

REVIEW

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Intravenous immunoglobulin and Alzheimer's disease: what now?

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Abstract

Intravenous immunoglobulin (IVIG) products are prepared from purified plasma immunoglobulins from large numbers of healthy donors. Pilot studies with the IVIG preparations Octagam and Gammagard in individuals with mild-to-moderate Alzheimer's disease (AD) suggested stabilization of cognitive functioning in these patients, and a phase II trial with Gammagard reported similar findings. However, subsequent reports from Octagam's phase II trial and Gammagard's phase III trial found no evidence for slowing of AD progression. Although these recent disappointing results have reduced enthusiasm for IVIG as a possible treatment for AD, it is premature to draw final conclusions; a phase III AD trial with the IVIG product Flebogamma is still in progress. IVIG was the first attempt to use multiple antibodies to treat AD. This approach should be preferable to administration of single monoclonal antibodies in view of the multiple processes that are thought to contribute to AD neuropathology. Development of "AD-specific" preparations with higher concentrations of selected human antibodies and perhaps modified in other ways (such as increasing their anti-inflammatory effects and/or ability to cross the blood-brain barrier) should be considered. Such preparations, if generated with recombinant technology, could overcome the problems of high cost and limited supplies, which have been major concerns relating to the possible widespread use of IVIG in AD patients. This review summarizes the recent AD IVIG trials and discusses the major issues relating to possible use of IVIG for treating AD, as well as the critical questions which remain.

Keywords: A β , Alzheimer's disease, Antibodies, Immunotherapy, Inflammation, Intravenous immunoglobulin, Mild cognitive impairment, RAGE, Tau

Introduction

The severity of the Alzheimer's disease (AD) problem in the US is indicated by recent statistics from the Alzheimer's Association [1]. Approximately 5.4 million Americans are currently diagnosed with AD, including one in eight individuals aged 65 and older. By 2025 the number of Americans aged 65 and older with AD is expected to reach 6.7 million. Payments for health care, long-term care, and hospice for AD patients, which are currently estimated at \$200 billion, are expected to be \$1.1 trillion (in 2012 dollars) by 2050.

Intravenous immunoglobulin (IVIG) products are being investigated as potential agents for treatment or prevention of AD. IVIG is prepared from plasma immunoglobulins from large numbers (>10,000) of healthy donors. It is

used to treat a range of autoimmune, infectious, and idiopathic disorders [2]. The IVIG product Octagam (Octapharma) was shown by Dodel et al. in 2002 to contain antibodies to A β , suggesting that IVIG might be useful for treatment of AD [3]. This provided the rationale for IVIG pilot studies in AD patients. The results of these studies were encouraging [4,5], leading to phase II AD trials with these products. Positive results were reported for one of the two IVIG products [6,7] but not the other one [8]. More recently, negative results were reported in a phase III IVIG study [9]. An additional phase III AD trial with another IVIG product is in progress.

As of this writing (May 2013) it is unclear whether any IVIG products will offer a breakthrough for treatment of AD. Because these preparations differ in their concentrations of antibodies to A β [10-12] and tau protein [13], there may be differences between them with regard to their efficacies in AD. This purpose of this review is to summarize the IVIG AD trials conducted to date, the

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issues raised by the potential use of IVIG for treatment of AD, and critical questions which remain.

Clinical trials with IVIG in AD patients

IVIG treatment of AD patients was first reported in a pilot study in 2004 [4]. Five patients with mild to moderate AD [Mini Mental State Examination (MMSE) mean score 19.4] received Octagam (Octapharma; dose = 0.4 g/kg) on 3 successive days, every 4 weeks for 6 months. MMSE scores improved slightly in four of the AD patients and were unchanged in the fifth one, while their Alzheimer's Disease Assessment Scale-Cognitive sub-scale (ADAS-cog) scores decreased, suggesting increased cognitive functioning, in four patients and did not change in the fifth one. In 2009 results were published [5] from a pilot study in which eight AD patients (mean MMSE score 23.5) were administered Gammagard S/D (Baxter Healthcare). After 6 months of treatment the mean MMSE score increased to 26.0, reflecting increased scores for six patients and no change in scores for two patients. After a 3-month washout period, the mean MMSE score returned to baseline (23.9). Following an additional 9 months of treatment, MMSE scores were essentially unchanged (mean 24.0).

Before publishing these results, in 2006 Baxter began a double-blind Phase II AD trial with Gammagard. Improved outcomes were noted in the Gammagard-treated subjects compared to those initially treated with placebo at 3, 6, and 9 months [6]. The four patients who received Gammagard at 0.4 g/kg every 2 weeks for 36 months showed no evidence of further cognitive or memory decline [7].

The results of a double-blind, placebo-controlled, 24-week phase II AD trial with Octagam were published in January 2013 [8]. Octagam had no apparent effects on cognitive or functional scores in the AD patients. No increase was found for plasma A β 1-40; this had been reported in the pilot studies and suggested that IVIG products might increase efflux of A β from the brain. The only positive finding reported in this study, less reduction in glucose metabolism in some brain regions in the Octagam-treated individuals, was of uncertain significance.

In May 2013, the results of a placebo-controlled phase III AD trial with Gammagard were announced [9]. Three hundred ninety patients had been treated every 2 weeks for 18 months with 200 mg/kg Gammagard, 400 mg/kg Gammagard, or placebo. No significant differences were found for the rate of cognitive decline between the Gammagard-treated group and placebo group.

Two AD-related IVIG trials are still in progress. Flebogamma (Grifols Biologicals) is being evaluated, together with albumin, in an AD phase III trial, and NewGam (Octapharma) is being investigated by Sutter Health in a phase II trial to determine its effects in patients with amnesic mild cognitive impairment (MCI)

and its influence on the risk for these patients to develop AD. A possible reason for the failures in the most recent IVIG trials is that by the time AD's clinical features become evident, its pathology, including extensive neuronal loss, is already well-established. The trial with MCI patients should provide an indication of whether earlier IVIG treatment may be beneficial. The findings of a retrospective study [14], that individuals 65 years of age and older who had received IVIG had a significantly reduced risk for developing AD and related disorders compared to subjects not receiving IVIG support this possibility.

Considerations relating to treatment of AD with IVIG products

Economic considerations

Approximately 22 million plasma donations were collected in the US in 2009. Processing of a plasma sample into IVIG requires about 9 months. The use of IVIG for treatment of AD could pose a threat to its supplies. Solutions that have been suggested to this problem include new manufacturing processes, use of recombinant technology to produce IVIG, or administration of specific antibodies in place of IVIG [15]. Because of problems with obtaining adequate amounts of IVIG, some hospitals require consideration of alternatives to IVIG for treatment of patients with neurological disorders [16].

IVIG treatment is expensive, although its actual cost varies with the dose, frequency of administration, and home vs. hospital infusion. The Medicare Modernization Act of 2003 fixed Medicare's IVIG reimbursement rate to doctors and hospitals at the average sale price for IVIG plus 6%. Although the federal "340B drug discount" program mandates discounted IVIG prices for hospitals that provide high volumes of care to low-income patients [17], some hospitals have been unable to buy IVIG at these prices [18].

Potential side effects of IVIG

Thromboembolic events

IVIG can lead to thromboemboli because it increases serum viscosity, resulting in reduced blood flow [19]. Pre-existing vascular disease and immobility, additional factors that increase the risk for thromboembolic events [20], are often present in elderly individuals, including those with AD [21,22]. In patients with neuropathies that received IVIG, immobility was found to be an independent predictor for the development of thromboemboli [23]. Vascular disease and immobility in AD patients could therefore increase the risk of these individuals for IVIG-induced thromboembolic events.

Renal problems

Renal dysfunction, acute renal failure, and osmotic nephrosis can result from IVIG treatment in patients with

predisposing conditions such as renal insufficiency, diabetes mellitus, age > 65, volume depletion, sepsis, or receiving nephrotoxic drugs [24,25]. This is particularly true for IVIG products that use sucrose as a stabilizing agent. The prevalence of chronic renal disease increases with age, peaking at nearly 24% at ages 70–74 [26], so elderly individuals are likely to have an increased risk for IVIG-induced kidney problems because of pre-existing renal disease. AD patients with impaired kidney function may therefore not be candidates for IVIG treatment.

Hematological deficits

Decreases in WBCs, RBCs, and platelets have been reported after IVIG treatment [27-30]. The mechanisms responsible for these alterations are unclear. IVIG can stimulate platelet aggregation [31], which could reduce platelet counts. Binding of high-molecular-weight IgG complexes in IVIG to RBCs could decrease hematocrit levels in IVIG-treated patients by increasing RBC sequestration [32]. Binding of neutrophils to the vascular wall and migration of these cells into a storage pool has been suggested as a mechanism for IVIG-induced neutropenia [33]. Similar to the situation with regard to renal problems, individuals with AD who have hematological abnormalities may not be able to receive IVIG.

Potential mechanisms of action of IVIG in AD

IVIG products are thought to contain the full range of antibodies present in the human repertoire, estimated at 10^9 [15]. IVIG's mechanisms of action in different disorders are generally poorly understood. It contains several antibodies that have the potential to reduce AD-type pathology, but whether these antibodies can actually do so is unclear.

Anti-A β effects

IVIG products contain antibodies to A β oligomers and fibrils [34] and perhaps also to monomeric A β [11,35]. These drugs differ in their levels of anti-A β antibodies [10-12]. IVIG has been shown *in vitro* to disaggregate preformed A β fibrils, promote A β phagocytic removal [36], protect against A β neurotoxicity [35,37], and prevent formation of A β soluble oligomers [11]. But studies in mouse models of AD have produced conflicting results as to whether IVIG products can reduce brain A β . Magga et al. [38] found that Gammagard promoted microglial-mediated clearance of A β in experiments with brain sections from APP/PS1 mice and reduced *in vitro* A β fibril formation, but the latter effect was not specific for its anti-A β antibodies. Dodel et al. [37] treated APP695 double mutant mice with purified anti-A β antibodies from Octagam for 4 weeks beginning at 3 or 12 months of age. Reduced plaque counts were found in the younger mice but not in the older mice. Puli et al. [39] treated TgApdE9

mice with Gammagard beginning at 4 months of age, for 3 or 8 months. In the 3-month-treated group, there were no effects on hippocampal plaque counts or brain A β . After 8 months, there were still no differences in plaque counts between treatment and control groups. Surprisingly, soluble A β levels in hippocampus were increased in treated mice.

IVIG's antibodies recognize multiple sites on conformational A β epitopes, and its main binding to A β is reportedly to A β 25-40 [12,37]. This differs from the monoclonal anti-A β antibodies that have been used in clinical trials, Bapineuzumab and Solanezumab, which recognize only one epitope in linear A β and bind to A β 1-5 and A β 13-28, respectively [40]. A recent review [41] suggested that using the IVIG polyclonal antibody approach in an effort to deplete the spectrum of aggregated A β species might be more promising than using monoclonal antibodies targeting a single A β species.

Anti-inflammatory effects

IVIG can inhibit complement activation [42], neutralize inflammatory cytokines [43], and modulate chemokine expression [44] and regulatory T cell subsets [45]. However, its main anti-inflammatory effects are thought to be due to its IgG Fc fragments [46,47]. IVIG may not have reduced brain inflammation in the AD clinical trials because high doses (1–2 g/kg) are required for it to exert these effects [48]. Ravetch and colleagues investigated the mechanism by which IVIG's Fc fragment produces anti-inflammatory effects. The constant domain of IgG's Fc contains a glycan (a core heptapolsaccharide containing N-acetylglucosamine and mannose at Asn²⁹⁷) [49]. In serum antibodies, this includes a terminal sialic acid, which is responsible for Fc's anti-inflammatory effects [50]. This form of the carbohydrate is present in only 1-3% of IVIG's IgG molecules, which may explain why high-dose IVIG is required to produce anti-inflammatory effects [51].

Possible anti-tau effects

Cognitive deficits in AD strongly correlate with neurofibrillary tangle (NFT) density and distribution [52,53]. Aggregation and hyperphosphorylation of tau are required to produce NFTs. Studies in transgenic mouse models of tauopathy found that administration of antibodies to phosphorylated tau reduced tau pathology [54,55], so if IVIG contains such antibodies, they might be beneficial for treatment of AD. We recently reported the presence of antibodies to recombinant human tau, which is unphosphorylated, in IVIG products [13]. The significance of these antibodies to "normal" tau (i.e., whether these antibodies can reduce tau oligomer formation or inhibit its neurotoxicity) and whether IVIG also contains antibodies to aggregated and hyperphosphorylated tau are unknown.

Alteration of A β passage in and out of the brain

Advanced glycation endproducts (AGEs) form when reducing sugars react with amino groups in proteins, lipids, and nucleic acids [56]. The receptor for AGEs (RAGE) is present on the blood–brain barrier (BBB) [57], where it transports A β into the brain [58]. Anti-RAGE antibodies have been reported in IVIG [59]. These antibodies could reduce A β influx into the brain.

Low-density lipoprotein receptor-related protein-1 (LRP1) is the main receptor for transporting A β out of the brain [60]. LRP-1 expression on the BBB is reduced in AD [61]. Soluble LRP (sLRP) has also been reported in IVIG [59]. sLRP binds 70–90% of plasma A β , preventing it from entering the brain [62], so increasing peripheral blood sLRP levels through IVIG treatment might help to lower brain A β levels.

Non-antibody-mediated effects

IVIG contains other non-antibody proteins in addition to sLRP, which could influence its actions in AD in ways that are not clear. Interferon- γ , an inflammatory cytokine that also has some anti-inflammatory actions [63], is present in IVIG [64]. Soluble human leukocyte antigen (HLA) class I and II molecules are present in some IVIG products, as are their “physiological ligands,” CD4 and CD8 [65,66]. Soluble CD4 in IVIG might interfere with HLA class II molecules on antigen-presenting cells, competing with HLA-class II-restricted T cells and possibly causing immunosuppression [66,67]. Transforming growth factor (TGF)- β 1 and TGF- β 2 are also present in IVIG [68].

TGF- β 1 is increased in AD brain, where it is associated with plaques [69], but it also may promote A β clearance [70], so its significance in AD is unclear.

Might IVIG products differ with respect to their effects in AD?

Differences have been reported between IVIG products for the concentrations of some of their antibodies and their biological activities [71-75]. These may be due to differences in manufacturing practices and/or the antigenic exposure of the plasma donors. With regard to AD, differences between IVIG preparations have been found for anti-A β [10-12] and anti-tau antibodies [13], as mentioned earlier. Determination of whether IVIG products differ in their ability to slow AD's progression will require comparative studies, as have been done for Kawasaki disease [76] and primary immune deficiency [77].

How might the IVIG approach to AD treatment be improved?

Production of an “AD-specific” human immunoglobulin preparation would allow selected antibodies to be administered in higher concentrations than is possible with

unfractionated IVIG. There are precedents for this. Polyclonal anti-D, a type of IVIG consisting of plasma from RhD-negative donors immunized to the D antigen [78], has been used to treat idiopathic thrombocytopenic purpura [79,80], and Shoenfeld and colleagues [81] have generated specific IVIG (sIVIG) preparations for a number of immune-mediated conditions including lupus and anti-phospholipid syndrome. These antibodies could be produced with recombinant technology to avoid potential supply difficulties. A second possibility could be to administer multiple “humanized” mouse monoclonal antibodies with antigenic specificities similar to those of the antibodies in the AD-specific human IgG preparations. Single chain antibody fragments, which have been suggested as alternatives to monoclonal antibodies for AD treatment [82], should have better BBB penetration than intact IgG molecules. Still another alternative could be administration of recombinant sialylated Fc fragments, as suggested by Bayry et al. [15] for autoimmune diseases; as discussed above, this modification increases Fc's anti-inflammatory properties [49,50]. Sialic acid-enriched immunoglobulins have been obtained from IVIG by lectin fractionation [49,83].

Critical questions remaining

The most important question relating to AD treatment with IVIG is clearly whether any IVIG products will consistently slow clinical progression of this disorder. Questions that, if addressed, could lead to improved efficacy for IVIG in the treatment of AD include the following:

1. Regarding the antibodies in IVIG that have been identified against AD pathological proteins: what are their effects in mouse transgenic models of AD that develop both plaques and NFTs? (Although the complement membrane attack complex, C5b-9, is present on plaques and neurofibrillary tangles in the AD brain [84,85], the currently available mouse transgenic models of AD do not demonstrate this late-stage complement activation [86], so the effects of IVIG's anti-complement antibodies on this process cannot presently be studied in animal models of AD.)
2. What other AD-related antibodies are present in IVIG? (Does IVIG have antibodies against aggregated or hyperphosphorylated tau or antibodies that have antioxidant effects? Do its anti-Fas antibodies [72] have any relevance for AD treatment?)
3. Do IVIG's anti-idiotypic antibodies influence its effects in AD? These antibodies are thought to be responsible for IVIG's benefits in autoimmune disorders [87], but their effects in AD are unknown.
4. Are IVIG's effects in AD similar between apoE4 carriers and non-carriers? (In the phase III

Gammagard trial [9], it was suggested that the 400 mg/kg dose may have been of some benefit to apoE4⁺ AD patients).

5. Does IVIG treatment of AD patients increase their risk for microhemorrhage? (In the phase II Octagam study, 14% of the Octagam-treated patients had microhemorrhages vs. none in the placebo group [8]).

Conclusions

The IVIG trials reported to date in AD patients have produced conflicting findings. Because the most recent trials produced negative results, enthusiasm for IVIG as a treatment for AD has been reduced, although hope remains that the phase III trial with Flebogamma will produce positive results. Multiple antibody therapy for AD, as typified by IVIG, should have advantages over administration of individual monoclonal antibodies. To identify which antibodies should be included in an AD-specific IVIG preparation, more must be known about the range of anti-AD antibodies in IVIG and their effects on AD pathology in animal models. Such an AD-specific IVIG preparation, modified to increase the concentration, anti-inflammatory activity, and perhaps the brain penetration of its antibodies, might be more beneficial to AD patients than treatment with unfractionated IVIG.

Competing interests

The author declares that he has no competing interests.

Authors' contributions

DAL wrote the manuscript.

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