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Featured Article

Demonstration of safety of intravenous immunoglobulin in geriatric patients in a long-term, placebo-controlled study of Alzheimer's disease

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Abstract

Introduction: We present safety results from a study of Gammagard Liquid intravenous immunoglobulin (IGIV) in patients with probable Alzheimer's disease.
Methods: This was a placebo-controlled double-blind study. Subjects were randomized to 400 mg/kg (n = 127), 200 mg/kg (n = 135) IGIV, or to 0.25% human albumin (n = 121) administered every 2 weeks ± 7 days for 18 months.
Results: Elevated risk ratios of IGIV versus placebo included chills (3.85) in 9.5% of IGIV-treated subjects (all doses), compared to 2.5% of placebo-treated subjects, and rash (3.08) in 15.3% of IGIV-treated subjects versus 5.0% of subjects treated with placebo. Subjects in the highest IGIV dose group had the lowest proportion of SAEs considered related to product (2 of 127 [1.6%]). Subjects treated with IGIV experienced a lower rate of respiratory and all other infections compared to placebo.
Discussion: IGIV-treated subjects did not experience higher rates of renal failure, lung injury, or thrombotic events than the placebo group. There were no unexpected safety findings. IGIV was well tolerated throughout 18 months of treatment in subjects aged 50–89 years.

Keywords: IGIV; Intravenous immunoglobulin; Adverse events; Alzheimer's disease; Safety of IGIV

1. Introduction

Intravenous immunoglobulin (IGIV) was developed over 30 years ago to serve as plasma protein replacement therapy for patients with primary immunodeficiency diseases. Since that time, IGIV has also been found to be beneficial for inflammatory and immune disorders, such as immune thrombocytopenic purpura, dermatomyositis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, myasthenia gravis, and stiff person syndrome [1]. IGIV exerts immune modulatory and anti-

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An article focused on the primary outcome measure of this study, the efficacy of IGIV treatment in Alzheimer patients, is currently under review. The current article is unique in scope in that it focuses on safety results only.

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inflammatory effects that are potentially relevant to treating Alzheimer's disease (AD). Human sera from normal donors contain antibodies to amyloid beta (Aβ) protein [2], which were shown to be neuroprotective in vitro [3]. Antibodies purified from human IGIV products reduced amyloid levels in the central nervous system when infused in Aβ transgenic mice [4]. IGIV was therefore considered a promising agent in passive immunotherapy because it contains naturally occurring polyclonal human antibodies that bind to Aβ aggregates, foster the dissolution of Aβ fibrils, and enhance microglia-mediated phagocytosis of amyloid deposits in vitro [5–7]. Previous early-phase, investigator-initiated clinical studies suggested that IGIV might halt or reverse symptoms of dementia in subjects with mild-to-moderate AD [8–11]. For this reason, a large randomized, placebo-controlled, phase 3 study in mild-to-moderate AD was initiated to test the safety and efficacy of 18 months of IGIV treatment at 200 or 400 mg/kg/2 wks [12,13]. There were 262 subjects exposed to IGIV, and 121 subjects exposed to human albumin as a control.

IGIV has an established safety profile in children and adults. Elderly subjects are treated with IGIV for both labeled and unlabeled conditions [1,14]; however, there are limited data available from appropriately placebo-controlled, double-blinded studies on the safety of IGIV in elderly patients, with most data derived from case studies and retrospective studies [15–19]. IGIV has been associated with uncommon but serious adverse events (SAEs) for which the elderly carry an increased risk such as thrombotic events, transfusion-related lung injury (TRALI), and renal failure. Although the study described in this report did not meet its primary or secondary efficacy endpoints of reducing cognitive decline and preserving functional abilities in AD [20], a substantial body of safety data was amassed in one of the largest placebo-controlled studies of intravenous immunoglobulin conducted in a geriatric population [21,22].

2. Methods

2.1. Study design and participants

This was a phase 3, randomized, double-blind, placebo-controlled, two-dose arm study in elderly subjects with mild-to-moderate AD. Subjects were enrolled in the study at 45 centers within the Alzheimer's Disease Cooperative Study (ADCS, San Diego, CA) consortium in the United States and Canada. Approximately 385 randomized subjects were planned to be enrolled.

At screening, each subject underwent mini-mental state examination (MMSE), as well as physical, neurological, and laboratory assessments. Subjects were randomly assigned in a 1:1:1 ratio to one of three treatment arms to receive infusions every 2 weeks for 70 weeks (a total of 36 infusions) as an add-on to conventional Food and Drug Administration approved AD pharmacotherapy. The three treatment arms were: IGIV 200 mg/kg, IGIV 400 mg/kg, and albumin placebo control at either 2 mL/kg or 4 mL/kg. A concentration of 0.25% albumin was chosen to match the volume, color, and foam-forming characteristics of the IGIV.

Clinical assessments were conducted every 3 months, and magnetic resonance imaging (MRI) was done every 9 months. End-of-study assessments were performed at week 76. An independent data safety monitoring board performed safety monitoring at regular intervals throughout the study.

Eligible participants of either gender were aged 50–89 years with a diagnosis of probable AD of mild-to-moderate severity as determined by a score of 16–26 on the MMSE scale. Subjects may have been receiving stable doses of AD medication (acetylcholinesterase inhibitor and/or memantine) for at least 12 weeks before screening and required the participation of an able caregiver. The main exclusion criteria were non-Alzheimer's dementia, residence in a skilled nursing facility, clinically significant cardiovascular disease, recent central or peripheral thrombosis and/or thromboembolic disease, or active renal disease.

At the investigator's discretion, subjects may have received investigational product infusions at a clinic, home or other suitable locations. Clinical and laboratory assessments were conducted every 3 months until the end-of-study visit.

2.2. Safety outcome measures

Safety objectives included the proportion of subjects experiencing: any adverse events (AEs), product-related AEs, or serious adverse events (SAEs), the number of infusions temporally associated (defined as during or within 72 hours of completion of an infusion) with AEs or SAEs, infusions causally associated with AEs and/or SAEs, and infusions discontinued, slowed, or interrupted due to an AE. Also examined were the proportions of IGIV-treated subjects experiencing a decrease in hemoglobin ($>$1.5 g/dL) and clinically significant rash requiring systemic therapy.

2.3. Randomization and statistical analysis

Randomization was conducted using a stratified permuted block method with an allocation ratio of 1:1:1. Assignments to the three treatment groups were stratified by site, *APOE* ε4 carrier status (Y/N), and disease severity as defined by MMSE category ($\leq$20, $>$20) at screening.

The sample size was powered for efficacy analyses, which constituted the primary and secondary endpoints of the study. The safety analysis set consisted of all subjects who received study product (IGIV or albumin placebo). Descriptive statistics (counts, percentages, and relative risk) were used to summarize safety outcome measures. Relative risk confidence intervals which were calculated using the approximation proposed by Katz et al. [23].

2.4. Role of the funding source

The study was conducted by Baxalta US Inc. in collaboration with ADCS, a clinical trial consortium supported by

the United States National Institute on Aging at the National Institutes of Health.

3. Results

Of 390 subjects who met inclusion/exclusion criteria and were randomized, 383 subjects received at least 1 dose of study product (262 received IGIV and 121 received albumin placebo) and were therefore part of the safety analysis data set. Of the 390 randomized subjects, seven did not receive treatment (two in the 400 IU/kg arm, three in the 200 IU/kg arm, and two in the placebo arm). There were comparable numbers of subjects who discontinued from each treatment group (Fig. 1). Of the 81 subjects who discontinued, 26 discontinued because of an adverse event, 16 were unwilling or unable to participate, 13 withdrew consent, seven had a study partner unwilling or unable to participate, four subjects died, two discontinued due to a protocol violation, and 13 discontinued for other reasons. An analysis of discontinuation by high and low dose was conducted to examine the effect of volume of infusion on discontinuation. Although there were numerically more subjects who discontinued from the low-dose (200 mg/kg) IGIV and low-dose (2 mL) placebo treatment groups (24.7%) compared with the high-dose (400 mg/kg) IGIV and placebo (4 mL) groups (17.3%), this trend did not reach statistical significance ($P = .081$). Similarly, the mean (SD) duration of treatment before withdrawal was similar between the IGIV dose groups (223.3 [146.75] days for high dose and 224.9 [138.61] days for low dose) and the placebo groups (212.9 [157.61] for high dose and 263.3 [141.88] days for low dose).

The mean age of study participants was 70.3 years: 57% of subjects were 65–80 years and 14% were >80 years, whereas 29% were <65 years. Most of the subjects were female (54.6%), and 60% of subjects had mild severity AD (MMSE score = 21–26) and 40% had moderate severity AD (MMSE score = 16–20). Most subjects were *APOE* ε4 carriers (68.2%), and 17.7% of subjects were homozygous *APOE* ε4/ε4. Disease characteristics were evenly balanced across the treatment groups (Table 1).

The median number of IGIV infusions/subject was 36 in the 400 mg/kg arm, 35 in the 200 mg/kg arm, and 35 in the combined placebo arms. Total exposure to IGIV/subject was 915.6 g in the 400 mg/kg cohort and 468.0 g in the 200 mg/kg cohort. As expected, at the month 18 assessment, serum levels of IgG were elevated in a dose dependent manner compared to baseline (Table 2). Levels of IgG in the cerebrospinal fluid (CSF) were also found to increase from baseline in a dose dependent manner in subjects treated with IGIV compared to the placebo arm (Table 2).

There were nine subjects who experienced SAEs considered related or probably related to IGIV, including 2 of 127 (1.6%) subjects in the high-dose group and 7 of 135 (5.2%) subjects in the low-dose group compared to 4 of 121 (3%) subjects in the albumin control group. IGIV-related SAEs in the high-dose group included congestive cardiac failure, myocardial infarction, and vasogenic cerebral edema; in the low-dose group, related SAEs included anaphylactic reaction, blood pressure increased, hemoglobin decreased, cerebral hemorrhage, partial seizures, mental status changes, and pulmonary embolism; and in the placebo group, the related SAEs included congestive cardiac failure, pyrexia, pulmonary embolism, and deep vein thrombosis (two cases). A lower percentage of subjects in the highest dose group experienced any SAE (16.5%) compared to the 200 mg/kg dose group (23.7%) and the combined placebo group (21.5%; Table 3).

Subjects were monitored for the known labeled risks of IGIV throughout this study. Of the related SAEs mentioned above, 1 case of anaphylaxis (resolved) occurred during an infusion of IGIV. No TRALI or respiratory failure occurred during the study. One subject, a 74-year-old female receiving 200 mg/kg, experienced a nonserious AE of cerebellar infarction. There were 2 female subjects who experienced myocardial infarction: a 72-year-old in the placebo group and a 77-year-old in the 400-mg/kg dose group. The proportion of subjects with thromboembolic events was lower in the IGIV treatment groups compared to the placebo group: (5/262 [1.9%] vs. 6/121 [5%]). Five subjects experienced new or worsening renal failure, including two in the

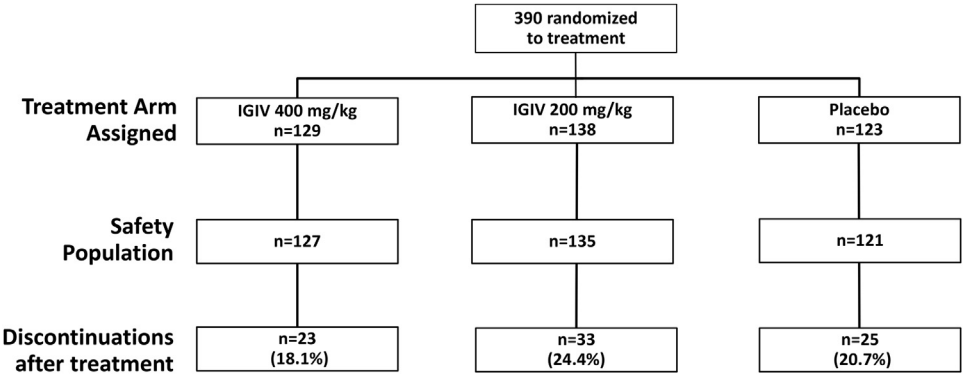

Fig. 1. Flow chart of subject disposition. 390 subjects were randomized and 383 subjects were treated (and therefore included in the safety population) in three treatment groups: IGIV 400 mg/kg ($n = 127$), 200 mg/kg ($n = 135$), and albumin placebo ($n = 121$). A total of 262 subjects were exposed to IGIV.

Table 1
Baseline demographics and disease characteristics overall and by treatment arm (Intent-to-treat population)

Demographic or baseline characteristic	400 mg/kg IGIV (N = 129)	200 mg/kg IGIV (N = 138)	Placebo (N = 123)	All (N = 390)
Age (y)				
N	129	138	123	390
Mean (SD)	70.6 (9.7)	70.1 (8.3)	70.2 (9.9)	70.3 (9.3)
Median (range)	71.0 (50–89)	71.0 (53–87)	70.0 (50–88)	71.0 (50–89)
Weight (kg)				
N*	128	137	121	386
Mean (SD)	71.0 (14.7)	72.4 (13.5)	72.7 (16.6)	72.1 (14.9)
Median (range)	71.8 (40.0–111.0)	73.5 (46.0–106.4)	71.4 (44.7–123.0)	72.0 (40.0–123.0)
Education (y)				
N	129	138	123	390
Mean (SD)	15.3 (2.9)	15.7 (3.2)	15.4 (3.0)	15.5 (3.0)
Median (Range)	16.0 (6–20)	16.0 (8–20)	16.0 (6–20)	16.0 (6–20)
MMSE total score†				
N	129	138	123	390
Mean (SD)	21.3 (3.2)	21.5 (3.1)	21.1 (3.2)	21.3 (3.2)
Median (range)	22.0 (16–26)	22.0 (16–26)	21.0 (16–26)	22.0 (16–26)
Gender, *n* (%)				
Male	59 (45.7)	61 (44.2)	57 (46.3)	177 (45.4)
Female	70 (54.3)	77 (55.8)	66 (53.7)	213 (54.6)
Race, *n* (%)				
White	128 (99.2)	133 (96.4)	120 (97.6)	381 (97.7)
Black	1 (0.8)	4 (2.9)	1 (0.8)	6 (1.5)
Asian	0	1 (0.7)	0	1 (0.3)
Other‡	0	0	2 (1.6)	2 (0.5)
Ethnicity, *n* (%)				
Hispanic§	3 (2.3)	4 (2.9)	5 (4.1)	12 (3.1)
Non-Hispanic	126 (97.7)	134 (97.1)	115 (93.5)	375 (96.2)
Other‖	0	0	3 (2.4)	3 (0.8)
AD severity, *n* (%)				
Mild	83 (64.3)	83 (60.1)	68 (55.3)	234 (60.0)
Moderate	46 (35.7)	55 (39.9)	55 (44.7)	156 (40.0)
Concomitant AD treatment at baseline, *n* (%)				
AChEI¶	117 (91)	124 (90)	112 (91)	353 (90.5)
Memantine	96 (74)	103 (75)	92 (75)	291 (74.6)
AChEl or memantine	126 (98)	137 (99)	120 (98)	383 (98.2)
None	3 (2)	1 (1)	3 (2)	7 (1.8)
APOE ε4 carrier and homozygous allele/ genotype, *n* (%)				
Yes	87 (67.4)	94 (68.1)	85 (69.1)	266 (68.2)
APOE ε4/ε4	23 (17.8)	24 (17.4)	22 (17.9)	69 (17.7)

*Some subjects were missing body weight measurements at baseline.
†MMSE score at screening; inclusion criterion range = 16–26 where lower scores indicate greater impairment.
‡Other includes: American Indian or Alaska Native, multiple, unknown, and not reported.
§Hispanic includes: Hispanic and Latino.
‖Other includes: unknown and not reported.
¶AChEI = acetylcholinesterase inhibitor.

400 mg/kg group (1.6%), one in the 200 mg/kg group (0.7%), and two in the placebo group (1.7%).

Although hemolysis is a labeled risk, there were no AEs of hemolysis. There were, however, three AEs of low hemoglobin. An assessment of clinical laboratory results showed that a greater number of subjects in the IGIV treatment groups than the placebo group experienced a drop in hemoglobin >1.5 g/dL between consecutive visits: 24.4% of subjects receiving 400 mg/kg and 17.8% of subjects receiving 200 mg/kg compared to 13.2% subjects receiving placebo (Table 4). There were no clinical signs linking this decrease in hemoglobin to hemolysis, as LDH was in the normal or near-normal range for all subjects. Furthermore, an increase in hemoglobin >1.5 g/dL between consecutive visits was also observed in some subjects, with slightly more occurring in the IGIV treatment groups compared to placebo. A review of anti-A and anti-B isoagglutinin titers present in the batches of IGIV used in this study was conducted. The highest titer of anti-A was 1:16 and all anti-B titers were lower than 1:16; well below the limit of 1:64 recommended by the European Pharmacopeia (using 2.6.20 Method B) [24].

Rashes requiring systemic treatment or discontinuation of an infusion were a safety outcome measure of the study. Five subjects in the IGIV treatment groups experienced a rash

Table 2
Exposure to IGIV

		Serum levels of IgG (g/L)		CSF levels of IgG (mg/dL)	
Time point	Arm	*n*	Mean (SD)	*n*	Mean (SD)
Baseline	400 mg/kg	127	9.9 (2.0)	8	2.20 (1.01)
	200 mg/kg	134	9.9 (2.2)	10	1.90 (0.96)
	Placebo	119	9.7 (2.6)	17	2.54 (1.33)
18 months	400 mg/kg	100	17.2 (3.5)	8	5.36 (4.77)
	200 mg/kg	99	13.6 (2.5)	10	2.77 (1.44)
	Placebo	93	9.6 (2.4)	17	2.52 (1.43)

NOTE. Safety data are presented descriptively without statistical testing.

requiring discontinuation of the infusion, including three subjects in the 400 mg/kg group and two subjects in the 200-mg/kg group. In contrast, no subjects in the placebo group experienced a rash requiring discontinuation of the infusion. A greater percentage of subjects in the IGIV treatment groups (35 of 262 [13.4%]) experienced a rash requiring systemic therapy (diphenhydramine, cortisone, dexamethasone, loratadine, prednisone, methylprednisolone, or cetirizine) than in the placebo group (8/121 [6.6%]).

There were not a greater number of deaths in the IGIV treatment groups compared to placebo. There were four deaths in 263 subjects in the IGIV treatment groups (including one subject treated with 400 IU/kg who had a possibly related congestive cardiac failure), and three subjects treated with 200 IU/kg (one case of possibly related cerebral hemorrhage; and two cases of multiorgan failure [one case not related and one case unlikely related]). There were two deaths in 121 subjects in the placebo group (not related metastatic colon cancer and possibly related pulmonary embolism).

The nonserious AEs that occurred in the highest number of subjects in the combined IGIV treatment groups were headache (24.0%), hypertension/blood pressure increased (22.9%), fall/contusion/laceration (18.3%), rash (15.3%), infusion site extravasation (14.5%), and diarrhea (14.1%). When compared to the incidence of nonserious AEs in the placebo group, only AEs of chills and rash exhibited statistically significant elevated risk ratios for IGIV treatment (3.85 [95% CI, 1.18–12.50] and 3.08 [95% CI, 1.34–7.07], respectively). The rates per subject for chills were 9.5% in subjects receiving IGIV (all doses) versus 2.5% in those receiving placebo, and for rash, they were 15.3% versus 5.0%. Neither of these AEs were unexpected. Statistically significant declines in risk were noted for combined AEs of fall/contusion/laceration (0.67 [95% CI, 0.46–0.99]) and bradycardia (0.29 [95% CI, 0.10–0.86]). As would be expected, subjects treated with IGIV reported fewer infections than did subjects treated with placebo (34.0% versus 47.9%). Instances of upper respiratory infections were also lower among those receiving IGIV compared to placebo (15.2% vs. 23.1%). An analysis of all AEs of infections demonstrated a lower relative risk for subjects receiving IGIV (0.71 [95% CI, 0.55–0.91]; Fig. 2).

Analyses of AEs and SAEs determined that percentages of infusions temporally or causally associated with AEs and/or discontinued or slowed due to an AE were similar whether IGIV or placebo was administered. For example, there were 396 of 3883 (10.2%), 467 of 3954 (11.8%), and 349 of 3691 (9.5%) infusions temporally associated with AEs and/or SAEs in the 400 IU/kg, 200 IU/kg, and placebo arms, respectively. Causally associated AEs and/or SAEs were reported in 225 of 3883 (5.8%), 265 of 3954 (6.7%), and 172 of 3691 (4.7%) infusions in the 400 IU/kg, 200 IU/kg, and placebo arms, respectively. The proportion of infusions discontinued, slowed or interrupted due to an AE/SAE were 48/3883 (1.2%), 28/3954 (0.7%), and 36/3691 (1.0%), respectively.

Subjects received an MRI for dual purposes of clinical safety assessment and volumetric measurements at screening, month 9, and month 18, or at the termination visit in the case of an early termination. One SAE of vasogenic asymptomatic cerebral edema (amyloid-related imaging abnormalities-E [ARIA-E]) was reported in a subject treated with 400-mg/kg IGIV. Approximately 10% of subjects developed treatment emergent cerebral microhemorrhages (amyloid-related imaging abnormalities-H [ARIA-H]), which was similar across all treatment groups. However, when examined by *APOE* ε4 status, *APOE* ε4 carrier subjects

Table 3
Number of subjects (%) with serious AEs and AEs of interest

	400 mg/kg, n = 127	200 mg/kg, n = 135	Placebo, n = 121
Any AEs	124 (97.6)	133 (98.5)	117 (96.7)
SAEs	21 (16.5)	32 (23.7)	26 (21.5)
SAEs related to study product	2 (1.6)	7 (5.2)	4 (3)
Deaths during or after treatment	1 (0.8)	3 (2.2)	2 (1.7)
Subjects hospitalized due to an AE	18 (14.2)	26 (19.3)	23 (19.0)
Rash requiring systemic therapy*	19 (15.0)	16 (11.9)	8 (6.6)
New or worsening renal failure	2 (1.6)	1 (0.7)	2 (1.7)
Thromboembolic events	2 (1.6)	3 (2.2)	6 (5.0)
Myocardial infarction, stroke, arterial thrombosis	1 (0.8)	1 (0.7)	1 (0.8)
Upper respiratory infections	16 (12.6)	24 (17.8)	28 (23.1)

*Diphenhydramine, cortisone, dexamethasone, loratadine, prednisone, methylprednisolone, or cetirizine.

Table 4
Changes in hemoglobin level

N (%)	IGIV, 400 mg/kg, n = 127	IGIV, 200 mg/kg, n = 135	All placebo doses, n = 121
Subjects with decrease in hemoglobin >1.5 g/dL	31 (24.4)	24 (17.8)	16 (13.2)
Subjects with increase in hemoglobin >1.5 g/dL	17 (13.4)	16 (11.9)	12 (9.9)

exhibited numerically more microhemorrhages than noncarriers both in the IGIV and placebo groups (Table 5). As the microhemorrhages were identified in routine scans and were asymptomatic, most microhemorrhages in the above analysis were not considered AEs by the investigators. The percentage of subjects (9 of 262 [3.4%]) in whom cerebral microhemorrhage was reported as an AE in the combined IGIV treatment group was similar to that in the placebo group (4 of 121 [3.3%]).

4. Discussion

Biweekly treatment with Gammagard Liquid (IGIV; 200 or 400 mg/kg) over 18 months in patients with AD of mild-to-moderate severity was well tolerated in a special (geriatric) population aged 50 to 89 years, with relatively few adverse events in either the placebo or active IGIV dose groups [25]. To date, limited information has been collected in controlled clinical trials about geriatric use of IGIV. The present study offered an opportunity to examine the safety of IGIV in a large (N = 390) sample of elderly patients.

Geriatric patients are considered to have an elevated risk of acute renal failure and arterial or venous thrombosis during IGIV treatment [15,25,26]. Subjects with significant cardiac conditions, thrombosis and or thromboembolic disease, or renal disease were therefore excluded from the study. The IGIV product used in this study does not contain sucrose, which has been demonstrated to be associated with renal complications [27]. Only five subjects experienced new or worsening renal failure, and they were distributed between the three study arms. The proportion of subjects with thromboembolic events was also lower in the IGIV treatment groups compared to the placebo group: (1.9% vs. 5.0%). The occurrence of thrombotic events has been considered one of the most serious health risks of IGIV products. In a recent publication of a retrospective cohort study, Daniel et al. compared the safety profiles of six IGIV products in 11,785 patients [28,29]. Of all six products studied, Gammagard Liquid

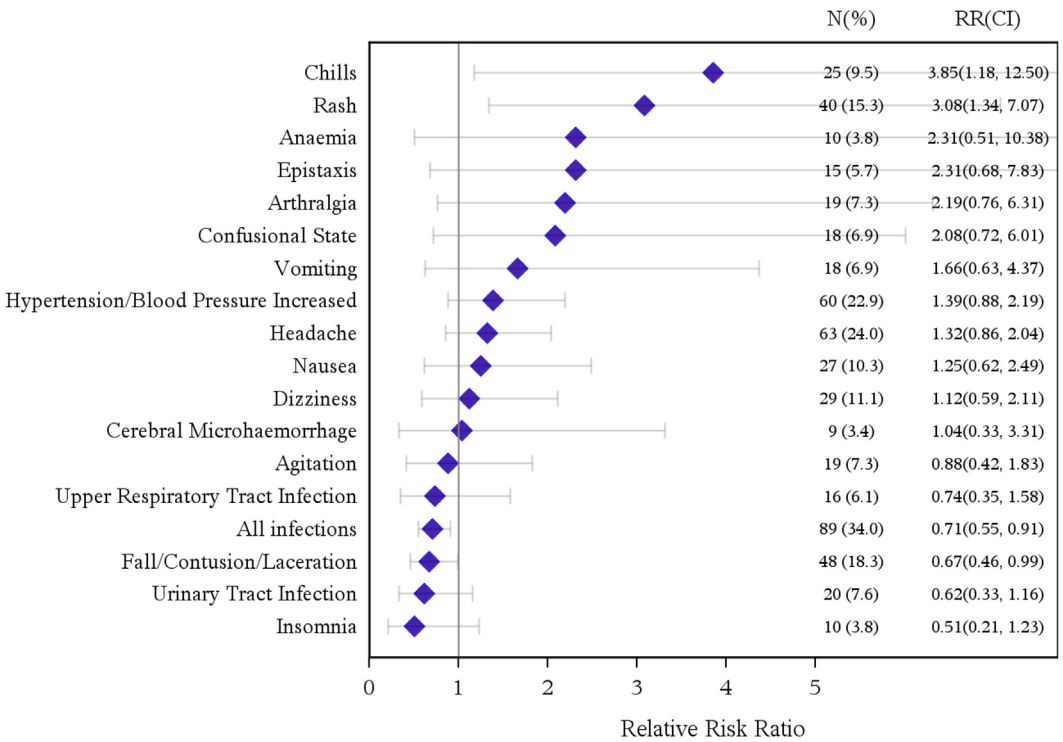

Fig. 2. Incidence (%) and risk ratio of AEs in subjects treated with IGIV. Risk ratio (indicated in forest plot above by diamonds) for AEs with respect to placebo treatment group is displayed in the forest plot. Ratios >1 represent higher risk than placebo group. Ratios <1 represent lower risk. 95% confidence intervals (CIs) were computed based on the method by Katz et al. [23]. Similar AEs were combined, including all infections; hypertension/blood pressure increased; and fall/contusion/laceration. The incidence values (%) are based on 262 subjects treated with at least one infusion of IGIV.

Table 5
Emergent intracerebral microhemorrhages at month 18 by *APOE* ε4 status

APOE ε4 carrier?	Change in microhemorrhages since baseline	All doses IGIV subjects (%)	Placebo all doses subjects (%)
Yes	No additional hemorrhage	118/133 (88.7)	58/68 (86.6)
	Additional hemorrhage	15/133 (11.3)	9/68 (13.4)
No	No additional hemorrhage	56/59 (94.9)	26/26 (100.0)
	Additional hemorrhage	3/59 (5.1)	0/26 (0.0)

(IGIV) had the lowest rate of same-day thrombotic events (7.4 cases per 1000 patients exposed) compared to the overall rate of 10.4 cases of same-day thrombotic events per 1000 patients exposed. The authors used Gammagard Liquid IGIV as the reference for analysis of odds ratios for same-day thrombotic event occurrence in all of the other IGIV products, because it had the lowest incidence of thrombotic events. In the present study, one SAE of asymptomatic vascular cerebral edema was reported in a subject treated with 400-mg/kg IGIV (a subsequent MRI demonstrated that the edema was resolved). This reflects approximately 0.4% of treated subjects, which is lower than the incidence of vasogenic edema which was reported in approximately 10% of AD subjects in a phase 1 trial of bapineuzumab [30].

The Alzheimer's Association Research Roundtable Workgroup recommends careful MRI monitoring for the occurrence of ARIA in clinical studies of amyloid modifying therapeutic agents [31]. Most subjects did not have additional microhemorrhages at month 18 according to MRI examination. The recent study reported by Dodel et al [32] using another intravenous immunoglobulin product (Octapharma) reported more patients experiencing microbleeds (the term that team used for "microhemorrhages" as they were referred to in our study), (20%) compared to those receiving placebo (7%). This is unlike the results of our study where the rate of new cerebral microhemorrhages observed was similar among the treatment arms (approximately 10%). However, the rate was numerically increased in subjects who are *APOE* ε4 carriers. The relative safety of IGIV with regard to neurologic adverse events (particularly cerebral microhemorrhage or stroke) is notable considering that levels of total IgG antibodies were observed to have increased dose dependently in CSF at the 18-month assessment, indicating that IgG had crossed the blood-brain barrier.

A documented potential risk of treatment with IGIV is hemolysis [33–37]. There were no AEs of hemolysis reported during the study. Decrease in hemoglobin (>1.5 g/dL) was defined as significant in the protocol; however, only three subjects experienced a clinically significant decrease in hemoglobin that was reported as an AE in the study. There were a greater number of subjects in the IGIV treatment groups experiencing a drop in hemoglobin >1.5 g/dL between consecutive visits compared to subjects receiving placebo. The decline in hemoglobin was mild to moderate, and no specific mechanism for the decline was identified. The higher rate of subjects with a substantial drop in hemoglobin levels in the 400-mg/kg group might be attributable to the fact that more of these subjects had a <1:3 ratio of iron to iron binding capacity at baseline compared to those in the two other study groups (data not shown). There were no clinical signs linking this decrease in hemoglobin to hemolysis, as LDH was in the normal or near-normal range for all subjects. Furthermore, analysis of isoagglutinins anti-A and anti-B in Gammagard Liquid IGIV demonstrate that the product has titers lower than the 1:64 recommended by the European Pharmacopoeia by at least 2-step dilution (the highest titer of anti-A was 1:16 and all anti-B titers were lower than 1:16).

When compared to the incidence of nonserious AEs in the placebo treatment group, only chills and rash exhibited statistically significant risk ratios for IGIV, 10% treatment (Fig. 2). Although IGIV treatment was associated with an elevated risk of rash, pre-treatment of subjects who experienced allergic reactions with antihistamine was permitted in the study protocol to protect them from further reactions. This approach may permit patients to be treated who would otherwise be unable to receive IGIV.

The most common adverse event in subjects treated with IGIV was headache, a known risk of IGIV [25,38]. However, there was not an elevated risk ratio for headache because patients receiving placebo had a similar incidence.

Beneficial decreases in infection rate and falls (Fig. 2) were observed with IGIV treatment. The reduction of infections may be accounted for by the protective effect of IGIV, 10%, which is well established in primary immunodeficiency [25]. Although no subjects had an IgG titer considered abnormally low, many subjects were on the lower limit of normal at baseline; 8.1% of subjects had an IgG concentration <7 g/L (data not shown), which suggests that their adaptive immune response to pathogen may have been limited and that supplementation with IGIV may reduce the infection rate in the elderly. Even elderly subjects with a normal IgG titer may exhibit reduced opsonophagocytic activity and low antibody avidity. Such a diminution of endogenous antibody function with age has been reported and may account for decreased vaccine efficacy [39]. Multiple lymphoid lineages may undergo changes in the elderly contributing to immunosenescence [40,41]. The reasons for IGIV infusion in a geriatric patient can be multifarious, ranging from chemotherapy support, to autoimmune disease and solid organ transplantations. This clinical trial was the first large, controlled study of IGIV in this unique patient population. Its results demonstrated IGIV to be safe and comparable in AE incidence rates to albumin infusion in the elderly.

Allergic/hypersensitivity reactions, hemolysis, TRALI, renal failure, and thrombotic/thromboembolic events are all considered risks with IGIV treatment, particularly in elderly patients, however in this placebo-controlled study, IGIV was found to be well tolerated and safe, with no new safety findings or unexpected AEs. Furthermore, patients treated with IGIV demonstrated a significantly lower risk ratio for infections and falls/lacerations/contusions, which could be a potentially important finding if demonstrated in a controlled clinical trial, considering the risks associated with falls in the geriatric population. The previously established safety record of IGIV has been confirmed in the present controlled analyses in a large geriatric population.

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RESEARCH IN CONTEXT

1. Systematic review: The literature was searched for articles and abstracts using PubMed and Embase. Most publications on IGIV use in the elderly were case studies, with few randomized, placebo-controlled, double-blinded studies.
2. Interpretation: The results of this study indicate that long-term IGIV treatment in an elderly population was safe and well tolerated.
3. Future directions: The reduction of infections in subjects treated with IGIV suggests that there is a need to assess secondary hypogammaglobulinemia and the functionality and avidity of IgG in the elderly population. Falls, lacerations, and contusions are common in geriatric patients and are associated with morbidity and mortality. If the role of IGIV in reducing the rate of this complication can be confirmed, the mechanism of action should be investigated. More safety data should be collected to confirm the low risk of thromboembolic events and hemolysis observed in this study.

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