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REVIEW

Alzheimers Disease: Review of Emerging Treatment Role for Intravenous Immunoglobulins

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Abstract: Alzheimer's disease (AD) is the most common neurodegenerative disorder. Currently available therapies are symptomatic but do not alter underlying disease progression. Immunotherapeutic approaches such as anti Aβ peptide active vaccination trials have had limited success to date. Intravenous immunoblobulin (IVIg) is widely used in immune-mediated neurological disorders such myasthenia gravis and Guillain-Barre syndrome. These preparations have been obtained from the pooled plasma of healthy human donors and contain natural anti-amyloid antibodies and are well tolerated. A small pilot study of passive immunotherapy using IVIg has suggested cognitive improvement. A multicenter phase III trial is ongoing and will determine whether or not this treatment can ameliorate cognitive deficits in mild-to-moderate AD. Here, we briefly review the pathogenic role of amyloid and tau in AD, as well as immunotherapeutic efforts to date. We also summarize what is known about naturally occurring anti-Aβ and tau antibodies in IVIg with a view toward explaining potential mechanisms underlying their therapeutic effects.

Keywords: Alzheimer`s, immunotherapy, conformation antibodies, tau oligomers, amyloid oligomers.

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Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder, with devastating personal and financial costs. In the absence of clear prevention strategies or disease modifying therapies, it is expected that the number of people affected by AD worldwide will exceed 100 million in 2050. With improved survival from acute diseases and the increasing lifespan of populations in developed and middle income countries, dramatic increases in the incidence of Alzheimer's disease (AD) are predicted, with dire consequences for the economic and social fabric of many nations.[1] Hence, development of effective disease-modifying therapies for AD is an urgent priority for research in both academia and pharmaceutical companies. AD is a complex disease with two principle hallmark events: 1) the misfolding, aggregation and brain deposition of amyloid-β (Aβ) peptide in amyloid plaques, and 2) the deposition of misfolded tau protein in neurofibrillary tangles (NFT).[2] The Aβ peptide is generated from the cleavage of amyloid precursor protein (APP) by β and γ secretases.[2] Given the preeminence of the amyloid hypothesis[3] in the AD field, extensive efforts have targeted various forms of Aβ aggregates for drug development; these include reduction and alteration of APP processing, prevention of Aβ misfolding and aggregation, minimization or elimination of its neurotoxicity, acceleration of its clearance and degradation,[4–9] as well as active (ie, stimulation of an immune response following administration of an immunogen), and passive (ie, provision of short term protection against infection or clinical condition by administration of antibodies) vaccination strategies to remove amyloid deposits.[10]

An ever-increasing body of evidence implicating tau in neurodegenerative diseases[11,12] supports tau as a potential target for the development of disease-modifying therapeutics.[13,14] Tau-based therapeutic approaches have historically lagged behind anti Aβ approaches. Recently, however, tau-based approaches have been the subject of renewed interest;[13] potential therapeutics may manipulate tau via inhibition of phosphorylation,[15,16] activation of proteolytic or proteasomal degradation pathways,[17,18] microtubule-binding drugs (eg, paclitaxel) for stabilization of microtubule networks,[19,20] inhibition of aggregation by small molecules,[21,22] or clearance by immunotherapy.[23–26]

Immunotherapy Against Aβ

Arguably the most exciting treatment approach for AD to have evolved recently is anti-Aβ immunotherapy using antibodies to Aβ administered on multiple occasions.[27] First introduced by Schenk and colleagues in 1999, promising results were described initially in animal models.[28] Ten years later, enthusiasm for anti Aβ immunotherapy has been largely replaced by frustration due to adverse effects including meningoencephalitis and leukoencephalopathy.[10,29–31] Results from the ongoing phase II trial of anti Aβ humanized monoclonal antibody (Bapineuzumab) have confirmed removal of amyloid plaques as detected by positron emission tomography (PET) scans using Pittsburgh compound B (^{11}C-PiB), but without concomitant cognition improvement.[32] In addition, despite evidence of amyloid plaque removal,[33] *post mortem* analysis of brains from those patients has failed to demonstrate changes in tau pathology, neuropil threads, synaptic dysfunction, or cerebral amyloid angiopathy.[29,34,35] Despite these disappointments, the research community has persevered with alternative regimens of administration in efforts to develop and optimize a more effective passive or active Aβ-based vaccine. These efforts have included the use of IVIg preparations that contain naturally occurring anti Aβ antibodies.[36–38] Recent literature reveals a shift in focus from cure toward understanding mechanisms associated with benefits in animal models and etiology of complications reported in both humans and animal models (reviewed in).[39–44]

Conformation-Specific Antibodies

Amyloid diseases, including many neurodegenerative disorders, are considered conformational diseases, since amyloid formation is triggered by conformational changes in a specific peptide or protein, resulting in its misfolding and deposition as amyloid.[45–47] Moreover, conformation-specific antibodies that recognize specific amyloid species, eg, fibrils or oligomers, from many types of amyloid proteins have been produced and characterized.[48–50] Conformation-specific antibodies were derived from observations reported more than thirty years ago[51,52] indicating that amyloid antibodies react with conformational epitopes and not with native protein structure, ie, suggesting that amyloid fibrils have a non-native structure.[51,52]

Numerous conformation-specific antibodies have been generated and characterized, including a few that are commercially available. Such antibodies have been used to characterize disease progression and to ameliorate amyloid toxicity (see review by Glabe).[50] Moreover, conformation-specific antibody domains and single chain fragment variable (scFv) constructs with similar specificity have been reported; of note, these can cross the blood-brain barrier more efficiently than antibodies and can be expressed intracellularly.[53–55]

The critical role of soluble amyloid oligomers in neurodegeneration has become more generally accepted for multiple neurodegenerative diseases, including AD.[56–60] Results obtained using oligomeric conformation-specific antibodies[49] indicate that oligomers (protofibrils) have a common, generic structure that is distinct from both fibrils and low molecular weight soluble monomer/dimers. Furthermore, such antibodies recognize soluble oligomers from a variety of different amyloids, including lysozyme, islet amyloid polypeptide (IAPP), synuclein, prion protein, polyglutamine, and insulin. The anti oligomer antibody (A11) that binds specifically to amyloid oligomers[49] has more robust effects as compared to other anti amyloid antibodies when injected intrathecally into the TgCRND8 AD mouse model.[61] Surprisingly, similar conformation-specific antibodies have been detected in humans using peptide microarrays. Britschgi et al demonstrated the presence of sequence-independent, oligomeric conformational antibodies in human plasma and CSF.[62] Although the diversity, abundance, and function of such endogenous conformational antibodies remain largely uncharacterized, these investigators have reported that these antibodies decline with age and advancing AD, suggesting that they may play a role in protection against toxic amyloid oligomers.[62]

Tau-Based Immunotherapy

Tau immunotherapy is a new concept.[23] To date, only three reports of tau immunotherapy in animal models have been published, all using active vaccination.[24,25,63] To date, no reports of passive vaccination have appeared. In the first report, the authors used a tau fragment (379–408) phosphorylated at Ser396 and Ser404 (phosphorylation sites commonly associated with NFT) to vaccinate the P301L mouse model.[64] Behavioral analysis showed improved performance after immunization as compared to controls. These data demonstrated that antibodies against this immunogen were able to cross the blood-brain barrier and bind to phosphorylated tau.[24] The Rosenmann group used phosphorylated tau with Freund's adjuvant and pertussis toxin adjuvants; these investigators reported a 40% reduction in NFTs and 20% increase in microglia.[25] In 2006, the Rosenmann group also reported that full-length tau was encephalitogenic, triggering a severe autoimmune response.[63] Mice vaccinated with soluble tau developed NFT-like structures, axonal damage, gliosis, mononuclear infiltrates, and motor phenotypes. These data demonstrate the potential dangers of using soluble tau as immunogen, or of antibodies recognizing epitopes of full-length tau for passive vaccination. Although the use of phosphorylated tau antigens seems promising for vaccination studies (ie, presenting specific phosphoepitopes to the immune system), such an approach has significant potential risks, as these phosphorylation sites are mainly associated with NFT.[65,66] An optimal vaccine should target pre-filament tau species (tau oligomers), which form at early stages of NFT development rather than mature, meta-stable NFT.[26] Pre-filament specific phosphorylation sites have yet to be conclusively identified due to the complexity of tau aggregation, the overlap between the three stages of NFTs development with regard to tau phosphorylation sites,[65] and the fact that tau phosphorylation is a physiological process that is essential for tau normal function and reversible.[67] *In vitro* assembled tau paired helical filaments (PHF) similar to those found in AD have β-structure similar to other amyloid fibrils.[68,69] Moreover, tau conformation-specific antibodies (eg, Alz50 and MC-1) recognize conformational tau epitopes associated with PHF.[70,71] Naturally occurring antibodies have been detected in the blood of normal and AD patients, including antibodies against both unphosphorylated and phosphorylated tau.[72] Both IgG and IgM anti-tau antibodies have been identified in serum collected from AD patients and controls; very few tau antibodies are found in CSF. Higher anti-phosphorylated-tau IgM antibodies have been found in AD patients relative to controls. In this work of Steinitz and coworkers, all subjects (both AD and controls) were greater than 70 years of age;[72] it is reasonable to assume that higher levels

of anti-phosphotau IgM would be present in healthy young controls, as reported for Aβ antibodies. If so, it seems likely that larger studies will confirm these findings and identify higher concentrations of neuroprotective tau antibodies in young healthy people.

IVIg Immunotherapy

Intravenous immunoglobulin (IVIg) is an antibody product obtained from human plasma from thousands of donors. For more than thirty years, IVIg has been used for the treatment of post-exposure to infectious diseases, immune disorders and the management of patients with neurological conditions.[73–76] IVIg treatment is used routinely for some immune-mediated neurological disorders such as Guillain-Barre syndrome, patients treated with IVIg have reduced risk of developing Alzheimer's disease and recently IVIg has been investigated for the treatment of neurodegenerative disorders.[77] Commercially available IVIg has been used in small pilot trial in AD.[36] In this open label study, 8 mildly affected patients received IVIg for a total of 15 months over two intervals (6 months, discontinued for 3 months, then followed by 9 months further treatment). Infusions were generally well-tolerated; of note, both anti-Aβ antibodies and Aβ levels in the serum increased after each infusion in proportion to IVIg dose, whereas Aβ levels in CSF decreased significantly at 6 months, returned to baseline after washout, and decreased again after IVIg was re-administered for the additional 9 months. Mini-mental state scores increased an average of 2.5 points after 6 months, returned to baseline during washout, and remained stable during subsequent 9 months treatment.[36] A smaller study previously had shown positive effects in five AD patients, each of whom received one dose of IVIg per month for 6 months.[38] Taken together, these findings justified a large-scale randomized phase III clinical trial that has enrolled more than 360 AD patients.[76,78]

Naturally occurring antibodies that can detect and block the toxicity of special conformations displayed by misfolded proteins, including amyloid-β, α-synuclein, and prion protein, are detectable in human serum and CSF. Although such antibodies are detectable in both healthy individuals and patients, it is clear that their levels are reduced in the latter.[62,78–82] However, an assay for precise quantification of endogenous human Aβ antibodies is not yet available. Efforts are underway to identify and overcome factors contributing to wide disparities among reported measurements.[83–85] Such efforts seem likely to improve the quality of IVIg preparations for AD treatment, and they may lead to the development of methods to isolate specific anti-amyloid antibody populations that can then be tested for their potential to treat AD and other neurodegenerative diseases by passive administration.[80,83–85] Humanized monoclonal antibodies have applications but they recognize only a single epitope whereas naturally occurring antibodies are polyclonal and will recognize multiple epitopes, and more likely to have stronger therapeutic effects.

Which Antibodies Should We be Looking for in IVIg Preparations?

In addition to the anti Aβ oligomer antibodies reported in IVIg,[82,83] these preparations may contain neuroprotective anti tau oligomer antibodies that may account, at least in part, for the positive results derived from IVIg treatment in AD. Recently, tau oligomers have emerged as a likely pathogenic entity in tauopathies. Although their formation and role in neurodegeneration has yet to be fully elucidated, an increasing literature argues that they play a crucial role in AD and other tauopathies. Stereological analysis of AD demonstrates that neuronal loss actually precedes NFT formation.[86,87] This observation, as well as data emerging from biochemical, cell-based and transgenic mouse studies, suggests that soluble tau aggregates may be the most toxic and pathologically significant tau species.[57,88–92] Studies using different animal models suggest that tau oligomers play a key role in impaired synaptic function, hippocampal synapse loss, and microgliosis leading to neurodegeneration and behavioral impairments. All of these phenomena are concurrent with accumulation of soluble aggregated tau species and dissociated from the accumulation of NFT.[57,93,94] Tau oligomers have been characterized biochemically in a conditional mouse model (rTg4510) expressing the P301L human tau mutant; surprisingly, the accumulation of oligomeric tau (but not NFT) correlated with neuronal loss and behavioral deficits in this model.[95,96] Tau oligomers have been characterized in human brain; a correlation between disease progression and the accumulation of granular tau oligomers in the brains of AD

patients has been reported.[97,98] Moreover, increased levels of tau oligomers are detected in the frontal cortex at very early stage of the disease (Braak stage I), before clinical manifestations of AD and NFT are believed to develop.[97,98] Given the heterogeneity of tau species, ranging from monomer to oligomer, to PHF/NFT, it seems prudent that future efforts should focus on complete characterization of all tau antibodies present in CSF, rather than on any particular species. Meticulous analysis of both anti tau and anti amyloid antibodies present in IVIg preparations is critical for a better understanding of mechanisms underlying potential benefits of such preparations in AD.

Conclusions

The results from the pilot clinical trial justify further investigation of IVIg for the treatment of AD. Further examination of endogenous neuroprotective antibodies should help us to better understand their mechanism of action. Given that anti-Aβ immunotherapy trials were disappointing, it seems unlikely that naturally occurring Aβ antibodies are likely to account for observed clinical benefits of IVIg; further, such IVIg preparations may be effective because they contain both anti-tau and anti-Aβ natural antibodies. Apart from the presence of these antibodies, IVIg may be useful for AD treatment due to anti-inflammatory effects at high doses mediated in part via Fc receptor uptake of IgG by inflammatory cells.[73,74] IVIg is a very expensive treatment, and despite its safety record in the treatment of multiple neurological disorders, potential complications include headache, dermatitis, infection, pulmonary edema, allergic/anaphylactic reactions, acute renal failure, venous thrombosis, and aseptic meningitis.[99,100] These side effects may hinder the use of IVIg in AD, which has a long asymptomatic phase and survival period once symptomatic. Therefore, critical analysis of IVIg preparations and further examination of endogenous neuroprotective antibodies are necessary to better understand their mechanism of action and optimize their role as a disease modifying therapeutic in AD and other neurodegenerative diseases. Finally, significant advances have been made in the use of humanized monoclonal antibodies for passive vaccination against infectious diseases that will do doubt have applications.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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