

REVIEW

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Should development of Alzheimer's disease-specific intravenous immunoglobulin be considered?

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Abstract

Recent phase II and III studies with intravenous immunoglobulin (IVIG) in patients with Alzheimer's disease (AD) did not find evidence for the slowing of AD progression compared to placebo-treated patients, in contrast to encouraging results in pilot studies. An additional phase III trial is ongoing. If negative results are found, then further AD studies with IVIG are unlikely unless a manufacturer opts for a trial with high-dose IVIG, which would increase its anti-inflammatory effects but also the risk for adverse events. An alternative approach could be an AD-specific IVIG, supplementing IVIG with higher concentrations of selected antibodies purified from it or produced via recombinant polyclonal antibody technology. These antibodies could include those to amyloid-beta ($A\beta$), tau protein, inflammatory cytokines, complement activation proteins, and the receptor for advanced glycation end products. IgG fragment crystallizable (Fc) fragments containing terminal sialic acid could be added to increase anti-inflammatory effects. While this product might be more effective in slowing AD clinical progression than current IVIG, there are difficulties with this approach. Preclinical studies would be required to determine which of the antibodies of interest for supplementing current IVIG (for example, antibodies to phosphorylated or oligomeric tau) are actually present (and, therefore, available for purification) in IVIG, and the effects of the product in mouse models of AD. An Investigational New Drug application for an AD-specific IVIG would require United States Food and Drug Administration approval. If the drug would be found to benefit AD patients, meeting the increased demand for IVIG would be challenging.

Keywords: $A\beta$, Alzheimer's disease, Antibodies, Complement activation, Cytokines, Immunotherapy, Intravenous immunoglobulin

Review

Introduction

Approximately 5.2 million Americans are currently diagnosed with Alzheimer's disease (AD). The prevalence of this disorder in the United States is 4% for individuals under 65 years of age, 15% for those between 65 and 74 years of age, 44% for those between 75 and 84 years of age, and 38% for individuals 85 years of age and older [1]. Estimates of individuals with AD or other dementias worldwide range from 36 to nearly 44 million people [2,3].

The five drugs approved by the United States Food and Drug Administration for treating AD provide short-term symptomatic benefits to approximately half of the patients

who receive them, but are not believed to influence neuro-pathological progression of the disease. Since the amyloid cascade hypothesis was published in 1991 [4], AD therapy has focused primarily on amyloid-beta ($A\beta$), but $A\beta$ vaccination [5], monoclonal anti- $A\beta$ antibodies [6-8], β -secretase inhibitors [9], and γ -secretase modulators [10] and inhibitors [11] have not succeeded in slowing the progressive loss of cognitive functioning that occurs in AD. Interest has increased in the targeting of tau pathology (neurofibrillary tangles (NFTs), dystrophic neurites, and neuropil threads) which correlates more strongly than plaque counts with AD's cognitive deficits [12-14].

Intravenous immunoglobulin (IVIG) is another approach that has been examined for the treatment of AD. IVIG products contain purified plasma immunoglobulins (primarily IgG) from large numbers of healthy donors. These drugs are used to treat many autoimmune,

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immunodeficiency, and inflammatory disorders. The full range of antibodies in the human immune repertoire, estimated at 10^9 [15], is thought to be present in IVIG. Among the antibodies in IVIG are naturally occurring auto-antibodies, which are produced against both self and altered self antigens in the absence of external antigen exposure (reviewed by Lutz *et al.* [16] and Schwartz-Albiez *et al.* [17]). Natural antibodies, which comprise approximately two-thirds of the human immune repertoire [18,19], are generated against intracellular constituents, plasma proteins, cell-surface antigens, and neoantigens [16]. Some of these antibodies, referred to as anti-idiotypic antibodies, can bind to variable regions of other antibodies, potentially interfering with the biological activities of these antibodies; with relevance to AD, IVIG was recently shown to contain A β anti-idiotypic antibodies (antibodies to its anti-A β antibodies [20]). IVIG's anti-idiotypic antibodies have been suggested to be responsible for its beneficial effects in some autoimmune disorders [21,22].

Many natural antibodies are polyreactive, meaning they can bind to more than one antigen [23]. Octapharma's IVIG Octagam™ was shown by Dodel *et al.* in 2002 to contain anti-A β antibodies [24], and these findings were subsequently replicated by others [25,26]. On this basis its effects, and then those of Baxter Healthcare's Gammagard™, were examined in AD pilot studies [27,28] which found that IVIG could decrease cerebrospinal fluid A β and increase plasma A β , suggesting increased removal of A β from the brain. This was followed by a phase II study with Gammagard [29] which indicated that IVIG might stabilize or improve cognitive functioning in AD patients. Subsequent phase II and III trials with Octagam and Gammagard, respectively, gave disappointing results. In the Octagam study [30], there were no significant differences in cognitive and functional scores between any of the treatment groups and the placebo group. No significant differences were found between five of the six IVIG dose (treatment) groups and the placebo group for plasma A β 1-40, and in the sixth treatment group, plasma A β 1-40 decreased versus placebo. Cerebrospinal fluid (CSF) A β 1-40 and A β 1-42, and hippocampal and total brain volume were not influenced by IVIG treatment. In the Gammagard trial [31], no significant differences were detected between the IVIG and placebo groups for measures of cognitive functioning or activities of daily living, despite the lowering of brain levels of fibrillar A β 1-42. Some benefits versus the placebo group with regard to cognitive scores were detected in Apolipoprotein E4⁺ AD patients and in patients with mild AD, but the trial was not powered to detect differences between subgroups. A phase III trial with Grifols' IVIG Flebogamma™ is underway in which AD patients will undergo plasmapheresis and be treated with albumin and Flebogamma [32]. The effects of Sutter Health's IVIG NewGam™ are

also being examined in individuals with mild cognitive impairment (MCI) [33], thought to be the transitional state between the cognitive changes of normal aging and very early dementia [34].

Svetlicky *et al.* [35] reviewed the beneficial results that have been obtained when 'target-specific' IVIG (which they referred to as 'sIVIG') preparations have been used to treat experimental animal models of autoimmune diseases. These disorders include systemic lupus erythematosus [36], anti-phospholipid syndrome [37], myasthenia gravis [38], pemphigus vulgaris [39], and small-vessel vasculitis [35]. In each case, the specific IVIG preparation consisted of anti-idiotypic antibodies purified from IVIG, which targeted the antibody responsible for the autoimmune disorder in the animal model. A study was cited in which IVIG prepared from donors with high levels of antibodies to West Nile virus was used to successfully treat patients with West Nile virus encephalitis [40]. Another disease-specific IVIG is polyclonal anti-D, which is prepared from plasma from rhesus D (RhD)-negative donors immunized to the D antigen and used to treat patients with idiopathic thrombocytopenic purpura [41]. It was recently suggested that an AD-specific IVIG preparation could be more effective than current IVIG products for the treatment of AD [42].

What options remain for intravenous immunoglobulin treatment of Alzheimer's disease?

The doses of IVIG employed in the AD trials were those used for antibody replacement in immunodeficiency syndromes, so whether the higher doses which are required for IVIG's anti-inflammatory effects (1 g/kg [43]) might be beneficial in AD is unknown [44]; an even higher dose, 2/g/kg, is required for efficient inhibition of complement activation [45]. Administration of high-dose IVIG has been associated with increased risk for thromboembolic complications, intravascular hemolysis, acute renal failure, and aseptic meningitis [46-48]. The study by Katz *et al.* [47] concluded that these problems can often be avoided by using slow infusion rates, maintaining adequate hydration, and avoiding patients with known risk factors such as advanced age, previous thromboembolic events, immobilization, diabetes mellitus, hypertension, and dyslipidemia. Unfortunately, most AD patients have one or more of these risk factors.

A second option could be an AD-specific IVIG. The effects of this product could initially be compared to those of current IVIG products in a mouse model of AD which develops both plaques and NFTs, such as the 3xTg-AD mouse [49]. Most IVIG studies in AD mouse models have been performed in mice which develop only A β pathology. These studies have found conflicting results [50-53]. Dodel *et al.* [54], using anti-A β antibodies purified from IVIG, reported reduced plaque

counts in three-month-old, but not 12-month-old APP695 double-mutant mice. In 3xTg-AD mice IVIG treatment had no effect on plaque deposition or insoluble A β , although it decreased 56 kDa A β oligomers by 60%, and no influence on tau pathology [55]. A second IVIG study in this mouse model reported a 25 to 30% decrease in AT-180⁺ (hyperphosphorylated tau-containing) hippocampal CA1 neurons [56]. Evidence for increased neuroprotective or behavioral benefits of treatment with AD-specific IVIG, compared to standard IVIG, in 3xTg-AD mice would provide support for a pilot study to assess the safety of an AD-specific IVIG preparation in AD patients.

What antibodies could be included in Alzheimer's disease-specific intravenous immunoglobulin?

An AD-specific IVIG product could be generated by simply supplementing a current IVIG product with higher levels of its anti-A β antibodies, which have been shown to exert neuroprotective effects *in vitro* and in some mouse models of AD [50,54,57-59]. A second approach would be to combine other AD-relevant antibodies and terminally-sialylated fragment crystallizable (Fc) fragments, in addition to anti-A β antibodies, that would also be purified from IVIG. The extent to which the concentrations of each of these components should be increased, in comparison to their levels in current IVIG preparations, could be examined in mouse studies and perhaps later in an AD pilot study.

The few studies that have compared the levels of AD-related antibodies between IVIG products found differences between the products [25,26,60]. These differences are likely to be due to variations in production methods and/or plasma donor populations. There have been no studies comparing the effects of various IVIG products in AD patients, so whether one product would be preferable to another for the preparation of AD-specific IVIG is unknown.

A potential advantage of IVIG over monoclonal antibodies for AD therapy is that it contains antibodies against multiple proteins that are thought to contribute to AD's development and progression. However, IVIG's polyvalent antibodies have a range of antigen-binding affinities [61]. An AD-specific IVIG might be more effective if the antibodies to be added to current IVIG possess at least moderate antigen-binding affinity. In practice, this would require using only the affinity-purified antibodies from later elution fractions, rather than pooling all of the eluted antibody fractions. AD-specific IVIG could be produced by supplementing a current IVIG product with some, or all, of the following antibodies:

Anti-Amyloid-beta (A β) antibodies

Some studies have reported that IVIG's anti-A β antibodies are limited to those that are 'conformation-specific' (they

do not recognize linear A β) [62], while others suggest that they may bind to monomeric A β , as well as A β aggregates [26,54,58]. A β 25-40 is a major region for IVIG binding, while its binding to A β 's N-terminus is minimal [25]. Phase III trials with two monoclonal anti-A β antibodies, Bapineuzumab and Solanezumab, which were generated against linear N-terminal and central-domain A β epitopes respectively, failed to slow the decline of cognitive functioning in AD patients [6,7], although in the Solanezumab trial some benefits to patients with mild AD were detected. More recently a phase II trial with another anti-A β monoclonal, Crenezumab, also produced negative results, although benefits were again observed in the mild AD group [8]. Crenezumab was generated against A β 12-23 and bound to A β monomer, oligomers, and fibrils [63]. Because the degradation of fibrillar A β , including by anti-A β antibodies, might shift the distribution of A β aggregates from fibrils to more neurotoxic A β oligomers [64], optimally the purified anti-A β antibodies to be used for supplementing current IVIG products should be specific for A β soluble oligomers, although this may not be possible. Of relevance is a recent study [65] in which repeated administration of monoclonal sequence-independent anti-oligomer antibodies to 3xTg-AD mice resulted in improved cognitive performance, reduced hippocampal plaques and brain levels of soluble and insoluble A β 40 and A β 42, and reduced microglial activation. This treatment also reduced tau hyperphosphorylation in hippocampal CA1 neurons, providing additional evidence for a relationship between AD's A β and tau pathology [66-68]. A β oligomers have been suggested to induce activation of the enzyme glycogen synthase kinase-3 β (GSK-3 β), which is thought to contribute to tau's hyperphosphorylation in the AD brain [69].

Anti-tau antibodies

Tau is an intraneuronal protein located primarily in axons, where it plays an important role in microtubule formation and stabilization through its binding to tubulin [70]. The extent of its phosphorylation controls its microtubule binding. Phosphorylation of normal tau is limited to two or three of its 441 amino acids, but when its hyperphosphorylation (phosphorylation of more than 39 of tau's amino acids) occurs in AD [71] its binding to microtubules decreases, resulting in reduced axonal transport and subsequent neuronal injury. The significance of NFTs in AD is unresolved; although NFT counts and distribution in the brain are positively correlated with AD's cognitive deficits [12,13,72], NFT-bearing neurons can survive for decades [73] so NFTs are not acutely neurotoxic. Hyperphosphorylation of tau, together with its aggregation, leads to formation of the paired helical filaments (PHF) found in NFTs [74], so both processes are potential targets for AD therapy. Administration of antibodies specific for

phosphorylated tau epitopes reduced tau pathology in transgenic NFT-bearing mice [75-77], and a tau aggregation inhibitor slowed AD's progression in a phase II trial [78]. A phase I trial to examine the safety of a vaccine targeting misfolded tau protein in AD patients is in the recruiting phase [79].

IVIG products contain anti-tau antibodies [60], including some which bind specifically to its microtubule-binding domains (MBD) [80], which are thought to be required for tau's aggregation [81,82]. Antibodies to tau's MBD could be included in AD-specific IVIG, based on the finding that monoclonal antibodies against these regions have been shown to reduce tau's aggregation [83]. The neuroprotective effects of IVIG's anti-tau antibodies, and whether some of these antibodies are specific for pathogenic tau conformations (phosphorylated or aggregated tau), are unknown. A recent study by Counts *et al.* [56] showed that IVIG treatment of 3xTg-AD mice reduced hippocampal CA1 tau pathology; however, this result could have been due to IVIG's anti-tau antibodies and/or its anti-A β antibodies. Rosenmann *et al.* [84] reported the presence of serum antibodies in healthy aged controls and AD patients to a phosphorylated tau fragment (tau 195-213, phosphorylated at tau 202/205), suggesting that such antibodies may be present in IVIG (and therefore be available for purification, and subsequent supplementation of these antibodies, in AD-specific IVIG). However, in that study, binding of serum antibodies to non-phosphorylated tau 195-213 was apparently not examined, so the possibility that the serum immunoglobulin binding could have been to non-phosphorylated rather than phosphorylated tau cannot be ruled out.

Antibodies to inflammatory cytokines (or inclusion of terminally sialylated Fc fragments as an alternative)

There is an extensive literature about increased inflammatory processes in the AD brain (reviewed by Akiyama *et al.*, [85] and Mrak and Griffin [86]). Central nervous system (CNS) inflammation may be a prerequisite for developing AD [87]. Anti-cytokine antibodies reported in IVIG include those to interleukin-1 α (IL-1 α) and interleukin-6 (IL-6) [88], interferon- α (IFN- α) and interferon- β (IFN- β) [89], interferon- γ (IFN- γ) [90], granulocyte macrophage-colony stimulating factor (GM-CSF) [91], BAFF (B-cell Activating Factor of the tumor necrosis factor (TNF) Family), and APRIL (A Proliferation-Inducing Ligand) [92]. IL-1 α , IL-6, and GM-CSF are inflammatory cytokines [93-95], while IFN- α and IFN- γ have both pro- and anti-inflammatory actions [96,97] and IFN- β is anti-inflammatory [98]. Treatment of the Tg2576 AD mouse model with anti-GM-CSF antibody decreased microglial activation and brain A β deposition [99], but, paradoxically, administration of GM-CSF reversed cognitive impairment and amyloidosis in transgenic AD mice [100],

so whether AD-specific IVIG should be supplemented with IVIG's anti-GM-CSF antibodies is unclear. The safest approach might be to limit the anti-cytokine antibodies used to supplement IVIG in an AD-specific preparation to those targeting IL-1 α and IL-6. The necessity for including even these antibodies is debatable because the anti-inflammatory effects of IVIG have been reported to be fully accounted for by its IgG Fc fragments (specifically, terminal sialic acid residues on the Asn297-linked glycan of IVIG, which is present on just 1 to 2% of its IgG molecules [101,102]). On this basis, Nimmerjahn and Ravetch [101] proposed that a sialic acid-enriched IVIG product could be prepared which would confer greater anti-inflammatory activity at far lower IVIG doses than those currently required to generate this activity. Therefore AD-specific IVIG could be supplemented with sialylated Fc fragments obtained from IVIG. Of relevance is a study by Käsermann *et al.* [103], in which sialic acid-enriched IgG fractions were obtained from IVIG. Sialic acid residues were identified in both Fab and Fc fragments. Surprisingly, anti-inflammatory activity was associated only with sialylated Fab. IVIG may also reduce inflammation by inducing the release of interleukin-10 [104] and IL-1 receptor antagonist (IL-1ra) [105], both of which have anti-inflammatory actions [106].

Anti-complement antibodies

IVIG inhibits cell surface deposition of early complement activation fragments, the opsonins C4b and C3b [107]. It binds to the anaphylatoxins C3a and C5a to neutralize their pro-inflammatory effects [108], and reduces the concentration of C3b2-containing complexes [109], despite the fact that IVIG can moderately activate complement [110]. C3b2 complexes are composed of two C3b molecules linked to IgG or another plasma protein, and function as efficient C3 convertase precursors [109,111]. IVIG also prevents development and deposition of C5b-9, the membrane attack complex (MAC) [112], which is neurotoxic [113] and present on AD plaques and NFTs [114]. IVIG's ability to prevent complement-mediated neuronal cell death was demonstrated in a mouse stroke model [115]. The role of complement activation in AD is complex and its significance is unclear, so whether IVIG's neuroprotective effects in AD would be helped or harmed by increasing its anti-complement activities is uncertain. Deposition of C4b and C3b on pathogenic conformations of A β (neurotic plaques) or tau (extracellular ('tombstone') tangles) should increase their removal by activated microglia, so if IVIG inhibits deposition of these opsonins on A β or tau, it could impair the ability of the CNS immune response to remove them. However, reduction of MAC formation by IVIG should be beneficial. Conflicting results as to the relationship of complement activation to AD-type pathology have been obtained in studies with mouse

transgenic models of AD [116-120]. Interpretation of these studies is complicated by the fact that complement is not activated to the same extent in the mouse AD models as in AD [121,122]. IVIG administration was shown to protect against synaptic dysfunction in the Tg2576 mouse model of AD by increasing brain levels of C5a [123], but the factor in IVIG responsible for this activity was not identified. A better understanding of IVIG's antibodies to complement activation proteins, and the effects of these antibodies, is needed to determine which, if any, of these antibodies should be supplemented in AD-specific IVIG.

Anti-receptor for advanced glycation end products antibodies

Advanced glycation end products (AGE) form when reducing sugars react with amino groups in proteins, lipids, and amino acids [124]. The receptor for AGE (RAGE) is present on microglia, neurons, and the blood-brain barrier (BBB) [125], and RAGE gene expression is increased in AD hippocampal pyramidal cells, cortical neurons, and glia [126]. Activation of microglial RAGE causes release of free radicals and inflammatory cytokines [127], inducing cytotoxic effects, while RAGE's presence on the BBB allows it to transport A β from peripheral blood into the brain [128]. The interaction between RAGE and A β at the BBB can lead to oxidative stress, inflammatory responses, and reduced cerebral blood flow [129]. RAGE is a therapeutic target of interest in AD because its blockade reduces neuronal and synaptic injury [130]. The anti-RAGE antibodies reportedly present in IVIG [131] could block the receptor, reducing the influx of A β into the brain, and thereby lowering brain A β levels [19]. It would be appropriate to include these antibodies in AD-specific IVIG.

Other antibodies

IVIG has additional neuroprotective actions, including antioxidant [132] and anti-apoptotic [133] effects. The latter study found that IVIG treatment reduced A β -induced neuronal p38MAPK, a kinase involved in cell death mechanisms, including apoptosis and excitotoxicity, which can be activated by A β [134]. The antibodies in IVIG which were responsible for these effects are unknown. Apoptosis is reported to be increased in the AD brain [135,136], and Fas (CD95), a member of the TNF receptor superfamily, can initiate this process [137]. Its binding by the cell surface molecule Fas ligand (Fas-L) can induce apoptosis. Anti-Fas antibodies can act as Fas agonists to trigger apoptosis [138,139] or they can function as neutralizing antibodies to prevent cell death from occurring via the Fas-L pathway [140]. Both apoptotic [141] and anti-apoptotic [133,142] effects have been reported for IVIG, which contains anti-Fas antibodies [143]. Which of these

actions IVIG exerts may depend on the dose of IVIG [144]. Until more is known about the actions of IVIG's anti-Fas antibodies, they should not be included in AD-specific IVIG.

Potential difficulties with Alzheimer's disease-specific intravenous immunoglobulin

Treatment with IVIG can raise serum viscosity, increasing the risk for thromboembolic events [145]. However, given the large number of antibodies in IVIG, supplementing it with increased levels of a few selected antibodies and possibly also Fc fragments should not appreciably increase its osmolality. Because this would be a new drug, approval of an Investigative New Drug (IND) application by the United States Food and Drug Administration would be required.

Even if an AD-specific IVIG would be found to exert beneficial effects in AD patients, its relatively short duration of action would require continued treatment, which would consume a great deal of IVIG. The subjects in the IVIG AD trials received IVIG every two or four weeks [27,28,30] and a similar regimen would likely be required for AD-specific IVIG. Neuroprotective effects would not be expected to be maintained if administration of AD-specific IVIG would be discontinued; in the AD pilot study with Gammagard performed by Relkin *et al.* [28], mini-mental state scores in AD patients increased by an average of 2.5 points after six months of treatment, but returned to baseline after a three-month washout period (the half-life of IgG in IVIG was reported to be 25.8 days, similar to endogenous IgG [146]). Further, if AD-specific IVIG would benefit AD patients, these effects might be seen only in mild-to-moderate AD patients, but not in individuals in which the disease had progressed further. In the phase III AD trial with Gammagard, one of the two subgroups for which 'favorable cognitive changes' were reported was AD patients with moderate impairments [31].

With the exception of IVIG's anti-A β antibodies [54], the effects of its other antibodies discussed above have not been examined using purified antibodies in mouse models of AD. IVIG manufacturers will need to decide if the effects of each of these antibodies should be evaluated separately in a mouse model of AD before determining which of the antibodies to include in AD-specific IVIG.

The anti-tau antibodies which were reported in IVIG [60] bound to full-length recombinant human tau (tau 1-441). The possibility is not ruled out that if the levels of these antibodies are increased in AD-specific IVIG, the resulting preparation could induce an autoimmune response. Although such an outcome has not been reported following IVIG treatment, Rosenmann *et al.* [147] found that vaccination of C57BL/6 mice with full-length human tau induced anti-tau antibodies which were associated with development of tau pathology and encephalitogenicity

(manifested by neurologic deficits). Two injections consisting of tau emulsified in complete Freund's adjuvant (CFA) were given one week apart. Pertussis toxin, which can induce a transient increase in BBB permeability [148], was given the same day as the first injection and 48 hours later. The immunopotentiating effects of CFA, combined with BBB impairment due to pertussis toxin, may have contributed to the autoimmune neuropathy which developed in these animals. Rosenmann *et al.* subsequently reported the development of paralytic disease in wild-type mice and 'tauopathy' mice that were repeatedly immunized with a mixture of three phosphorylated tau fragments emulsified in CFA and pertussis toxin [149]. However, they found no evidence for encephalitogenicity when only one injection of the CFA and pertussis-emulsified phosphorylated tau was given, followed by the phosphorylated tau fragments alone one week later [150]. The rationale for emulsifying phosphorylated tau with CFA and pertussis toxin in these studies was that the pro-inflammatory environment induced by this protocol in the CNS might more closely model the situation in AD patients, perhaps allowing for a better assessment of the potential risks of immunizing AD patients with phosphorylated tau than could be obtained using less inflammation-promoting adjuvants. Studies in tauopathy mice in which anti-phospho-tau antibodies were administered [75-77] found no autoimmune problems.

Regulatory issues would be of concern with regard to United States Food and Drug Administration approval of an AD-specific IVIG. There is a precedent for United States Food and Drug Administration approval of a multi-component plasma product: Factor Eight Inhibitor Bypassing Activity (FEIBA, produced by Baxter Healthcare) is an activated prothrombin complex concentrate which, similar to IVIG, is produced from pooled human plasma. It contains four coagulation factors, namely factors II, VII, IX, and X [151,152]. FEIBA is used for the treatment of hemophilia patients with inhibitors (inhibitory antibodies produced secondary to treatment with clotting factors). It has been used therapeutically for more than 35 years (reviewed by Cromwell and Aledort [153]).

If studies in mouse AD models suggest increased benefits of AD-specific IVIG compared to standard IVIG, then consideration could be given to producing the antibodies required to supplement current IVIG through recombinant technology, rather than purifying them from IVIG. The technology is available for production of recombinant human polyclonal antibodies on an industrial scale [154,155]. This approach would assure lot-to-lot uniformity for each of the antibodies and would reduce the amount of IVIG required to produce AD-specific IVIG.

A final obstacle would be the economic one. The question of how adequate supplies of IVIG could be maintained if there is an increased demand for it in AD

patients was discussed previously [156] and will be briefly summarized here. Processing of a plasma sample into IVIG requires about nine months [157], so the supply of IVIG cannot be rapidly replenished in the event of a shortage of the product. Extensive use of AD-specific IVIG would reduce the IVIG available for individuals with severe primary immunodeficiencies, for whom IVIG is the standard of care [158]. Further, IVIG treatment is expensive, with costs for IVIG treatment of the 5.4 million Americans with AD estimated to be \$280 billion per year [159]. Based upon an IVIG price of \$75 per gram, the cost to administer 0.4 g/kg of IVIG (a dose used in AD trials) to an 80 kg individual every other week for a year would be \$62,400. This would be prohibitive for many AD patients.

Conclusions

Although the multiple antibodies in IVIG should give it an advantage over monoclonal antibody for treatment of AD, its encouraging results in pilot studies have not been replicated in larger trials. Administration of high-dose IVIG would increase its anti-inflammatory effects but would likely be associated with increased adverse events, and many AD patients have risk factors which could preclude their receiving high-dose IVIG. An alternative approach could be to develop an AD-specific IVIG. This would require additional time and expense, but it might be the last and best chance for IVIG treatment of AD to succeed.

Abbreviations

AD: Alzheimer's disease; AGE: Advanced glycation end products; APRIL: A proliferation-inducing ligand; BAFF: B-cell activating factor of the tumor necrosis factor family; BBB: Blood-brain barrier; CFA: Complete Freund's adjuvant; CNS: central nervous system; CSF: cerebrospinal fluid; Fas-L: Fas ligand; Fc: fragment crystallizable (fragment of IgG); FEIBA: Factor eight inhibitor bypassing activity; GM-CSF: Granulocyte macrophage-colony stimulating factor; GSK-3 β : Glycogen synthase kinase-3 β ; IL-1 α : Interleukin-1 α ; IL-1ra: IL-1 receptor antagonist; IL-6: Interleukin-6; IFN- α : Interferon- α ; IFN- β : Interferon- β ; IFN- γ : Interferon- γ ; IVIG: Intravenous immunoglobulin; MAC: Membrane attack complex; MBD: Microtubule binding domains; MCI: Mild cognitive impairment; NFTs: Neurofibrillary tangles; sIVIG: Target-specific IVIG; RAGE: Receptor for AGE; RhD: Rhesus D; TNF: Tumor necrosis factor.

Competing interests

The author declares that he has no competing interests.

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