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Intravenous immunoglobulin for Alzheimer's disease

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The foundation for using intravenous immunoglobulin (IVIg) to treat Alzheimer's disease (AD) can be traced back to the discovery, in the early 1990s, of naturally occurring anti-amyloid antibodies in human blood. A decade later, a number of independent investigators reported reduced levels of naturally occurring anti-amyloid antibodies in the spinal fluid and blood of AD patients relative to age-matched controls [1–3]. Dodel subsequently reported that IVIg contained elevated levels of antibodies against amyloid-β (Aβ) monomers and proposed its use as a potential treatment for AD [4].

Initial studies suggested that IVIg contained antibodies against monomeric forms of Aβ [5]. However, several subsequent studies found that normal human plasma and IVIg contain predominantly conformation-selective antibodies against neurotoxic oligomeric and fibrillar Aβ aggregates [6,7]. The conformational specificity of anti-amyloid antibodies in IVIg provides a potential therapeutic advantage over antibodies targeting linear monomeric epitopes, because amyloid aggregates are neurotoxic assemblies whereas monomeric Aβ is produced physiologically.

The immune modulating effects of IVIg provide another important mechanism of action that may be relevant in the treatment of AD [8]. Chronic inflammatory changes in the brain are a well-established component of the pathology of AD. However, conventional anti-inflammatory medications have not been effective in treating AD [9]. Human antibodies in IVIg have been shown to alter the activation state of microglia [10]. Recent work has identified other intriguing effects of IVIg such as modulation of microglial activation states and enhancement of hippocampal neurogenesis [10].

IVIg's established safety record makes it an attractive alternative to other immune therapies such as humanized murine monoclonal antibodies. Amyloid-related imaging abnormalities (ARIA) such as micro-haemorrhage and vasogenic brain oedema, that have been seen in several patients treated with anti-amyloid monoclonal antibodies [11], have rarely been reported after IVIg treatment.

A major concern that emerged around the testing of IVIg for AD is the limited availability of this biological agent. Production of IVIg is limited, as it is derived from the blood plasma of healthy donors and there are currently no synthetic substitutes available. Consequently, available supplies are inadequate to treat a large population such as the AD patient population. However, testing of IVIg as a potential AD treatment is not the only possible benefit. The potential exists for identifying treatment-relevant antibodies and alternative mechanisms of action to enable treatment of AD in other ways.

Two Phase I trials of IVIg in mild- to moderate-stage AD were carried out in the early 2000s in Germany [5] and the United States [12]. These small, open-label studies provided some encouraging results, including improvements in cognitive test scores in addition to alterations in the levels of circulating Aβ indicating target engagement. In the US Phase I study, washout of IVIg during 3 months led to a return to the pretreatment baseline cognitive status, suggesting that IVIg treatment needed to be sustained to provide benefit. Subsequent resumption of treatment in an extension study resulted in a stabilization of cognition during the subsequent 9 months [13].

A subsequent epidemiological study examined the US health records of more than 700 patients receiving IVIg for various indications and compared them to more than 70 000 controls. Exposure to IVIg for 4 years or less was sufficient to reduce incidence of AD by as much as 42% [12]. This retrospective study used a case–control design. Reported incidence of AD among patients treated with IVIg has yet to be confirmed in a prospective clinical study.

Following Phase I trials, a Phase II double-blind, placebo-controlled futility study was carried out in the United States involving 24 patients with mild to moderate AD for 6 months, followed by a 12-month open-label extension phase [14]. This study aimed to evaluate whether further development of IVIg as a treatment for AD was warranted. After 6 months, IVIg-treated subjects ($n = 16$) had

statistically superior Clinical Global Impression of Change (CGIC) ratings and numerically superior outcomes on the Alzheimer's disease assessment scale – cognition (ADAS-Cog) compared to placebo-treated patients ($n = 8$). The best outcomes were obtained in subjects who received the 0·4 g/kg/2-week dose ($n = 4$) [14]. Positive imaging findings included improvements in cerebral metabolism on fludeoxyglucose positron emission tomography (FDG PET) and a reduction in the rate of ventricular enlargement on volumetric magnetic resonance imaging (MRI). As the dual primary outcomes (CGIC and ADAS-Cog) met predefined criteria for lack of futility, further development of IVIg for AD went forward.

A second double-blind placebo-controlled Phase II study, sponsored by Octapharma in Europe and the United States, enrolled approximately 58 patients with mild to moderate AD who were treated with IVIg for 6 months [15]. With the exception of favourable FDG PET outcomes in patients receiving low-dose IVIg, no positive clinical outcomes were observed in this trial. This trial had a high ratio of investigational sites ($n = 12$) to subjects ($n = 58$), as well as a large number of dosing arms, the design of which resulted in a large variance in the clinical outcomes and consequently did not establish or refute efficacy of IVIg in the doses tested. It is noteworthy, however, that no case of aseptic meningitis, meningo-encephalitis or amyloid-related imaging abnormalities were reported in this trial.

The primary outcomes of the North America Phase III pivotal study of IVIg for AD (also known as the Gammaglobulin Alzheimer Partnership or 'GAP' study) were reported to be negative in May 2013 [16]. This trial was appropriately powered to test the clinical efficacy and safety of IVIg for treating mild to moderate AD. The study enrolled 390 AD patients meeting National Institute of Neurological Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINDS–ADRDA) criteria for probable AD with baseline Mini-Mental State Examination (MMSE) scores of 16–26 inclusive. Participants received one of two doses of IVIg (400 or 200 mg/kg) every 2 weeks or a low-dose albumin placebo at the same frequency. Clinical assessments were performed every 3 months during a period of 18 months. Brain imaging with MRI and PET as well as multiple biomarker assessments were carried out. A subset of patients underwent lumbar punctures at baseline, 9 months and 18 months, FDG PET at baseline and 9 months and/or florbetapir ^{18}F amyloid PET imaging at baseline and 18 months.

The primary outcomes were change in score on the ADAS-Cog and Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) from baseline to 18 months. No significant difference was observed on either of these measures in the intent-to-treat analysis or protocol analyses. Similarly, the majority of secondary outcome measures were negative. However, positive cognitive signals were observed in preplanned subgroup analyses among APOE-e4 carriers and moderately impaired AD patients. Biomarker studies revealed dose-dependent increases in immunoglobulins in plasma and cerebrospinal fluid (CSF) and decreases in plasma beta amyloid-42 levels [16]. In addition, IVIg treatment was found to be generally safe and well tolerated, showing no increased propensity to promote amyloid-related imaging abnormalities.

Although the Phase III study did not provide evidence that IVIg was efficacious for treating symptomatic AD at the doses tested, it provided several findings that advance our understanding of AD and AD immunotherapy. IVIg treatment resulted in measurable alterations in plasma amyloid levels, suggesting that the naturally occurring anti-amyloid antibodies may play a role in clearing amyloid from the body. Evidence of CSF penetration of antibodies from IVIg established that peripherally administered human IgG can reach the brain and may, under some circumstances, accumulate in CSF. Finally, positive clinical signals were observed in subgroups of patients, particularly among APOE-e4 carriers. This raises the possibility that IVIg may be useful in treating some AD patients with specific genetic or other yet-to-be-identified biological markers.

The results of the IVIg studies to date must be considered in context. No anti-amyloid medication tested to date has had a major impact on the progression of AD symptoms, including the anti-amyloid monoclonal antibodies such as bapineuzumab (Bapi) and solanazumab (Sola). In Phase II, Bapi was reported to reduce brain fibrillar amyloid burden in AD patients on ^{11}C-PIB PET [17]. However, Bapi failed to meet primary outcomes in two large Phase III clinical trials [11]. Sola, which binds soluble forms of amyloid, also failed to meet its primary outcomes in two large Phase III trials [18]. However, in a preplanned subgroup analysis pooling results of two of the Sola Phase III trials, positive signals were obtained on cognitive measures in the mildly affected AD patients. Development of Sola is ongoing in a clinical trial in mild AD as well as a novel prevention trial being carried out in asymptomatic cerebral amyloid carriers.

In the case of AN-1792 and Bapi, evidence of significant plaque reduction was obtained either by postmortem studies and PET imaging, respectively. In neither case was this associated with significant clinical benefits. The failure of AN-1792 and Bapi to produce positive clinical outcomes despite reducing fibrillar brain amyloid suggests that plaque removal alone is inadequate to arrest the progression of symptomatic AD.

The original premise for testing IVIg as a treatment for AD related to promoting amyloid clearance; however, other mechanisms of action may be salient to AD treatment. The doses of IVIg tested in AD trials to date were in the range used for antibody repletion in immunodeficiency syndromes. Higher doses were not used because of concerns about supply and increased potential for adverse effects in

elderly AD patients. Given the positive safety outcomes in the GAP study, it may be worthwhile to study higher doses that can exert central anti-inflammatory and immune modulatory effects. Additional trials of IVIg are under way, including a clinical trial in patients with amnestic mild cognitive impairment (MCI) and another trial combining IVIg with plasmapheresis.

Recently, clinical studies are preferentially targeting very early stages of AD in the hope that these phases will prove more amenable to anti-amyloid treatments. Broader efforts are being made to develop treatments that address other aspects of AD pathology. In this context, IVIg is still a viable candidate, as well as a rich source of information about the relationship of the immune system to age-related neurodegenerative disorders.

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