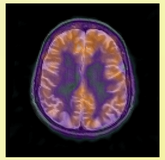

A retrospective chart review of the tolerability and efficacy of Intravenous Immunoglobulin (IVIg) in the treatment of Alzheimer's disease

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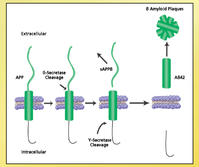
BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by insoluble beta-amyloid peptide (Aβ42) plaque deposition in the brain (1, 2). Reducing insoluble plaque burden, by decreasing the production of Aβ42 or by increasing its clearance from the brain, is a goal of several treatment strategies currently being researched (3).

Some small studies have investigated the efficacy of passive immunization with intravenous immunoglobulin (IVIg) in treating AD (4-6). Patients diagnosed with AD have decreased levels of polyclonal anti-Aβ antibodies with possible reduction in Aβ clearance resulting in increased plaques and cerebrovascular amyloid deposits (7). Studies of IVIg treatment have shown an increase in anti-Aβ antibodies in patients' cerebrospinal fluid (CSF), possibly leading to increased clearance of Aβ (4-6).

Based on this data, we treated a sample of our patients with AD with IVIg (4, 5).



OBJECTIVE

To retrospectively investigate the tolerability and efficacy of IVIg in AD. We hypothesized that IVIg would be well tolerated and effective in treating cognitive symptoms in this group.

METHODS

Design: Retrospective chart review.

Setting: Outpatient neurology practice.

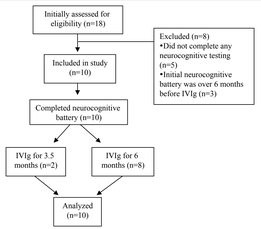
Participants: Ten patients (five men, five women; mean age 74 ± 7.5 years) with probable or possible AD, completing 3.5 to 6 months of treatment. All patients underwent a standardized neurocognitive battery [(Wechsler Adult Intelligence Scale-III (WAIS); Wechsler Memory Scale-III (WMS-III); Bushke Selective Reminding Test (BSRT); 60-item Boston Naming Test (BNT)] both before and after receiving IVIg treatment.

Interventions: Patients received IVIg at 0.4g/kg every two weeks.

Measurements: Outcome variables on the neurocognitive battery before and after IVIg treatment were evaluated using Student's paired t-tests. Nonparametric tests were used to test for differences between genders.

MORE ON THE PARTICIPANTS

Figure 1: Flow of Participants through Study



Participants were patients who had previously been diagnosed with probable or possible AD according to the NINCDS-ADRDA* criteria. All patients had to have taken the extensive neurocognitive battery to be included in the final analysis.

*National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association

RESULTS

Tolerability: Two patients developed a pruritic, maculopapular generalized rash, resolving with appropriate treatment and both continued with IVIg therapy.

Efficacy: Patients showed stability on their neurocognitive scores. Amongst subscores, there was a trend towards decline on the WAIS verbal scale ($p<0.1$), full scale ($p<0.1$), and information subtests ($p<0.1$), and on the BNT ($p=0.1$). Trends towards improvement were seen on the WMS logical memory recall ($p<0.1$), verbal paired associates ($p=0.15$), and auditory delayed memory tests ($p=0.1$). Nonparametric tests showed a trend towards a differential gender effect, with men exhibiting more improvement on IVIg than women.

Table 1: Tests Showing Significant Cognitive Change over Time

Subtest*	Baseline (mean)	SD	Post-treatment (mean)	SD	Mean Change (Post-Pre)	SD	Sig.
WAIS Verbal Scale Intelligence	101.50	2.297	99.20	24.184	-2.30	3.802	0.088
WAIS Full Scale Intelligence	97.20	23.112	94.20	23.532	-3.00	5.142	0.098
WAIS Information	9.10	4.358	8.20	4.158	-0.90	1.524	0.095
WMS-III Verbal Paired Associates	4.30	0.823	5.10	1.792	0.80	1.619	0.15†
WMS-III Logical Memory II Recall	4.90	2.885	6.00	3.399	1.10	1.10	0.093
WMS-III Auditory Delayed Memory	69.89	8.477	74.44	8.918	4.56	7.876	0.1
BNT Total	46.70	15.861	44.80	17.511	-1.90	3.381	0.1

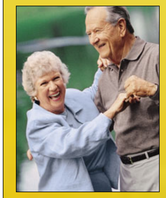
*Approaching trend at the p<0.1 level. WAIS and WMS-III Primary Index Normal Distribution: 100±15, Scaled Score Normal Distribution: 10±3 (Range: 1-19) (Wechsler D. Wechsler Adult Intelligence Scale [3rd Ed]. The Psychological Corporation. 1997.); BNT (Range: 1-60) (Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea & Febiger, 1983).
†Approaching trend at the p<0.1 level.

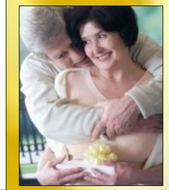
CONCLUSIONS / DISCUSSION

In our review, we found that IVIg was well tolerated in chronic administration in our patients with AD. It stabilized cognitive decline with trends for improvement in some cognitive domains, particularly among men.

Such clinical improvement may be related to decreased levels of Aβ in the brain, based on the theory that insoluble, extracellular Aβ plaque deposition is central to AD pathogenesis and the hypothesis that removing insoluble Aβ either directly (through active immunization) or indirectly (through passive immunization, as is the case with IVIg) is beneficial to cognitive functioning (8, 9).

Overall, results from our retrospective chart study appear promising, but are preliminary. A currently ongoing, rigorous trial should definitively determine the role of IVIg in treating Alzheimer's Disease.





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DMT may stimulate visual functions and planning more than memory, but the findings are inconclusive. A benefit was previously observed in the information content of speech output,[5] and this was partly replicated. The behavioral symptoms remained relatively stable, but self-care ability and IADLs seemed to improve slightly.

DMT therefore seems to offer one option in treating dementia, having effects on cognition and self-care abilities.

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Author Contributions: L. Hokkanen: Participation in the study design; design of the cognitive testing; analysis of the data; preparation of the manuscript; L. Rantala: Design the language collection procedure; tutoring the nurses for recording the data; analysis of the language data by linguistic methods; A. Remes: Participation in the study design; analysis of the clinical patient data, collaboration on the manuscript; B. Härkönen: Design of the dance/movement therapy intervention; training and tutoring the nurses to give the intervention; P. Viramo: Participation in the study design; analysis of the clinical patient data; statistical analysis of the data; collaboration on the manuscript; I. Winblad: Initial idea of the study; participation in the study design; subject recruitment; supervision of the interventions on site; collaboration on the manuscript.

Sponsor's Role: Covering the costs for meetings, costs for travel, costs for testing materials.

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A RETROSPECTIVE CHART REVIEW OF THE TOLERABILITY AND EFFICACY OF INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF ALZHEIMER'S DISEASE

To the Editor: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by insoluble beta-amyloid peptide ($A\beta_{42}$) plaque deposition in the brain.[1,2] Reducing insoluble plaque burden, by decreasing the production of $A\beta_{42}$ or by increasing its clearance from the brain, is a goal of several treatment strategies currently being researched.[3]

Some small studies have investigated the efficacy of passive immunization with intravenous immunoglobulin (IVIg) in treating AD.[4–6] Patients diagnosed with AD have low levels of polyclonal anti-Aβ antibodies with possible reduction in Aβ clearance resulting in more plaques and cerebrovascular amyloid deposits.[7] Studies of IVIg treatment have shown an increase in anti-Aβ antibodies in patients' cerebrospinal fluid (CSF), possibly leading to greater clearance of Aβ.[4–6]

Based on these data, a sample of patients with AD was treated with IVIg.[4,5] The tolerability and efficacy of IVIg in the treatment of cognitive loss in this group of 10 patients was retrospectively investigated. It was hypothesized that IVIg would be well tolerated and effective in treating cognitive symptoms in this group.

A total of 18 patients had received IVIg, at 0.4 g/kg every 2 weeks, for the treatment of AD. Five patients were cognitively unable to complete a neurocognitive battery

Table 1. Tests Showing Significant Cognitive Change over Time

Subtest*	Pretreatment	Posttreatment	Change (post–pre)	*P*-Value
	Mean ± Standard Deviation			
WAIS verbal scale intelligence	101.50 ± 2.30	99.20 ± 24.18	−2.30 ± 3.80	.09
WAIS full-scale intelligence	97.20 ± 23.11	94.20 ± 23.53	−3.00 ± 5.14	.098
WAIS information	9.10 ± 4.36	8.20 ± 4.16	−0.90 ± 1.52	.095
WMS-III verbal paired associates	4.30 ± 0.82	5.10 ± 1.79	0.80 ± 1.62	.15†
WMS-III logical memory II recall	4.90 ± 2.89	6.00 ± 3.40	1.10 ± 1.10	.09
WMS-III auditory delayed memory	69.89 ± 8.48	74.44 ± 8.92	4.56 ± 7.88	.1
BNT total	46.70 ± 15.86	44.80 ± 17.51	−1.90 ± 3.38	.1

*Wechsler Adult Intelligence Scale (WAIS) and Wechsler Memory Scale (WMS)-III Primary Index normal distribution 100 ± 15, scaled score normal distribution 10 ± 3 (range 1–19) (Wechsler D. Wechsler Adult Intelligence Scale (3rd Ed). San Antonio: The Psychological Corporation, 1997); Boston Naming Test (BNT) (range 1–60) (Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Philadelphia: Lea and Febiger, 1983).
†Approaching trend at the $P<.1$ level.

(Wechsler Adult Intelligence Scale (WAIS) III; Wechsler Memory Scale (WMS) III; Bushke Selective Reminding Test (BSRT); 60-item Boston Naming Test (BNT)) before or after IVIg treatment and were therefore not included in the analysis. Three of the patients completed their first neurocognitive battery more than 6 months before they began receiving IVIg treatment and were also excluded. The remaining 10 patients (5 men, 5 women; mean age ± standard deviation 74 ± 7.5) were analyzed in the retrospective analysis. Seven of these patients had been diagnosed with probable AD and three with possible AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[8] Eight of the patients completed 6 months of treatment; two completed 3.5 months of treatment. Two patients developed a pruritic, maculopapular, generalized rash, resolving with appropriate treatment, but both continued with IVIg.

The institutional review board of Lenox Hill Hospital in New York, New York, approved the retrospective chart review. Outcome variables on the neurocognitive battery before and after IVIg treatment were evaluated using Student paired *t*-tests. Nonparametric tests were used to test for differences between sexes.

Patients showed stability on neurocognitive scores overall, with trends toward decline on their WAIS verbal scale and full-scale intelligence scores ($P<.1$), as well as on the WAIS information ($P<.1$) subtest and the BNT ($P=.1$). Patients showed trends toward improvement on the WMS logical memory II recall ($P<.1$), WMS verbal paired associates ($P=.15$), and the WMS auditory delayed memory test ($P=.1$). These results are summarized in Table 1. Because of the small number of patients included in the analysis ($n=10$) and the resulting low power of the study, a significance level of $P<.1$ was used to indicate trends toward improvement or decline in this group.

Stratifying the data according to sex showed that the mean proportion was higher and variability lower for men (1.05 ± 0.07) than women (0.93 ± 0.10). Nonparametric tests showed differences approaching significance between the sexes. Significance values for each of these tests were as follows: analysis of variance, $P=.05$; Wilcoxon rank sum, $P=.07$; Kruskal-Wallis, $P=.08$; and Median Score, $P=.07$. This difference may be attributed to differential plaque clearance between the sexes. Various studies have shown an existing disparity in Aβ plaque load between men and women, with women having an overall higher plaque burden.[9,10]

Overall, results from this retrospective chart review appear promising, notwithstanding a few limitations. It was found that IVIg was well tolerated and effective in this sample, with patients showing stability on neurocognitive test scores and trends toward improvement in some areas. However, this study was relatively small. A larger study of IVIg treatment of cognitive loss in this cohort would be ideal, as well as future research into potential differences between the sexes. Researchers and practitioners are currently awaiting the results of a Phase II Trial of IVIg for the treatment of cognitive loss in AD conducted by Elan Pharmaceuticals, Inc. Results of this larger trial may have important implications for the direction of future IVIg and Alzheimer's research. Meanwhile, smaller studies such as this retrospective chart review continue to support the use of IVIg for treating cognitive loss in AD, both through neurocognitive test measures and clinical improvements.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the author and has

determined that none of the authors have any financial or any other kind of personal conflicts with this letter.

Author Contributions: Dr. Gayatri Devi was the principal investigator for this study. Dr. Devi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sarah Schultz contributed to this study through her research of the subject, analysis of the data, and writing of this manuscript under Dr. Devi's supervision. Lynn Khosrowshahi contributed to the study through her analysis of the data and summary of results. Abby Agnew administered the neurocognitive battery to all patients in this study under Dr. Devi's supervision. Esther Olali administered the IVIg treatment to all patients in this study, under Dr. Devi's supervision.

Sponsor's Role: This study did not have a sponsor.

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COCKCROFT-GAULT FORMULA FOR DIAGNOSING MODERATE KIDNEY FAILURE

To the Editor: The article by Giannelli et al.[1] concerning specificity and sensitivity of various laboratory methods of estimating glomerular filtration rate (GFR) may be of practical importance relative to Medicare D reimbursement for the use of erythropoietin (EPO) stimulators.

One of the approved diagnoses for using EPO stimulators is when anemia is associated with moderate kidney failure, defined as GFR <60 mL/min per 1.73 m^2. The laboratory at the Bergen Regional Medical Center conventionally employs the Modification of Diet in Renal Disease 4 equation which is reported as greater than 60 when a lesser degree of renal failure is present, insufficient to meet Medicare criteria for using EPO stimulators. However, when GFR was recalculated for four such anemic patients using the older and apparently more-sensitive Cockcroft-Gault formula, in each case, the GFR was <60 (52.8, 55.9, 46.5, and 32.8).

We suggest that, when confronted with anemic elderly patients whose diagnosis is uncertain and whose renal function appears to be normal according to conventional methods, GFR should be recalculated using the Cockcroft-Gault formula. Clinicians may be surprised to find that moderate kidney failure exists and that EPO stimulation might be worth a try—and may even be compensable.

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Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the author and has determined that none of the authors have any financial or any other kind of personal conflicts with this letter.

Author Contributions: Michael Nevins and Michael Bright participated in the drafting of this letter.

Sponsor's Role: No sponsors.

REFERENCE

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SOUND-ALIKE SYNDROMES: FIRST REPORT OF MORVAN'S, AND NOT MARFAN'S, SYNDROME

To the Editor: "Can you handle a case of Marfan's syndrome?" was asked of our 720-bed subacute and long-term care facility in the Bronx, New York.

"Sure, why not?" came the immediate reply, with thoughts of Abraham Lincoln and the connective tissue genetic disease affecting the limbs, valves, and aorta. Life expectancy for this disease has improved with better treatments, and it would not be surprising that a patient with this syndrome would require nursing home placement.

"Sound-alike" medications have been a notable concern for the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), pharmacies, physicians, and patients, but this example of "sound-alike" syndromes was new to us, as was this specific syndrome, which has yet to be reported in the geriatric or long-term care literature.

CASE REPORT

Mr. M, a 67-year-old man from Bangladesh, was admitted to Kings Harbor Multicare Center from a referring hospital. He had been in his usual state of health until January 2007, when he developed personality changes including excessive crying and banging his head against the wall, as well as visual hallucinations, insomnia, apathy, lethargy, muscle twitching, inability to walk, and seizures. An extensive examination included a computed tomography scan of the head showing old ischemic changes and lacunar infarcts, a magnetic resonance imaging (MRI) scan revealing increa-