

Editorial

Is intravenous immunoglobulin a potential new treatment for Alzheimer's disease?

Context: In 2006, the number of people with dementia in the UK was estimated to be 750,000.[1] Alarming, it is predicted that, with increasing longevity in the population, this number could reach 1.5 million by the year 2051.[1] Available drug treatments for dementia (predominantly acetylcholinesterase inhibitors) do not stop or reverse neurodegeneration, and so management of long-term treatment and care for people with dementia is fundamental. This places considerable demand on social and health resources. However, improved understanding of the pathology of dementia has led to the identification of new targets for treatment. In the case of Alzheimer's disease, which is the most common form of dementia and accounts for 50%–60% of all cases,[2] it is anticipated that immunotherapies for amyloid protein could reduce amyloid-beta levels and thus improve cognition. There is limited evidence from two small open-label pilot studies that, in people with Alzheimer's disease, intravenous immunoglobulin (IVIg) increased serum amyloid-beta and reduced amyloid-beta in cerebrospinal fluid.[3][4] A recent retrospective case–control analysis by Fillit and colleagues in the USA investigated whether administration of IVIg in usual care is associated with a lower risk of developing Alzheimer's disease and related disorders (ADRD).[5]

Summary: Fillit and colleagues searched a national database (compliant with the Health Insurance Portability and Accountability Act) of physician claims using procedure codes to identify medical claims data for administration of IVIg.[5] People included in the analysis were ≥ 65 years of age, and received at least one injection of IVIg (average dose of $\leq 90,000$ mL) between 1 April 2001 and 31 August 2004. The authors specified that, to be included in the analysis, people must have:

- made one or more claims over a period of 1 year or more before their treatment with IVIg
- had at least one medical claim in each of the three consecutive 1-year periods after first treatment with IVIg.

This was to ensure that patients at risk of developing ADRD were followed in the database for the duration of the analysis, to confirm that people did not have a prior diagnosis of ADRD, and to identify IVIg risk factors. People diagnosed with ADRD left the study on the date of diagnosis, and those undiagnosed with a condition of interest left the study on the last recorded date of receiving medical care. Diagnosis codes were used to identify patients diagnosed with ADRD (diagnoses were listed as Alzheimer's disease, senile dementia, pre-senile dementia, other specified senile psychotic conditions, unspecified senile psychotic condition, Pick's disease, other frontal temporal dementia, senile degeneration of the brain, and senility without mention of psychoses) and to identify risk factors for these conditions. Controls were matched 100:1 to cases on age (based on five categories: 65–69, 70–74, 75–79, 80–84, and ≥ 85 years), sex, and risk factors for ADRD. Fillit and colleagues identified 847 people treated with IVIg and included 84,700 people in their control population.

Findings: The study found a significantly lower incidence of people with ADRD (all ages included in analysis) in the IVIg-treated group compared with the control group at the end of the observation period (see table 1). However, subgroup analyses based on age found disparate results. Whereas a subgroup analysis of people aged 65–74 years found the difference between groups to be significant, subgroup analyses of people aged 75–84 years and over 84 years found no significant difference between the IVIg-treated groups and the control groups in incidence of ADRD at the end of the observation period, although incidence was lower in the IVIg-treated groups (see table 1). The authors found that the projected incidence of ADRD at 60 months was lower in the IVIg-treated group compared with the control group (see table 2). Comparison of baseline characteristics of the groups found no

significant difference between the groups in mean age or sex, or in proportion of people with ADRD risk factors (hypercholesterolaemia, diabetes, hypertension, chronic kidney disease, hyperhomocysteinaemia, and obesity). However, the authors found a significant difference between groups in length of follow-up (3.64 years with IVIg v 4.23 years with no IVIg; $P < 0.0001$). The authors attributed this difference to the finding that a larger proportion of the control group had an index date that was early in the sample intake period, which allowed a longer period of follow-up (confirmed by sensitivity analysis). After adjustment of weighting to take into account the longer follow-up observed in the control group, the difference in proportion of people diagnosed with ADRD at the end of the study period remained significantly lower in the IVIg-treated group compared with the control group (see table 1).

Appraisal: In their paper, Fillit and colleagues aimed to augment the evidence base on the effects of IVIg in the treatment of ADRD by comparing the incidence of ADRD in people treated with IVIg for non-Alzheimer's disease conditions versus a control group of people who had not received IVIg. It is a rigorous and well-planned case-control study; but, as is often the case with observational data, some areas may be open to interpretation — many of which are considered by the authors in their discussion of their results.

- The authors state that their preliminary results warrant further investigation of the effects of IVIg in the management of Alzheimer's disease. By retrospectively assessing the effects of treatment with IVIg, the authors have put forward evidence that IVIg may afford protective effects against neurodegeneration in the general population rather than that IVIg may be used to treat the effects of neurodegeneration in people diagnosed with Alzheimer's disease, which is the therapeutic action investigated by the two small pilot studies.^{[3][4]} The putative findings of a preventative role for IVIg raise interesting implications for future research. For example, Alzheimer's disease is difficult to diagnose, particularly in its early stages, and determining who would benefit from prophylactic treatment with IVIg would be problematic. Furthermore, prophylactic benefit would need to be balanced against adverse effects of treatment.
- The authors highlight that the lower rate of diagnosis of ADRD in the IVIg-treated group could be a result of under-diagnosis of these types of dementia rather than a therapeutic effect of IVIg. Over 30% of people treated with IVIg had a diagnosis of cancer (lymphoid leukemia, lymphoma, or multiple myeloma), which is a considerably higher rate than the average for these conditions observed in the general population and therefore in the control group. Under-diagnosis could occur if clinicians attributed cognitive impairment in these patients to be a symptom of their condition or to treatment with chemotherapy (received by 10% of people in the IVIg group). Conversely, the reduced risk of dementia could perhaps be associated with treatment with chemotherapy agents or a combination of chemotherapy plus IVIg, and not with IVIg alone.
- Using claims data as a reference tool has, as the authors point out, limitations. Because of the difficulties associated with diagnosis of Alzheimer's disease, the condition is under-coded in claims data. Again, under-coding/under-diagnosis could have influenced the observed lower incidence of Alzheimer's disease in the IVIg group. However, it could be anticipated that under-coding would be randomly distributed between the IVIg and control groups.
- The authors included a broad range of diagnoses codes of dementia in the analysis, based on codes used in other studies: the use of a comprehensive set of diagnosis codes has been shown to increase the identification rate of Alzheimer's disease. In addition, the authors specifically excluded codes for dementia with aetiologies that were not relevant for treatment with IVIg (e.g., drug-induced dementia and other organic brain syndromes). They also carried out a sensitivity analysis in which people with a diagnosis other than Alzheimer's disease, senile dementia, and pre-senile dementia were classified as not having ADRD: the difference between groups in diagnosis of ADRD remained significant ($P = 0.025$). Although the authors attempted to exclude non-ADRD dementia, it is possible that some types of dementia included, in both the overall analysis and sensitivity analysis, may be the result of vascular causes or Lewy body formation, which do not typically exhibit deposition of amyloid-beta, the hallmark characteristic

of Alzheimer's disease. The disparity in the diagnoses included makes it difficult to discern the therapeutic effect of IVIg. If IVIg acts, as has been postulated, by reducing toxicity of amyloid-beta or inhibiting amyloid-beta fibrillation, then it would not protect against development of other types of dementia.

- Although the authors stipulate in their introduction that controls were matched based on five age categories (65–69, 70–74, 75–79, 80–84, and ≥85 years), data are analysed in three ranges (65–74, 75–84, and >84 years). It is not clear why the authors did not analyse the data based on the age ranges listed initially for matching of controls. Furthermore, the authors do not discuss the implications, if any, of their findings that there were no significant differences between groups in observed incidence of Alzheimer's disease and ADRD at 74–84 years and at >84 years. Age is the greatest risk factor for dementia — it affects one in 14 people over the age of 65 and one in six over the age of 80[6] — and these data could highlight potential restrictions on the utility of IVIg as a protective agent.
- The authors reviewed the literature for potential risk factors for ADRD and identified several factors thought to increase risk of ADRD (listed as diabetes, hypercholesterolaemia, hypertension, chronic kidney disease, hyperhomocysteinaemia, alcohol abuse, obesity, and smoking). However, their review of the literature was not systematic, and so some risk factors may not have been accounted for (e.g., family history).[6] Furthermore, the retrospective case–control design of the study restricted the data that could be collected on patient risk factors. Thus, the data collected may not adequately control for differences in risk factors between the treatment and control groups. To minimise potential biases, the authors carried out multivariate analyses. However, the authors highlighted that this would not consider the effects of unobserved differences, which could lead to bias in estimated treatment effect.

Overview: Fillit and colleagues have used an innovative approach to acquire a large volume of data to tackle an important question in a clinically complex condition. The findings of the authors raise interesting possibilities for the role of IVIg in the prevention of development of Alzheimer's disease. However, we agree with the authors that their results cannot be taken to show conclusively that prior treatment with IVIg is associated with a reduced risk of Alzheimer's disease and related disorders. Alzheimer's disease is clinically complex, being difficult to diagnose and of unknown aetiology. Although the authors attempted to compensate for confounders and bias, uncertainty regarding diagnosis of Alzheimer's disease and differing results in the effects of IVIg between age groups raise additional questions about the true protective effects of IVIg in usual care, which we think could have been explored further in this analysis.

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Table 1: Incidence of Alzheimer's disease or related disorder at end of observation period					
Age range (years)	Proportion of population in age range analysed (%)		Proportion diagnosed in IVIg-treated group	Proportion diagnosed in control group	P value
	IVIg-treated group (n = 847)	Control group (n = 84,700)			
≥65 (all ages included)	–	–	2.0%	4.1%	P = 0.002
Sensitivity analysis of ≥65 (all ages included)	–	–	2.0%	3.6%	P = 0.013
65–74	57	57	0.6%	2.2%	P = 0.021
75–84	39	39	3.7%	6.2%	P = 0.062
>84	5	5	5.0%	12.0%	P = 0.177

Cox proportional hazard ratio for diagnosis of ADRD: 0.577, 95% CI 0.359 to 0.930, P = 0.024
 Absolute numbers of proportion of people with outcome not reported.
 Mean age of groups: 73.8 years in IVIg-treated group compared with 73.9 years in control group.

Table 2: Projected incidence of Alzheimer's disease or related disorder at 60 months	
Outcome	Proportion with outcome
Diagnosis of ADRD (Kaplan–Meier analysis)	2.6% with IVIg v 4.6% with no IVIg
Diagnosis of ADRD (Cox proportional hazard analysis)	2.8% with IVIg v 4.8% with no IVIg

ADRD, Alzheimer's disease or related disorder.

References

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