 patients (given 0·2 g/kg or 0·4 g/kg once every 2 weeks or 0·4 g/kg or 0·8 g/kg per month for 6 months) has been done. Patients who were treated with intravenous

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immunoglobulin 0·4 g/kg every 2 weeks had the best outcome, with no decline in cognitive and functional measures. The results have not yet been published in full.

The most effective dose and the best treatment interval to maximise effectiveness while minimising safety risks are unknown, although preliminary data[5,8,9] support the use of a 2 week infusion schedule rather than a 4 week schedule. We did an exploratory phase 2 dose-finding study to test the safety, effective dose, and infusion interval of treatment with intravenous immunoglobulin for patients with mild-to-moderate Alzheimer's disease.

Methods

Study design and participants

We did this double-blind, block-randomised, placebo-controlled, parallel group, multicentre trial at 12 sites (hospitals, research centres, and private clinics; five in Germany and seven in the USA). The inclusion criteria were: probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria,[10] mini-mental state examination score of 16–26,[11] age 50–85 years at baseline, a modified Hachinski-Rosen score of less than 5, and an MRI scan consistent with Alzheimer's disease. Patients had to have been taking a stable dose of an approved Alzheimer's disease drug for at least 3 months before screening.

Exclusion criteria were: any suspected cause of dementia other than Alzheimer's disease, history or presence of another significant disease of the CNS, a score of more than 7 on the geriatric depression scale,[12] present significant psychiatric disorder, insulin-dependent diabetes mellitus, uncontrolled hypertension, severe liver or kidney disease, history of thromboembolic events, or history of hypersensitivity to blood-derived or plasma-derived products or intravenous immunoglobulin in the previous 6 months.

The study was approved by each site's ethics committee or institutional review board and by the regulatory authorities (US Food and Drug Agency and the Paul-Ehrlich-Institute [Germany]). Each patient provided written informed consent before study participation. An independent data-monitoring committee assessed treatment safety throughout the trial.

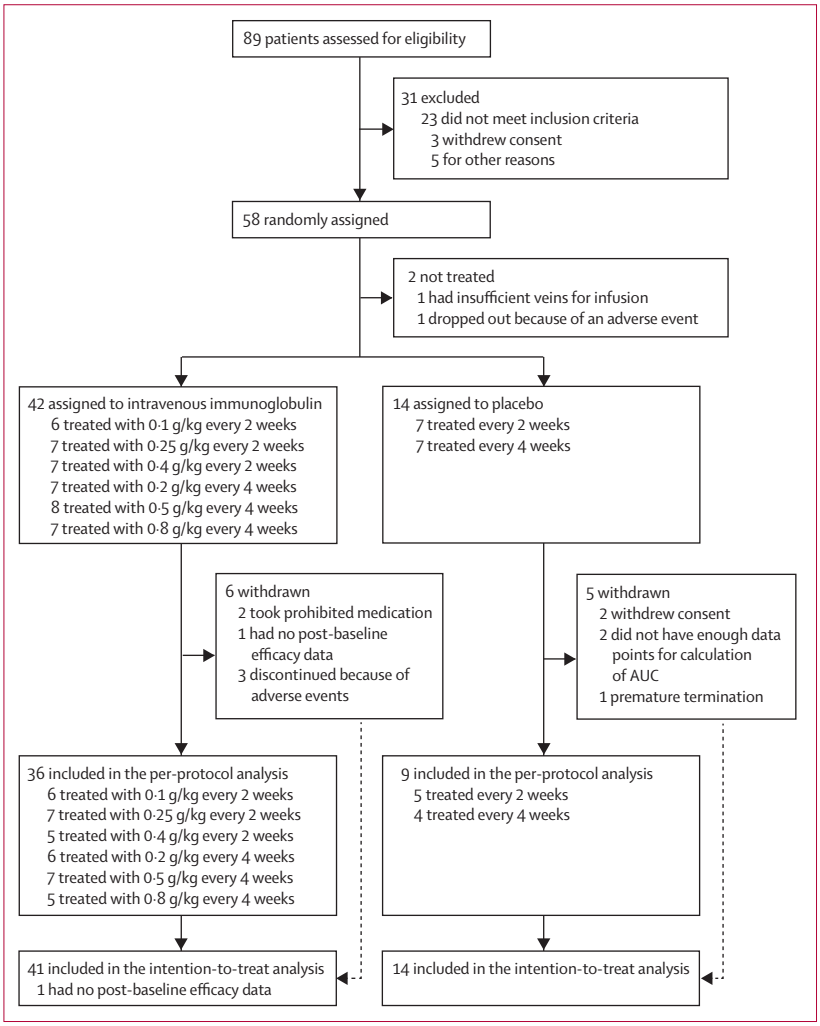

Figure 1: **Trial profile**
AUC=area under the curve.

Randomisation and masking

Patients were randomly allocated to receive one of three doses of intravenous immunoglobulin (0·2 g/kg, 0·5 g/kg, or 0·8 g/kg) or placebo (0·9% isotonic sodium chloride) every 4 weeks, or half of that dose (0·1 g/kg, 0·25 g/kg, or 0·4 g/kg) every 2 weeks. The randomisation was done with a computer-generated randomisation list created by the contract research organisation with SAS (version 9.1.3). Patients were allocated through an interactive web response service in block sizes of eight.

The study drug was contained in ethylene vinyl acetate bags masked by opaque pouches. It was prepared at local pharmacies and dispensed by pharmacists who were not masked to the allocation. Infusion was done by a physician who was masked to the patient's allocation and not involved in any assessments. Patients, caregivers, investigators assessing outcomes, staff of imaging facilities and of the clinical research organisation were masked to treatment allocation, but the statistician and the person responsible for the final PET analyses were not.

Procedures

Study drug and placebo were pooled aseptically by the hospital pharmacist in three separate 0·5 L bags (depending on the dose group, patients received either three of intravenous immunoglobulin, two of intravenous immunoglobulin and one of placebo, one of intravenous immunoglobulin and two of placebo, or three of

placebo) and were administered intravenously after neuropsychometric tests at the respective visits. The same volume and infusion rate (appendix) were used in the intervention and corresponding placebo groups.

Each patient took part in the trial for 24 weeks. Patients on a 2-week treatment interval received their last treatment at week 22, while patients on a 4-week treatment interval received their last treatment at week 20. Blood sampling (to calculate area under the curve [AUC]) was done before the last infusion and on days 1 (±1), 4 (±1), 7 (±1), and 14 (±2) after the week 22 infusion for patients on the 2-week interval schedule, and on days 1 (±1), 4 (±1), 7 (±1), 14 (±2), 21 (±2), and 28 (±2) after the week 20 infusion for patients on the 4-week interval schedule. For safety and volumetric analyses, MRI scans were done at screening and after 12 and 24 weeks with 1·5 T MRI scanners. We also did ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scans at baseline. The appendix shows details of ^{18}F-FDG PET and MRI procedures, and CSF sampling and analyses.

The primary outcome was the median AUC of plasma concentration of $A\beta_{1–40}$ between the last infusion and the final visit (2 weeks or 4 weeks depending on infusion interval) in the intention-to-treat population. Peripherally administered antibodies against Aβ can induce a shift of Aβ from the CSF to the blood, thereby reducing the cerebral Aβ burden (the peripheral sink hypothesis).[13] In agreement with this hypothesis, earlier studies[2,5] showed that intravenous immunoglobulin increased plasma concentration and decreased CSF concentration of Aβ. $A\beta_{1–40}$ is the most abundant and, at the time of the study, the most reliably measured Aβ moeity in human plasma, thus, we used it as our primary marker.[14] Because of the dynamics of the effects of intravenous immunoglobulin over time, we judged that the AUC[15] was a more appropriate measure than was a single time point measure. We compared the primary endpoint measures for the six different study drug dose groups with their corresponding placebo groups.

Secondary outcome measures included: the AUC for plasma concentration of $A\beta_{1–42}$ and of anti-Aβ autoantibodies, plasma concentration of $A\beta_{1–40}$, $A\beta_{1–42}$, and anti-Aβ autoantibodies at week 24 compared with baseline, and change in CSF concentration of $A\beta_{1–40}$, $A\beta_{1–42}$, and anti-Aβ autoantibodies, total tau, and p-tau_{181}, 24 h (±8 h) after last infusion compared with baseline, all assessed in the intention-to-treat population.

Other secondary outcomes were scores on: the Alzheimer's disease assessment scale—cognitive part, the clinical dementia rating scale—sum of boxes, the Alzheimer's Disease Cooperative Study—activities of daily living scale, and the mini-mental state examination at baseline and at week 12 or 24. Secondary brain imaging outcomes were: change in whole brain volume and change in hippocampus volume between baseline and week 12 and week 24, and change in glucose metabolism between baseline and week 24, all assessed in the intention-to-treat population.

Statistical analysis

Because this trial was an exploratory phase 2 study, we did no confirmatory hypothesis testing. The sample size was determined empirically, on the basis of a previous study.[2] We estimated that we would need 48 patients with a complete AUC for plasma $A\beta_{1–40}$. Accounting for a potential dropout rate of 14%, we planned to enrol 56 patients.

We calculated concentrations for each blood sample. The AUC was calculated by the linear trapezoidal rule (ie, by summation of the trapezoid areas formed by the time intervals t_n to $t_{n–1}$ and the change in the baseline plasma concentrations as heights). Areas below the abscissa reduced the overall AUC.

We assessed the differences between the AUC for each dose of study drug and its corresponding placebo by calculating the Hodges-Lehmann estimate of the difference between the two medians and the

See Online for appendix

	Intravenous immunoglobulin (n=41)	Placebo (n=14)
Demographics		
Age (years)	69·4 (7·3)	72·0 (10·2)
Women	15 (37%)	9 (64%)
White	40 (98%)	12 (86%)
Weight (kg)	77·6 (14·1)	71·8 (17·7)
Duration of symptoms (months)	29·6 (27·3)	23·6 (21·9)
APOE ε4 carrier	30 (73%)	10 (71%)
Use of acetylcholinesterase inhibitor or memantine	36 (88%)	11 (79%)
Clinical measurements		
Modified Hachinski-Rosen score	0·6 (0·6)	1·0 (0·4)
Geriatric depression scale score	1·6 (1·5)	1·7 (2·0)
Mini-mental state examination score	21·3 (2·8)	21·9 (2·4)
Alzheimer's disease assessment scale cognitive behaviour subscale score	20·5 (8·5)	19·5 (10·5)
Clinical dementia rating—sum of boxes score	4·7 (2·0)	5·0 (3·1)
Alzheimer's Disease Cooperative Study—activities of daily living inventory score	65·1 (9·2)	63·3 (11·1)
Laboratory measurements		
$A\beta_{1–40}$ concentration (×10^{-9} g/L)		
CSF	8366·8 (2428·3)	9237·0 (2799·7)
Plasma	180·6 (43·9)	174·4 (57·1)
$A\beta_{1–42}$ concentration (×10^{-9} g/L)		
CSF	300·6 (122·9)	363·9 (138·0)
Plasma	42·3 (11·8)	38·1 (9·2)
Total tau concentration (CSF; ×10^{-9} g/L)	711·9 (432·2)	600·4 (257·7)
p-tau_{181} concentration (CSF; ×10^{-9} g/L)	105·7 (53·0)	93·7 (28·3)
Anti-Aβ autoantibodies		
CSF (relative units)	3·6 (6·7)	5·8 (9·9)
Plasma (relative units)	646·6 (1342·2)	794·1 (1062·1)
Microbleeds (number of patients)	8 (20%)	1 (7%)
Normalised whole brain volume (cm^3)	1288·9 (73·3)	1275·9 (120·3)
Left hippocampus volume (mm^3)	2650·5 (478·3)	2608·2 (491·0)
Right hippocampus volume (mm^3)	2829·6 (491·8)	2665·6 (434·3)

Data are mean (SD) or n (%). Aβ=amyloid β.

Table 1: **Overall baseline characteristics of patients in the intention-to-treat population**

corresponding non-parametric 95% CI. We also calculated the p value by Wilcoxon rank sum test; p<0·05 was deemed significant. We used *t* tests to assess treatment effects for changes in plasma and CSF biomarkers, and MRI measurements. We assessed the difference in change of cognitive and functional scales with Wilcoxon rank sum tests, by calculating Hodges-Lehmann estimates and the corresponding 95% CI. We did not correct for multiple comparisons. For safety data, continuous variables were analysed with standard summary statistics and frequency tables.

We analysed normalised ^{18}F-FDG PET in the intravenous immunoglobulin and placebo dose groups with paired *t* tests comparing baseline with follow-up data at week 24. The different dose intervals were combined within the intravenous immunoglobulin and placebo dose groups to increase power. We used a significance threshold of p<0·001, uncorrected for

	4-week dosing interval				2-week dosing interval			
	Intravenous immunoglobulin (n=21)			Placebo (n=7)	Intravenous immunoglobulin (n=20)			Placebo (n=7)
Dose (g/kg)	0·2	0·5	0·8	..	0·1	0·25	0·4	..
n	6	8	7	..	6	7	7	..
Demographics								
Age (years)	74·8 (5·5)	65·9 (10·2)	68·4 (8·6)	71·4 (11·8)	66·8 (5·5)	68·3 (4·2)	72·9 (5·0)	72·6 (9·2)
Women	2 (33%)	3 (38%)	3 (43%)	5 (71%)	1 (5%)	3 (15%)	3 (15%)	4 (20%)
White	5 (83%)	8 (100%)	7 (100%)	6 (86%)	6 (30%)	7 (35%)	7 (35%)	6 (30%)
Weight (kg)	72·9 (15·9)	74·8 (13·5)	81·9 (13·6)	65·6 (17·9)	84·8 (10·9)	74·8 (14·0)	77·1 (17·6)	78·1 (16·3)
Duration of symptoms (months)	17·7 (16·3)	17·9 (18·3)	16·0 (12·1)	21·3 (16·4)	38·3 (39·6)	43·8 (39·4)	44·9 (15·4)	25·9 (27·6)
APOE ε4 carrier	4 (67%)	3 (38%)	7 (100%)	4 (57%)	6 (100%)	5 (71%)	5 (71%)	6 (86%)
Use of acetylcholinesterase inhibitor or memantine	5 (83%)	8 (100%)	6 (86%)	5 (71%)	6 (100%)	7 (100%)	5 (71%)	6 (86%)
Clinical measurements								
Modified Hachinski-Rosen score	0·3 (0·5)	0·6 (0·9)	0·9 (0·7)	1·0 (0·6)	0·8 (0·4)	0·6 (0·5)	0·1 (0·4)	1·0 (0·0)
Geriatric depression scale score	1·3 (0·8)	1·9 (1·8)	1·0 (1·2)	2·4 (2·6)	1·2 (1·2)	1·7 (2·1)	2·1 (2·0)	1·0 (0·8)
Mini-mental state examination score	19·3 (3·4)	20·9 (2·7)	21·9 (2·7)	22·1 (3·1)	21·8 (2·6)	21·4 (2·4)	22·4 (3·2)	21·6 (1·7)
Alzheimer's disease assessment scale cognitive subscale score	27·2 (9·7)	21·0 (9·7)	20·0 (9·5)	21·2 (14·7)	18·5 (6·3)	19·4 (8·2)	17·6 (6·5)	17·7 (4·2)
Clinical dementia rating—sum of boxes score	6·6 (3·3)	5·1 (1·7)	3·9 (2·1)	5·3 (3·7)	4·4 (1·4)	4·3 (1·8)	4·3 (1·1)	4·8 (2·6)
Alzheimer's Disease Cooperative Study—activities of daily living inventory score	60·5 (11·2)	65·9 (8·3)	67·0 (8·3)	64·4 (12·5)	64·2 (6·6)	65·3 (14·0)	67·1 (6·8)	62·1 (10·4)
Laboratory measurements								
$A\beta_{1-40}$ concentration (×10^{-9} g/L)								
CSF	8499·2 (2030·6)	8654·6 (2357·5)	7656·0 (1882·2)	10 191·0 (2825·4)	9783·0 (2634·0)	7277·0 (2701·1)	8534·8 (3030·3)	8283·0 (2622·3)
Plasma	169·2 (62·7)	150·9 (17·9)	184·3 (43·4)	194·7 (56·5)	192·5 (49·5)	201·5 (37·5)	189·5 (40·6)	154·1 (53·9)
$A\beta_{1-42}$ concentration (×10^{-9} g/L)								
CSF	333·8 (156·9)	279·8 (47·5)	240·0 (52·3)	358·3 (161·1)	355·8 (204·5)	321·4 (138·8)	286·0 (101·0)	369·4 (123·5)
Plasma	42·7 (9·4)	36·6 (16·0)	45·9 (8·7)	42·0 (8·5)	41·8 (13·3)	48·2 (12·2)	39·8 (8·7)	34·3 (8·8)
Total tau concentration (CSF; ×10^{-9} g/L)	861·3 (848·6)	803·6 (239·9)	629·4 (399·3)	714·9 (283·0)	955·2 (327·2)	468·3 (291·5)	577·2 (174·4)	486·0 (182·4)
p-tau_{181} concentration (CSF; ×10^{-9} g/L)	113·8 (84·9)	116·5 (27·8)	91·4 (40·9)	105·9 (29·4)	153·8 (68·2)	77·1 (37·1)	84·8 (16·6)	81·6 (22·9)
Anti-Aβ autoantibodies								
CSF (relative units)	7·4 (11·9)	2·2 (2·6)	5·4 (6·3)	4·7 (9·2)	2·1 (1·0)	2·2 (2·7)	2·9 (3·1)	6·9 (11·1)
Plasma (relative units)	431·3 (161·3)	493·1 (252·7)	1765·9 (3048·1)	502·1 (480·5)	189·2 (72·3)	562·7 (625·1)	316·0 (272·1)	1086·0 (1419·3)
Normalised whole brain volume (cm^3)	1268·2 (43·8)	1319·4 (98·1)	1329·4 (90·3)	1286·3 (78·7)	1276·0 (63·0)	1294·0 (47·7)	1237·1 (49·0)	1265·6 (157·9)
Left hippocampus volume (mm^3)	2530·3 (387·6)	2747·6 (444·4)	2568·4 (579·9)	2529·9 (353·7)	2611·0 (450·1)	2818·3 (660·9)	2590·4 (392·7)	2686·6 (618·7)
Right hippocampus volume (mm^3)	2693·8 (333·9)	2842·1 (557·7)	2761·9 (547·8)	2679·1 (428·4)	2754·5 (609·5)	2923·6 (590·3)	2969·9 (368·2)	2652·1 (474·2)

Data are mean (SD) or n (%) unless stated otherwise. Aβ=amyloid β.

Table 2: **Baseline characteristics of patients in the intention-to-treat population**

	4-week dosing interval							2-week dosing interval						
	Intravenous immunoglobulin (n=21)			Placebo (n=7)	Placebo *vs* intravenous immunoglobulin (difference; 95% CI)			Intravenous immunoglobulin (n=20)			Placebo (n=7)	Placebo *vs* intravenous immunoglobulin (difference; 95% CI)		
	0·2 g/kg (n=6)	0·5 g/kg (n=8)	0·8 g/kg (n=7)		0·2 g/kg	0·5 g/kg	0·8 g/kg	0·1 g/kg (n=6)	0·25 g/kg (n=7)	0·4 g/kg (n=7)		0·1 g/kg	0·25 g/kg	0·4 g/kg
$A\beta_{1-40}$	–18·0 (–1347·0 to 1068·5; n=6)	–364·3 (–5834·5 to 1953·5; n=8)	–351·8 (–1084·0 to 936·5; n=6)	–116·3 (–1379·0 to 5266·0; n=6)	–32·5 (–1358·0 to 4197·5; p=0·8102)	195·3 (–1005·5 to 5302·0; p=0·7469)	235·5 (–984·5 to 4329·5; p=0·5752)	–13·8 (–1729·0 to 307·0; n=6)	–32·5 (–1102·5 to 451·5; n=7)	47·0 (–341·0 to 72·5; n=5)	159·5 (51·5 to 303·0; n=5)	159·8 (–124·5 to 1838·5; p=0·2353)	200·5 (–51·0 to 474·5; p=0·0740)	134·5 (4·5 to 500·5; p=0·0216)
$A\beta_{1-42}$	–41·8 (–244·4 to 336·6; n=6)	–119·3 (–1220·6 to 375·0; n=8)	–107·5 (–173·5 to 231·0; n=6)	–20·5 (–183·7 to 489·0; n=6)	30·3 (–234·6 to 346·4; p=0·5752)	114·8 (–64·5 to 622·0; p=0·2200)	87·00 (–95·7 to 275·5; p=0·2298)	3·0 (–109·5 to 74·5; n=6)	–33·5 (–190·6 to –16·5; n=7)	–9·5 (–57·0 to 5·0; n=5)	24·0 (2·0 to 125·5; n=5)	26·5 (–45·0 to 133·5; p=0·1207)	63·0 (40·0 to 178·0; p=0·0058)	39·0 (–11·5 to –135·0; p=0·0216)
Anti-Aβ auto-antibodies	932·5 (–2991·5 to 3577·0; n=6)	5770·0 (2892·5 to 14426·0; n=8)	8658·8 (5532·5 to 11517·5; n=6)	636·0 (–1207·5 to 1075·5; n=6)	–915·5 (–2844·5 to 1784·0; p=0·5752)	–5339·5 (–7203·5 to 3814·5; p=0·0024)	–8398·3 (–10785·0 to –5343·5; p=0·0051)	299·3 (–105·0 to 987·0; n=6)	1256·0 (1059·0 to 5160·0; n=7)	2172·0 (–710·5 to 5516·0; n=5)	593·0 (–1090·5 to 7747·5; n=5)	580·8 (–1258·0 to 7316·5; p=0·4113)	–641·5 (–2346·5 to 6009·5; p=0·6261)	–380·0 (–4923·0 to 6600·0; p=1·000)

Data are median (range) for treatment groups. Differences are assessed by Hodges-Lehmann estimates of the difference between the two medians with non-parametric 95% CI (exact) and by Wilcoxon rank sum test (normal approximation, two-sided, α=0·05). Data missing for some groups because of missed study visits. Aβ=amyloid β.

Table 3: **Change in area under the curve for amyloid β plasma concentration in the intention-to-treat population**

multiple comparisons, because of the small sample sizes of the different groups. In an additional whole brain voxel-wise analysis, we combined all intravenous immunoglobulin groups and used a significance level of $p<0·05$, corrected for false discovery rate. We calculated contrasts for changes in metabolism. We used age and sex as covariates. We used SPM5, implemented in Matlab (version 7.1), for voxel-wise PET analyses. We used SAS (version 9.2) for all other statistical analyses.

This trial is registered at ClinicalTrials.gov (NCT00812565) and controlled-trials.com (ISRCTN64846759).

Role of the funding source

The study sponsor was partly responsible for the study design. The clinical research organisation (ClinResearch, now Aptiv Solutions, Cologne, Germany) had responsibility for data monitoring and analysis according to the statistical analysis plan developed by the sponsor as well as for writing trial reports for regulatory authorities. The sponsor had a role in data interpretation, but no role in data collection. After the database lock and study unmasking, all of the investigators had full access to the study data and had final responsibility for data analysis. The report was written and reviewed by the authors and the sponsor. The decision to submit the report for publication was made jointly by RD, FJ, MF, and the sponsor.

Results

89 patients were screened and 58 were enrolled, between Feb 2, 2009, and Mar 30, 2010 (figure 1). The last patient's visit was on Sept 21, 2010. Tables 1 and 2 show baseline characteristics. The median AUC for plasma concentration of $A\beta_{1-40}$ in the 0·4 g/kg every 2 weeks group (47·0, range –341·0 to 72·5) was significantly lower than that of the placebo group (159·5, 51·5–303·0; p=0·0216; table 3). No significant differences existed between the other intervention groups and their respective placebo groups (table 3) or in the pooled groups (appendix).

The median AUC for plasma concentration of $A\beta_{1-42}$ in the 2-week interval group was significantly lower for patients taking the 0·25 g/kg dose (p=0·058) and the 0·4 g/kg dose (p=0·0216) compared with placebo (table 3). The AUC for plasma $A\beta_{1-42}$ did not differ significantly for the 4-week dose interval groups. When intravenous immunoglobulin dose groups were pooled, the AUC for $A\beta_{1-42}$ was significantly lower compared with placebo (p=0·0061; appendix). The concentration of anti-Aβ autoantibodies in plasma increased in a dose-dependent manner between baseline and 24 weeks in the 4-week interval group (table 4); no significant difference existed between the 2-week interval groups (table 5), however two patients had ten times higher anti-Aβ concentrations than other patients (data not shown).

At 24 h (±8) after the last infusion in either week 20 or week 22, changes from baseline of concentration of $A\beta_{1-40}$, total tau, and p-tau_{181} were not significant for any individual treatment group (tables 4, 5), or for the pooled intravenous immunoglobulin group compared with the pooled placebo group (appendix). CSF concentration of $A\beta_{1-42}$ for patients taking the the 0·25 g/kg dose differed significantly between groups.

Cognitive and functional scales did not differ significantly between any of the individual dose treatment groups and the placebo group (tables 4, 5). In the analysis of the pooled intravenous immunoglobulin dose groups, patients in the intervention group had a significantly higher clinical dementia rating—sum of boxes score than did patients in the placebo group at week 24 (p=0·0247; appendix). No other significant differences between pooled groups were noted for the other cognitive and functional scales at week 24 (appendix). The groups did not differ significantly on the scales at week 12 (data not shown).

	Intravenous immunoglobulin (n=21)			Placebo (n=7)	Placebo *vs* intravenous immunoglobulin (difference; 95% CI)		
	0·2 g/kg (n=6)	0·5 g/kg (n=8)	0·8 g/kg (n=7)		0·2 g/kg	0·5 g/kg	0·8 g/kg
$A\beta_{1-40}$ concentration (×10⁻⁹ g/L)							
CSF*	561·7 (1195·5; n=6)	403·9 (588·1; n=8)	642·2 (1171·3; n=6)	42·0 (874·0; n=6)	–519·7 (–1866·7 to 827·4; p=0·4102)	–361·9 (–1210·4 to 486·6; p=0·3711)	–600·2 (–1929·5 to 729·2; p=0·3382)
Plasma	–20·3 (29·2; n=6)	15·7 (29·7; n=8)	–30·5 (42·3; n=6)	–6·0 (23·8; n=6)	14·3 (–19·9 to 48·6; p=0·3729)	–21·7 (–55·0 to 11·6; p=0·1788)	24·5 (–19·7 to 68·7; p=0·2446)
$A\beta_{1-42}$ concentration (×10⁻⁹ g/L)							
CSF*	18·8 (40·3; n=6)	10·5 (40·9; n=8)	24·7 (43·2; n=6)	–5·2 (36·3; n=6)	–24·0 (–73·3 to 25·3; p=0·3037)	–15·7 (–61·6 to 30·3; p=0·4718)	–29·8 (–81·1 to 21·4; p=0·2239)
Plasma	–3·5 (5·8; n=6)	–0·1 (4·4; n=8)	–7·0 (6·2; n=6)	–2·0 (4·8; n=6)	1·5 (–5·3 to 8·3; p=0·6349)	–1·9 (–7·2 to 3·5; p=0·4606)	5·0 (–2·2 to 12·2; p=0·1509)
Anti-Aβ autoantibody concentration							
CSF* (relative units)	0·4 (1·4; n=6)	1·1 (1·5; n=8)	0·7 (2·3; n=6)	0·1 (0·3; n=6)	–0·3 (–1·6 to 1·1; p=0·6881)	–1·0 (–2·3 to 0·4; p=0·1083)	–0·6 (–2·7 to 1·5; p=0·5596)
Plasma (relative units)	96·7 (133·7; n=6)	256·6 (214·1; n=8)	501·3 (514·6; n=6)	–56·3 (58·3; n=6)	–153·0 (–285·6 to –20·4; p=0·0279)	–313·0 (–510·4 to –115·6; p=0·0039)	–557·7 (–1028·8 to –86·6; p=0·0450)
Total tau* (CSF; ×10⁻⁹ g/L)	–141·8 (419·5; n=6)	1·3 (86·7; n=8)	131·3 (301·0; n=6)	–33·2 (69·7; n=6)	108·7 (–278·2 to 495·5; p=0·5575)	–34·4 (–128·6 to 59·8; p=0·4416)	–164·5 (–445·6 to 116·6; p=0·2438)
$p\text{-}tau_{181}$* (CSF; ×10⁻⁹ g/L)	3·3 (21·2; n=6)	–2·5 (8·6; n=8)	10·2 (19·3; n=6)	–1·3 (10·1; n=6)	–4·7 (–26·0 to 16·7; p=0·6370)	1·2 (–9·7 to 12·0; p=0·8192)	–11·5 (–31·3 to 8·3; p=0·2243)
Alzheimer's disease assessment scale cognitive subscale score	5·3 (–4·7 to 8·7; n=6)	1·8 (–8·0 to 24·0; n=8)	–1·5 (–4·3 to 18·3; n=6)	0·3 (–3·3 to 5·0; n=5)	–3·8 (–9·3 to 4·0; p=0·2353)	–0·3 (7·0 to 5·7; p=0·8835)	0·8 (–13·3 to 7·3; p=0·6466)
Mini-mental state examination score	–3·0 (–8·0 to 2·0; n=6)	–1·5 (–4·0 to 1·0; n=8)	–1·5 (–7·0 to 2·0; n=6)	–1·5 (–11·0 to 4·0; n=6)	2·0 (–6·0 to 7·0; p=0·5725)	0·5 (–5·0 to 5·0; p=0·8453)	0·0 (–6·0 to 5·0; p=1·0000)
Clinical dementia rating—sum of boxes	0·5 (–1·0 to 3·0; n=6)	0·0 (–1·0 to 5·0; n=8)	0·3 (–1·5 to 3·0; n=6)	–0·5 (–6·0 to 0·0; n=5)	–1·5 (–6·5 to 0·0; p=0·0641)	–0·5 (–6·0 to 0·0; p=0·1879)	–1·3 (–5·5 to 0·5; p=0·1961)
Alzheimer's Disease Cooperative Study—activities of daily living inventory score	–3·0 (–31·0 to 11·0; n=6)	0·0 (–15·0 to 11·0; n=8)	–1·5 (–5·0 to 3·0; n=6)	–3·0 (–8·0 to 7·0; n=5)	–19·0 (–13·0 to –25·0; p=0·9273)	–4·5 (–14·0 to 7·0; p=0·3387)	–1·5 (–8·0 to 6·0; p=0·7144)
Normalised whole brain volume (cm³)	–1·4 (1·8; n=6)	–1·1 (1·0; n=8)	–1·6 (1·1; n=6)	–0·9 (0·8; n=4)	0·5 (–1·7 to 2·7; p=0·6196)	0·2 (–1·1 to 1·5; p=0·7094)	0·7 (–0·7 to 2·2; p=0·2851)
Left hippocampus volume (mm³)	–191·2 (111·7; n=6)	–188·4 (228·2; n=8)	–153·5 (91·2; n=6)	–137·0 (114·8; n=5)	54·2 (–100·8 to 209·1; p=0·4494)	51·4 (–193·0 to 295·7; p=0·6526)	16·5 (–123·7 to 156·7; p=0·7961)
Right hippocampus volume (mm³)	–140·8 (60·3; n=6)	–193·1 (137·7; n=8)	–230·5 (165·8; n=6)	–132·4 (122·1; n=5)	8·4 (–118·9 to 135·8; p=0·8842)	60·7 (–105·2 to 226·6; p=0·4375)	98·1 (–104·6 to 300·8; p=0·3021)

Data for treatment groups are mean (SD) or median (range). Change is from baseline to week 22 + 1 day unless stated otherwise. Differences between treatment groups were assessed by *t* test (two-sided, α=0·05) for biomarkers and MRI results and by calculating Hodges-Lehmann estimates and non-parametric 95% CIs, compared with Wilcoxon rank sum test (normal approximation, two-sided, α=0·05) for the cognitive and functional scales. Aβ=amyloid β. *At the seventh visit (last infusion at week 20 + 1 day).

Table 4: **Mean change from baseline in the intention-to-treat population (4-week dosing interval)**

Hippocampus and whole brain volume did not differ significantly between individual dose groups and placebo groups or between pooled dose groups and the placebo group at week 12 (data not shown) or week 24 (tables 4, 5, appendix).

54 patients had baseline ^{18}F-FDG PET scans. A PET scanner was not available in one centre, so three patients did not have any PET examinations. Voxel-wise analyses in the combined placebo groups showed that glucose metabolism was decreased in the bilateral hippocampal and temporomesial brain regions compared with patients in the intervention groups within the 24-week follow-up period (figure 2). Figure 2B shows stereotactic coordinates including brain area, peak z-scores, and cluster sizes. Within these clusters, uptake of ^{18}F-FDG decreased by 4·3% in the placebo group compared with baseline. In the same clusters, glucose metabolism changed by +0·4% in patients receiving low-dose intravenous immunoglobulin, by –0·9% in those receiving medium-dose intravenous immunoglobulin, and by –1·8% in those receiving high-dose intravenous immunoglobulin (figure 2C). Across all patients receiving intravenous immunoglobulin, glucose metabolism was reduced by significantly less than in the placebo group (–0·7% *vs* –4·3%; p<0·01). Furthermore, metabolism increased in the low-dose and high-dose groups in parietal and frontal cortical regions compared with baseline (figures 2D–G). In the medium-dose group, no increase occurred (uncorrected p<0·001). Across all intravenous immunoglobulin groups, metabolism increased in parietal and frontal regions after statistical correction for whole brain analysis (p<0·05; figures 2H, 2I). No increases occurred in the placebo group.

The safety analysis was based on 56 patients, of whom 42 patients were in the intravenous immunoglobulin group and 14 were in the placebo group (table 6). The proportion of individuals with one or more adverse event in the placebo group (n=9; 64%) and treatment group (n=25; 60%) did not differ significantly (p=0·75). Similarly, the groups did not differ significantly in the proportion of serious adverse events, with a total of ten events in eight patients (placebo group: n=4, 29%; intravenous immunoglobulin group: n=4, 10%; p=0·078). In the treatment group, one patient had an ischaemic stroke that affected middle cerebral artery territory. Otherwise, most adverse events in the treatment group were either mild or moderate in severity. No deaths occurred.

At screening, the MRI scans of nine patients (one in the placebo and eight in the intravenous immunoglobulin groups) showed microbleeds. The incidence of microbleeds in patients who had microbleeds at baseline was 37·5% (three of 8 patients in the intravenous immunoglobulin groups). One microbleed was noted at week 12 and two at week 24. The incidence of microbleeds in patients without microbleeds at baseline was 7·1% (three of 42 patients in the intravenous immunoglobulin groups). One microbleed was observed at week 12. This patient had 14 new microbleeds and was therefore removed from the study. The other two patients had microbleeds at week 24. We recorded no dose effects. No incident microbleeds occurred in the placebo group. No clinical symptoms were associated with microbleeds. We did not record any changes in white matter (amyloid-related imaging abnormalities—eg, vasogenic oedema or sulcal effusions).

	Intravenous immunoglobulin (n=20)			Placebo (n=7)	Placebo *vs* intravenous immunoglobulin (difference; 95% CI)		
	0·1 g/kg (n=6)	0·25 g/kg (n=7)	0·4 g/kg (n=7)		0·1 g/kg	0·25 g/kg	0·4 g/kg
$A\beta_{1-40}$ concentration (×10⁻⁹ g/L)							
CSF*	266·7 (996·0; n=6)	10·6 (1104·0; n=7)	−147·0 (1067·9; n=5)	939·4 (1670·8; n=5)	672·7 (−1160·8 to 2506·3; p=0·4280)	928·8 (844·7 to 2702·3; p=0·2703)	1086·4 (−958·5 to 3131·3; p=0·2554)
Plasma	5·5 (64·5; n=6)	−0·3 (22·1; n=6)	−6·5 (61·4; n=6)	27·1 (40·2; n=7)	21·6 (−42·8 to 86·1; p=0·4755)	27·5 (−13·2 to 68·1; p=0·1650)	33·6 (−28·7 to 96·0; p=0·2602)
$A\beta_{1-42}$ concentration (×10⁻⁹ g/L)							
CSF†	−8·7 (38·2; n=6)	9·7 (54·7; n=7)	4·0 (40·3; n=5)	32·4 (67·0; n=5)	41·1 (−31·5 to 113·7; p=0·2327)	22·7 (−55·9 to 100·9; p=0·5325)	28·4 (−52·2 to 109·0; p=0·4403)
Plasma	−2·3 (7·8; n=6)	−4·5 (6·3; n=6)	−2·7 (7·6; n=6)	4·1 (3·8; n=7)	6·5 (−0·8 to 13·8; p=0·0759)	8·6 (2·4 to 14·8; p=0·0107)	6·8 (−0·3 to 13·9; p=0·0592)
Anti-Aβ autoantibody concentration							
CSF† (RTF)	0·2 (1·8; n=6)	1·9 (1·9; n=7)	−0·8 (1·6; n=5)	0·4 (3·7; n=5)	0·2 (−3·7 to 4·0; p=0·9271)	−1·5 (−5·1 to 2·2; p=0·3861)	1·2 (−3·0 to 5·4; p=0·5378)
Plasma (RTF)	74·3 (35·0; n=6)	163·9 (136·6; n=7)	310·2 (193·0; n=6)	109·7 (284·8; n=7)	35·4 (−223·8 to 294·6; p=0·7553)	−54·1 (−314·3 to 206·0; p=0·6583)	−200·5 (−503·3 to 102·4; p=0·1732)
Total tau† (×10⁻⁹ g/L)	209·3 (416·0; n=6)	−3·4 (35·6; n=7)	−7·8 (51·3; n=5)	17·4 (38·6; n=5)	−191·9 (−618·1 to 234·3; p=0·3110)	20·8 (−27·2 to 68·9; p=0·3571)	25·2 (−41·0 to 91·4; p=0·4056)
p–tau_{181}† (×10⁻⁹ g/L)	−3·2 (14·7; n=6)	0·4 (3·6; n=7)	2·6 (5·0; n=5)	0·6 (7·5; n=5)	3·8 (−12·7 to 20·2; p=0·6172)	0·2 (−7·0 to 7·4; p=0·9586)	−2·0 (−11·3 to 7·3; p=0·6328)
Alzheimer's disease assessment scale cognitive subscale score	2·5 (−3·7 to 6·0; n=6)	−1·3 (−7·3 to 4·0; n=7)	4·5 (−4·0 to 8·3; n=6)	−0·3 (−5·3 to 5·0; n=7)	−3·0 (−7·0 to 1·7; p=0·1979)	2·0 (−4·0 to 7·0; p=0·6540)	−4·3 (−10·7 to 2·3; p=0·1004)
Mini-mental state examination score	−2·0 (−10·0 to 2·0; n=6)	0·0 (−3·0 to 4·0; n=7)	−1·5 (−4·0 to 1·0; n=6)	−1·0 (−5·0 to 1·0; n=7)	1·0 (−4·0 to 7·0; p=0·6643)	−1·0 (−5·0 to 2·0; p=0·4392)	1·0 (−2·0 to 4·0; p=0·6656)
Clinical dementia rating—sum of boxes score	0·0 (−1·0 to 5·0; n=6)	0·5 (−2·0 to 2·0; n=7)	0·8 (−1·5 to 4·0; n=6)	0·0 (−2·5 to 1·5; n=7)	−1·3 (−3·5 to 0·5; p=0·4236)	−0·5 (−2·5 to 1·0; p=0·4356)	−2·5 (−3·5 to 0·0; p=0·0953)
Alzheimer's disease cooperative study—activities of daily living inventory score	−0·5 (−11·0 to 4·0; n=6)	−3·0 (−17·0 to 3·0; n=7)	−4·0 (−25·0 to 2·0; n=6)	2·0 (−6·0 to 10·0; n=7)	3·0 (−3·0 to 10·0; p=0·3153)	5·0 (−1·0 to 13·0; p=0·0839)	6·5 (0·0 to 18·0; p=0·0734)
Normalised whole brain volume (cm³)	−2·0 (0·8; n=5)	−1·5 (0·7; n=6)	−1·4 (1·7; n=5)	−1·4 (1·0; n=4)	0·6 (−0·8 to 2·0; p=0·3620)	0·1 (−1·1 to 1·3; p=0·8766)	−0·0 (−2·3 to 2·2; p=0·9899)
Left hippocampus volume (mm³)	−166·2 (64·0; n=6)	−183·5 (117·4; n=6)	−131·4 (98·0; n=5)	−216·5 (133·2; n=4)	−50·3 (−193·2 to 92·6; p=0·4401)	−33·0 (−216·9 to 150·9; p=0·6899)	−85·1 (−266·6 to 96·4; p=0·3042)
Right hippocampus volume (mm³)	−106·2 (112·7; n=6)	−182·2 (179·0; n=6)	−153·6 (226·0; n=5)	−198·3 (30·5; n=4)	−92·1 (−227·6 to 43·4; p=0·1557)	−16·1 (−228·6 to 194·4; p=0·8373)	−44·7 (−317·4 to 228·1; p=0·6838)

Data for treatment groups are mean (SD; patients analysed) or median (range; patients analysed). Differences between treatment groups were assessed by *t* test (two-sided, α=0·05) for biomarkers and MRI results and by calculating Hodges-Lehmann estimates and non-parametric 95% CIs, compared with Wilcoxon rank sum test (normal approximation, two-sided, α=0·05) for the cognitive and functional scales. Aβ=amyloid β. *At the seventh visit (last infusion at week 20 + 1 day). †At the 13th visit (last infusion at week 22 + 1 day).

Table 5: **Mean change from baseline at week 24 in the intention-to-treat population (2-week dosing interval)**

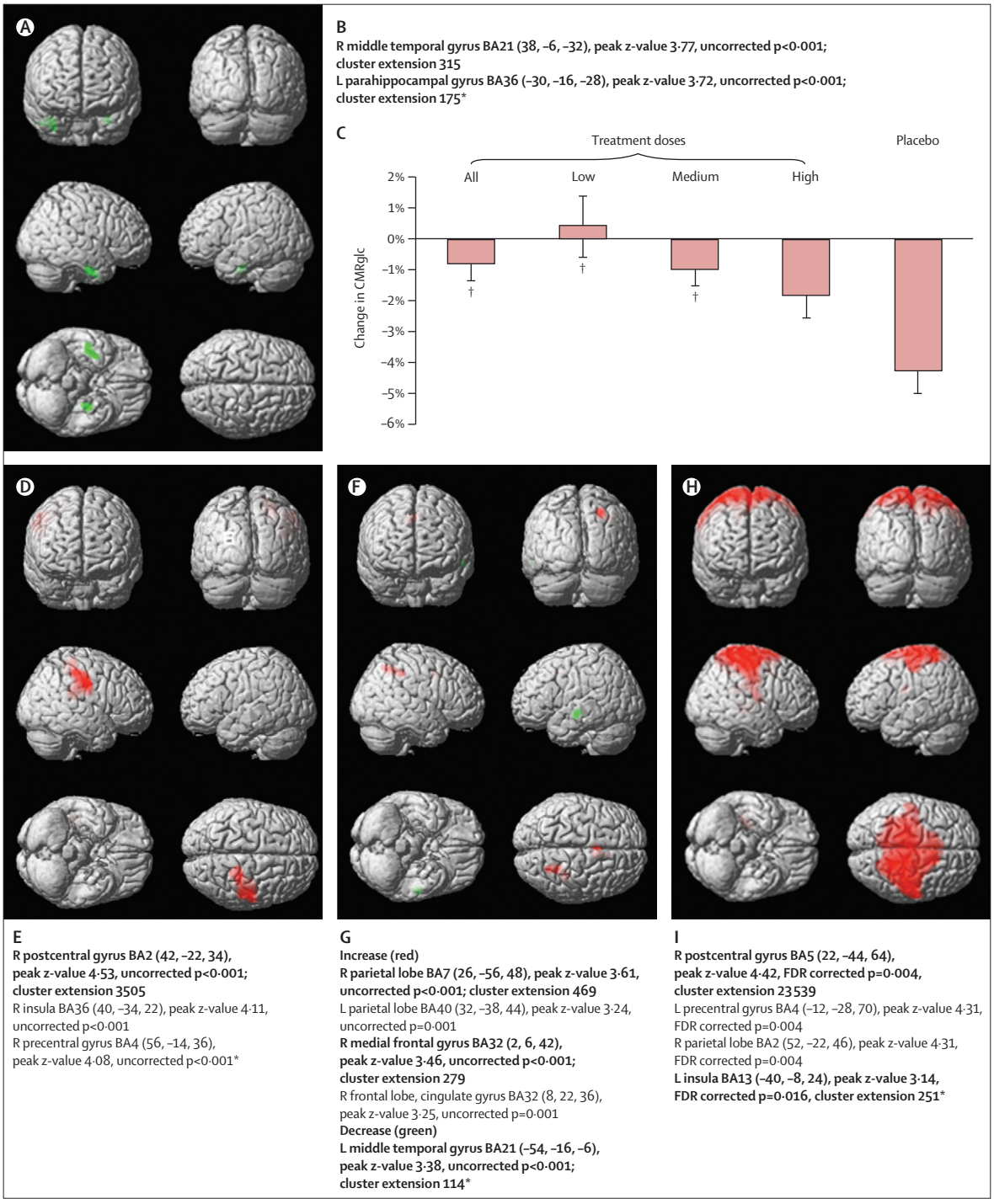

Figure 2: **Findings of ^{18}F-fluorodeoxyglucose PET analyses**
(A) Statistical parametric mapping (T; surface rendering projections) of decrease in cerebral metabolic rate of glucose consumption (CMRglc; green) between baseline and follow-up in the placebo group (n=8; p<0·001). (B) Details of the clusters in the placebo group. (C) Changes in CMRglc in each group (bars are SE; high, middle, and low dose pooled for each dose interval). (D) Statistical parametric mapping (T) of increase in CMRglc (red) between baseline and follow-up in patients in the low-dose group (n=12; uncorrected p<0·001); cluster sizes of >50 voxels are displayed. (E) Details of the clusters in the low-dose group†. (F) Statistical parametric mapping (T) of increases (red) and decreases (green) in CMRglc between baseline and follow-up in patients in the high-dose group (n=10; uncorrected p<0·001). (G) Details of the clusters in the high-dose group. (H) Statistical parametric mapping (T) of increases (red) in CMRglc between baseline and follow-up for all patients treated with intravenous immunoglobulin (n=36; FDR-corrected p<0·05). (I) Details of the clusters in the pooled intervention group. R=right. L=left. BA=Brodmann area. FDR=false discovery rate. *Bold data delineate a cluster, subsequent non-bold data identify further peaks within the same cluster. Data in parentheses are Talairach and Tournoux coordinates (x, y, z; mm). †p<0·01 versus placebo.

Discussion

This study is the largest completed trial assessing intravenous immunoglobulin for patients with Alzheimer's disease (panel). Our data suggest that intravenous immunoglobulin has an acceptable safety profile for patients with mild-to-moderate Alzheimer's disease, which is consistent with previous studies.[2,5] We recorded no cases of aseptic meningitis, meningoencephalitis, or amyloid-related imaging abnormalities.[21] Development of microbleeds was slightly higher than expected in Alzheimer's disease.[22] In all cases, microbleeds were asymptomatic. Incident microhaemorrhages and haemosiderin deposits have been reported in other immunisation trials of Alzheimer's disease. The pooled data on bapineuzumab showed an overall incidence of 16%.[23] The clinical side-effects and systemic reactions we recorded were consistent with known adverse events of treatment with intravenous immunoglobulin.[24] One 68-year-old woman in the high-dose treatment group with a medical history of Hashimoto's thyroiditis and depression had a stroke during the trial. The risk of ischaemic stroke increases with treatment with intravenous immunoglobulin.[25]

We did not record an effect of intravenous immunoglobulin treatment on the AUC for plasma concentration of $A\beta_{1-40}$, except for the 0·4 g/kg dose every 2 weeks. The secondary analyses of single point changes of plasma and CSF concentrations of $A\beta_{1-40}$ did not show any treatment effects. Thus, our analyses do not accord with results from previous studies using 0·4 g/kg, 1·2 g/kg, and 0·8 g/kg intravenous immunoglobulin per month.

Similar to the decrease for the primary endpoint, we recorded a decrease in AUC for plasma concentration of $A\beta_{1-42}$ in the 2-week interval middle-dose and high-dose groups and in the pooled analysis, compared with placebo. Plasma $A\beta_{1-42}$ concentration was significantly lower at week 24 compared with baseline in the pooled analyses; an opposite effect to that reported previously.[2,5] This difference could be related to differences in study designs—ie, intercentre, variation in sample preparation,[26] different exposure to intravenous immunoglobulin, or other factors. Additionally, the sample sizes used in the studies were small. Currently, we cannot explain the differences between the results of our study and previous studies. Little is understood about Aβ exchange between the brain and blood.

Further studies with larger sample sizes and longer exposure to intravenous immunoglobulin are needed before any decisive conclusions can be made about effects of intravenous immunoglobulin on concentrations of $A\beta_{1-40}$, $A\beta_{1-42}$, total-tau, and p-tau_{181} in CSF and blood. Based on this study, 0·25 g/kg and 0·4g/kg administered at 2-week intervals might have the largest effects on Aβ.

Our study showed a significant dose-dependent attenuation of glucose metabolism in the temporal and hippocampal brain regions within 24 weeks of treatment. These brain regions are affected in patients with Alzheimer's disease.[27] Progressive hypometabolism has been well documented[28] in several brain regions, including the temporal lobe, the precuneus and cuneus, and the parietal, frontal, and occipital cortices. Furthermore, patients treated with intravenous immunoglobulin had significantly increased glucose metabolism in parietal and frontal brain regions at follow-up, even when applying a conservative threshold, whereas patients in the placebo group did not. However, this increased metabolism is not localised to regions that are usually affected in ^{18}F-FDG PET studies of Alzheimer's disease. Thus, the biological meaning of this finding is unclear. Our ^{18}F-FDG PET data

	Intravenous immunoglobulin (n=42)	Placebo (n=14)
Serious adverse events	4 (10%)	4 (29%)
Knee replacement surgery	..	1 (7%)
Gastric antral vascular ectasia	..	1 (7%)
Post-surgery delirium and lumbar laminectomy	1 (2%)	..
Stroke (middle cerebral artery infarction)	1 (2%)	..
Nausea and vomiting	1 (2%)	..
Acute aggression	..	1 (7%)
Possible seizure	..	1 (7%)
Progressively severe Alzheimer's disease	1 (2%)	..
Adverse events	25 (60%)	9 (64%)
Microbleeds	6 (14%)	..
Dizziness	..	1 (7%)
Headache	3 (7%)	1 (7%)
Paraesthesia	..	1 (7%)
Chills	1 (2%)	..
Influenza-like illness	1 (2%)	..
Hypoaesthesia	2 (5%)	..
Tremor	1 (2%)	..
Increased CSF white-blood-cell count	..	1 (7%)
Muscle spasms	1 (2%)	..
Atrial fibrillation	..	1 (7%)
Procedural hypertension	1 (2%)	..
Agitation	..	1 (7%)
Actinic keratosis	1 (2%)	..
Hyperkeratosis	1 (2%)	..
Pruritus	1 (2%)	..
Blood pressure fluctuation	1 (2%)	..
Hypotension	1 (2%)	1 (7%)
Increased aspartate aminotransferase concentration	1 (2%)	..
Increased lactate dehydrogenase concentration	1 (2%)	..
Impaired hearing	1 (2%)	..
Dyspepsia	1 (2%)	..
Post-lumbar puncture syndrome	1 (2%)	..
Haematuria	1 (2%)	..
Infusion site extravasation	1 (2%)	..
Fatigue	1 (2%)	..
Pyrexia	1 (2%)	..
Falls	1 (2%)	..

Data are number of patients (%).

Table 6: **Adverse events**

suggest that intravenous immunoglobulin might reduce the speed of metabolic decline in the medial temporal lobe in patients with Alzheimer's disease, with low doses more beneficial than high doses. Although these results are promising, they should be interpreted with caution in view of the small number of patients in this study.

We recorded effects in favour of placebo for the clinical dementia rating—sum of boxes score. The decrease across all treatment groups was much the same as the decrease in the natural course of Alzheimer's disease and in placebo groups in other trials of mild-to-moderate Alzheimer's disease.[29–32] However, the effect noted for the clinical dementia rating—sum of boxes score might have occurred by chance. We conclude that intravenous immunoglobulin most likely had no symptomatic effect in this short-term trial. Longer studies are needed to detect the effects on speed of cognitive and functional decline.

Our study has limitations, despite careful design and execution. The small size of each treatment group with large variations in disease trajectories reduces the likelihood of recording clinically significant data favouring one dose over another. Extrapolation of our findings to other patient groups is limited by the small sample size in each group (especially in the placebo groups) and by the inclusion and exclusion criteria. Furthermore, patients were exposed to treatment for only 6 months, which prevents detection of a disease-modifying effect. Finally, as in other studies of antiamyloid drugs, the disease course of Alzheimer's disease might have been too advanced in our study population to detect an effect. Intervention at an earlier disease stage might be more beneficial, particularly for clinical outcomes. Although different doses and intervals have been used in this and previous small trials and are being used in an ongoing large trial (ranging from 0·1 to 0·4 g/kg every 2 weeks or 0·2 to 1·2 g/kg every 4 weeks; registered at ClinicalTrials.gov, number NCT00818662),[20] we cannot conclude whether higher or more frequent doses are needed. Lastly, we cannot rule out that intravenous immunoglobulin treatment might not be effective in patients with Alzheimer's disease.

In conclusion, this trial showed favourable safety and tolerability of intravenous immunoglobulin and the absence of severe autoimmune reactions. Longer studies of larger populations are needed to assess effects on cognition and function in patients with Alzheimer's disease.

Panel: Research in context

Systematic review

We searched Medline (Jan 1, 2000–Oct 10, 2012) and the Cochrane Central Register of controlled trials (up to Oct 10, 2012) with the terms "Alzheimer's disease", "immunotherapy", "immunoglobulins", and "clinical trials". Searches were restricted to human studies. All types of trial design were included. Our search returned 18 results. We identified two systematic reviews[16,17] assessing in detail trials of active and passive immunisation targeting amyloid β (Aβ). Six active and eight passive trials of immunotherapies that target Aβ are in different stages of development. These trials are of ACC-001, CAD-106, ACI-24, UB-311, V950, and affitopes AD-01/AD-02 for active immunotherapy and bapineuzumab, GSK933776A, solanezumab, ponezumab, gantenerumab, MABT-5102A, BAN-2401, and immunoglobulin for passive immunotherapy. Most recently, two large clinical trials of bapineuzumab,[18] which targets the N-terminal sequence of Aβ, and solanezumab,[19] which targets the mid-terminal sequence (aminoacids 17–24), were negative for the primary outcome, with solanezumab seemingly having a statistically significant but clinically questionable effect on cognition in a predefined subgroup of patients with mild Alzheimer's disease. Complete results from these trials are not yet available. Two small pilot trials[2,5] have shown an effect of immunoglobulin on the drain of Aβ from the CSF to the periphery. A large, 18-months, phase 3 study[20] of immunoglobulins for patients with mild-to moderate Alzheimer's disease is underway in the USA (registered with clincialtrials.gov, number NCT00818662) and a second is planned to end in 2014.

Interpretation

Passive immunisation targeting Aβ is a potential therapeutic approach. However, several issues need to be addressed—ie, the disease stage at which immunotherapy should be started, and the role of biomarkers and whether they have any link to clinical cognitive outcomes. More clinical trials of sufficient length and power to assess cognitive and functional outcomes are needed to establish the efficacy of passive immunisation and intravenous immunoglobulin for patients with Alzheimer's disease.

Contributors

RD, FJ, and MF planned the study. RD and FJ collected data and wrote the first draft. FB wrote the sections on MRI. PB, AR, and SF wrote the sections on ^{18}F-FDG PET. KB wrote the sections on and collected data for biomarkers. All authors reviewed the final draft. JA, PA, KB, J-PB, MF, JG, MJ, IM, MO, JP, RR, JS, JW, and YW collected data. SW planned the study and analysed and interpreted data. SH planned the study. The sponsor planned the study.

Conflicts of interest

RD has received consulting fees, support for travel to meetings and fees for participation in review activities from Octapharma AG. Investigator fees per patient enrolled were paid to his institution by Octapharma AG. He has served as a consultant for Eli Lilly, AstraZeneca, Merz, TEVA/Lundbeck, Pfizer, and Baxter and served as a board member for Solvay, Affiris, GE Healthcare, Baxter, and Lilly. He was a consultant for Octapharma AG, TEVA/Lundbeck, Pfizer, and Baxter. He was paid for lectures by Boehringer Ingelheim, Novartis, Pfizer, Baxter, GlaxoSmithKline, Lundbeck, Merz, Solvay, Eisai, Octapharma AG, Orion Pharma, UCB, CSL Behring, TevaPharma, and the Canadian Blood Service. He has received grants from ZLB Behring, Behring-Röntgen-Stiftung, MJ Fox Foundation, Rentschler, International Parkinson Fund, Faber Stiftung, Movement Disorder Society, Novartis, Hector-Stiftung, Alzheimer Forschung Initiative, DGSM, Lundbeck, Abbott, and Baxter. He holds patents on naturally occurring autoantibodies in neurodegenerative disorders. AR has received fees for participation in review activities from Octapharma AG paid to his institution. He is a consultant for Bayer Healthcare and General Electric. PB received fees for participation in review activities from Octapharma AG paid to his institution. He is a consultant for General Electric. He is also a consultant for Bayer Healthcare and Siemens with money paid to his institution. He received a grant from Siemens paid to his institution. FB was paid by Octapharma MG to do the MRI analysis for this study. He is a paid consultant for Roche, Baxter, and Sanofi-Aventis. He is also a consultant for Biogen-Idec, Merck-Serono, Novartis, Bayer-Schering, Roche, Synthon BV, Jansen Research, and TEVA, with money paid to him and his institution. KBe received consulting fees from Octapharma AG for sitting on an advisory board in 2011. He received payment from Octapharma AG for biomarker analyses and for plasma samples paid to his institution. He has served on advisory boards for Pfizer, Roche, Eli Lilly, and Innogenetics and has been a consultant for AstraZeneca. SF received fees for participation in review activities from Octapharma AG, paid to his institution. He is a consultant for Bayer Healthcare, General Electric, and Merck. Money was also paid to his institution for his consultancy for Bayer Healthcare and Merck. YW is a board member for UCB and received a grant from the Behring-Röntgen Foundation, paid to his institution. J-PB has received a grant from Octapharma AG, paid to his institution. He has received grants from Baxter and Grifols, with money paid to the institution. He received

payment for a lecture from Teva Pharmaceuticals and travel expenses from Baxter in 2011. KBu received support from Octopharma for travel and registration to the International Conference of Alzheimer's Disease in 2009, at which a study meeting was held by Octapharma AG. She received a fee for doing the study from Octapharma, paid to her institution. She received a grant from DZNE (Germany), paid to her institution. MO received a grant from Octapharma to include patients into this study, paid to his institution. He is a board member for UCB. He has received a grant from Boehringer Ingelheim, paid to his institution. He has received payment for lectures from Fisher Scientific, Beckman Coulter, and Teva. He holds a patent related to CSF markers for Parkinson's disease dementia with the foundation of the state Baden-Wuerttemberg, with money paid to his institution. MJ received a fee for doing the study from Octapharma AG, paid to his institution. RR received a grant from Octapharma for this study, paid to his institution. He received a grant from Octapharma, paid to his institution. JS is a board member for Biogen-Idec, Teva Neuroscience, and Genzyme. He has received grants from Biogen-Idec, Teva Neuroscience, Sanofi-Aventis, and Octapharma AG, paid to his institution. JG received a grant from Octapharma AG for doing this study, paid to his institution. He received travel support from Octapharma AG for a poster presentation at an international Alzheimer's disease meeting in 2010. SH was an employee of Octapharma AG. SW is employed by Octapharma PPG. MF received consulting fees and support for travel to meetings for the study from Octapharma AG. He received a grant from Octapharma, paid to his institution. He is a consultant for Accera, Alltech, Astellas, Avanir, Bayer, Bristol MyersSquibb, Eisai, General Electric, Helicon, Medavante, Medivation, Merck, Novartis, Pfizer, Prana Biotech, QR Pharma, Roche, Sanofi-Aventis, Schering-Plough, Toyama, Eli Lilly, Shire Pharmaceuticals, and UCB. He has received grants from Eli Lilly, Novartis, Genentech, Roche, and Eisai, paid to his institution. He has received payment for lectures from Novartis, Pfizer, Forest, and Eisai. FJ received a fee for a consultation on study design and fees for travel to meetings for the study from Octapharma AG. He also received payments for the study from Octapharma AG, paid to his institution. He is a board member for AC Immune and a consultant for Eli Lilly, General Electric Healthcare, Janssen, USB, and Schwabe. He has received a grant from Schwabe, paid to his institution. He was paid for lectures from Pfizer, Novartis, Schwabe, Eli Lilly and General Electric Healthcare. The other authors declare that they have no conflicts of interest.

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