HHS Public Access

Author manuscript

Curr Alzheimer Res. Author manuscript; available in PMC 2018 March 27.

Published in final edited form as:

Curr Alzheimer Res. 2014 ; 11(7): 623–625.

Overview of Immunotherapy in Alzheimer's Disease (AD) and Mechanisms of IVIG Neuroprotection in Preclinical Models of AD

Scott E. Counts[1] and **Debomoy K. Lahiri**[2]

[1]Department of Translational Science and Molecular Medicine, Department of Family Medicine, Michigan State University, 333 Bostwick Ave NE, Grand Rapids, MI 49503, USA

[2]Department of Psychiatry, Department of Medical & Molecular Genetics, Indiana University School of Medicine, Institute of Psychiatric Research, Neuroscience Research Center, 320 West 15th Street, Indianapolis, IN 46202, USA

Epidemiologic studies suggest that we are on the precipice of a worldwide epidemic of Alzheimer's disease (AD), yet current treatment options are limited to short term symptomatic relief. Recent advances in our knowledge of the neurobiology of AD have resulted in the development of several potential disease-modifying approaches based on immunotherapy. The present special 'Hot Topic' (HT) issue of "Current Alzheimer Research" deals primarily with the mechanisms of passive vaccination with Intravenous Immunoglobulin (IVIG), particularly within the context of neuroprotection in preclinical models of AD. This HT issue is not meant to report exhaustively on the many other research efforts in the broader immunotherapy arena. Indeed, this journal has recently covered various other aspects of immunotherapy relevant to AD and related disorders. However, we will briefly overview current immunotherapeutic strategies for AD prior to discussing the main topic of IVIG neuroprotection.

One of the most significant approaches involves the removal of brain amyloid-β peptide (Aβ) using anti-Aβ antibodies. Aβ immunotherapy emerged as a promising treatment strategy based on human neuropathology and preclinical studies. The hallmark accumulation of parenchymal and vascular Aβ pathology observed in the brains of AD subjects suggested a logical target, and naturally occurring anti-Aβ antibodies were found to be reduced in the cerebrospinal fluid and blood of AD patients [1, 2]. In addition, both active and passive amyloid immunization of AD transgenic mouse models resulted in increased clearance of amyloid plaquelike deposits and improved cognitive performance [3, 4], whereas brain imaging and neuropathological studies suggested the ability of both active and passive anti-Aβ immunotherapies to clear Aβ deposits from the AD brain.

AN1792 was the first active immunotherapy strategy for AD using full length Aβ42 as the immunogen; however, a Phase II trial of this anti-amyloid vaccine was halted when meningo-encephalitis appeared in a small subset of patients [5]. Despite this setback, long-term follow-up of patients immunized with AN1792 showed reduced functional decline in antibody responders [6], supporting the hypothesis that Aβ immunotherapy may have long-term functional benefits. In this regard, novel Aβ immunogens with shorter peptide sequences are in development which may avoid the autoimmune responses to full length Aβ42 [7]. The first passive anti-Aβ immunotherapy for AD focused on bapineuzumab.

Bapineuzumab, which is composed of humanized anti-Aβ monoclonal antibodies, reduced Aβ burden in the brains of AD patients in two Phase II trials. However, bapineuzumab did not improve clinical outcomes in patients with AD, despite treatment differences in biomarkers observed in APOE ε4 carriers [8, 9]. Other recent approaches, such as systemic co-administration of clioquinol and Aβ42 vaccines, significantly reduce Aβ deposits in the brains of transgenic AD mice [10]. In non-rodent models, a rapid improvement of canine cognitive dysfunction with amyloid immunotherapy suggests the important use of the canine model in testing vaccines for AD [11]. So far, the limitations of Aβ-based immunotherapy include the development of encephalitis, the lack of clinical improvement, and the lack of effect on neurofibrillary tangles (NFTs), another major neuropathological feature of AD. Other critical points relate to the study design and several variables in imunotherapy trials, which are essential for optimizing trial designs and improving conditions for participants [12].

Due to the central role of NFTs in dementia, immunotherapy targeting these tau proteinous aggregates is an important area of research [13, 14]. Notably, an active immunotherapy targeting the tau pathological epitope phospho-Ser422 was found to be efficient, resulting in tau clearance and improved cognitive deficits promoted by tau pathology in a well-defined tau transgenic model [15]. Like Aβ oligomers, the putative role of tau oligomers in AD pathophysiology has prompted an investigation into tau oligomers as potential immunotherapeutic targets for AD and tauopathies [16].

Taken together, these results suggest that immunotherapies targeting Aβ alone may be insufficient for disease modification. To this end, researchers also began testing whether IVIG might serve as an alternative immunotherapeutic strategy. IVIG is a mixture of naturally occurring human IgG antibodies derived from the plasma of healthy young volunteers. Notably, IVIG has been used for nearly half a century for primary humoral immune deficiencies and autoimmune syndromes and, more recently, a number of neurologic disorders such as chronic inflammatory demyelinating polyradiculoneuropathy and Guillain-Barré syndrome [17, 18].

The rationale for using IVIG for the treatment of AD gained traction for a number of reasons. IVIG was found to contain elevated levels of antibodies against multiple conformations of Aβ monomers and aggregates [19, 20], yet its repertoire of naturally occurring antibodies might also be predicted to normalize the inflammatory component of AD. The safety profile of IVIG for other diseases also mitigated concerns for AD clinical trials. Furthermore, if IVIG was found to be beneficial in AD, the potential existed for identifying treatment-specific antibodies to elucidate pathogenic mechanisms and allow for more targeted therapeutic designs. However, despite the initial promise of Phase I and II clinical trials conducted in Germany and the US, a recent multicenter double-blinded Phase III study of 390 subjects, called the Gammaglobulin Alzheimer's Partnership (GAP), did not meet primary endpoints of slowing cognitive and functional decline [21]. Then again, the GAP study results continued to support IVIG's positive safety profile and showed potentially beneficial effects for pre-specified moderate AD and apoE4 carrier subgroups. Concurrent with these clinical trials, several preclinical studies demonstrated that IVIG was neuroprotective against Aβ toxicity *in vitro* and enhanced microglia-mediated Aβ clearance

ex vivo, whereas *in vivo* IVIG delivery reduced inflammation in AD transgenic mice [22, 23]. Hence, the mechanism of action for IVIG is still of considerable interest in the field and there remains the opportunity for testing the extent to which optimized doses of IVIG delivered early enough in the AD trajectory might yet prove beneficial for modifying disease progression.

In the present HT issue, we summarize the state of the field with respect to IVIG as a potential therapy for AD and explore further the potential mechanisms of IVIG neuroprotection in preclinical models of AD. Puli and colleagues review our current understanding of the biologic and therapeutic properties of IVIG relevant to AD therapy and highlight their *in vitro* and *in vivo* studies on IVIG biological activities, including the suppression of neuroinflammatory microglial activation and concomitant increase in neurogenesis in APP/PS1 mice [24]. Gong and colleagues expound upon IVIG immunomodulatory mechanisms by showing that IVIG regulates complement-derived anaphylatoxins, such as C5a and C3, which in turn upregulates AMPA receptor-PKA-CREB signaling pathways and improves synaptic function and cognition in the Tg2576 mouse model of AD [25]. Lahiri and Ray add to the diverse repertoire of IVIG neuroprotection by reporting that treatment with IVIG protects neuronal viability and synaptic proteins in primary rat hippocampal neurons as well as in primary human brain cultures challenged with oxidative stress, suggesting a potent neuropre- servatory effect of IVIG against oxidative insults [26]. In addition, although IVIG has been reported to reduce amyloid burden in some AD transgenic models, its potential effects on tau NFT-like pathology in rodent models of disease are unclear. Counts and colleagues show that IVIG reduces hippocampal tau pathology in the 3xTg mouse model of AD that exhibits NFT as well as plaque-like deposits. In addition, this study reveals that IVIG preserves plasma levels of mRNAs regulating neuronal cytoskeletal plasticity function and calcium-mediated signaling compared to placebo [27]. It is important to note that not all IVIG preclinical studies have produced consistently positive results [28]. In this issue, Joly-Amado and colleagues describe how four weeks of IVIG infusion in Tg2576 mice led to widespread distribution of human IgG in the forebrain, but had no effect on amyloid burden or cognition [29]. However, the authors conclude by agreeing that the beneficial effects of IVIG in mouse models of AD are not likely due to its anti-Aβ antibody components alone, but must also involve its wide range of antiinflammatory, anti-oxidant, and other prosurvival and neuroprotective properties. Hence, despite the negative topline results from the GAP trial, these unique properties of IVIG suggest that this polyclonal IgG mixture can potentially be a safe and highly effective “top down” therapy for a complex multifactorial disease like AD. Moreover, the data derived from preclinical study designs may help guide current and future IVIG clinical trials targeting early stage patients with more optimized treatment regimens to prevent or delay the onset of AD symptomology [30]. Finally, since efforts to immunize against tau [31] and other AD-related targets have been encouraging, these studies would potentially be excellent subject matters for a future HT issue of the journal.

References

1. Du Y, Dodel R, Hampel H, Buerger K, Lin S, Eastwood B, et al. Reduced levels of amyloid beta-peptide antibody in Alzheimer disease. Neurology. 2001; 57:801–5. [PubMed: 11552007]

2. Weksler ME, Relkin N, Turkenich R, LaRusse S, Zhou L, Szabo P. Patients with Alzheimer disease have lower levels of serum antiamyloid peptide antibodies than healthy elderly individuals. Exp Gerontol. 2002; 37:943–8. [PubMed: 12086704]

3. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid-beta attenuates Alzheimer-diseaselike pathology in the PDAPP mouse. Nature. 1999; 400:173–7. [PubMed: 10408445]

4. Dodart JC, Bales KR, Gannon KS, Greene SJ, DeMattos RB, Mathis C, et al. Immunization reverses memory deficits without reducing brain Abeta burden in Alzheimer's disease model. Nat Neurosci. 2002; 5:452–7. [PubMed: 11941374]

5. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology. 2005; 64:1553–62. [PubMed: 15883316]

6. Vellas B, Black R, Thal LJ, Fox NC, Daniels M, McLennan G, et al. Long-term follow-up of patients immunized with AN1792: reduced functional decline in antibody responders. Curr Alzheimer Res. 2009; 6:144–51. [PubMed: 19355849]

7. Lemere CA, Maier M, Peng Y, Jiang L, Seabrook TJ. Novel Abeta immunogens: is shorter better? Curr Alzheimer Res. 2007; 4:427–36. [PubMed: 17908047]

8. Panza F, Frisardi V, Imbimbo BP, Seripa D, Paris F, Santamato A, et al. Anti-beta-amyloid immunotherapy for Alzheimer's disease: focus on bapineuzumab. Curr Alzheimer Res. 2011; 8:808–17. [PubMed: 21592055]

9. Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014; 370:322–33. [PubMed: 24450891]

10. Zhang YH, Raymick J, Sarkar S, Lahiri DK, Ray B, Holtzman D, et al. Efficacy and toxicity of clioquinol treatment and A-beta42 inoculation in the APP/PSI mouse model of Alzheimer's disease. Curr Alzheimer Res. 2013; 10:494–506. [PubMed: 23627708]

11. Bosch MN, Gimeno-Bayon J, Rodriguez MJ, Pugliese M, Mahy N. Rapid improvement of canine cognitive dysfunction with immunotherapy designed for Alzheimer's disease. Curr Alzheimer Res. 2013; 10:482–93. [PubMed: 23566345]

12. Solomon A, Akenine U, Andreasen N, Mangialasche F, Wimo A, Jelic V, et al. Practical lessons from amyloid immunotherapy trials in Alzheimer disease. Curr Alzheimer Res. 2012; 9:1126–34. [PubMed: 22631442]

13. Rosenmann H. Immunotherapy for targeting tau pathology in Alzheimer's disease and tauopathies. Curr Alzheimer Res. 2013; 10:217–28. [PubMed: 23534533]

14. Sigurdsson EM. Tau-focused immunotherapy for Alzheimer's disease and related tauopathies. Curr Alzheimer Res. 2009; 6:446–50. [PubMed: 19874269]

15. Troquier L, Caillierez R, Burnouf S, Fernandez-Gomez FJ, Grosjean ME, Zommer N, et al. Targeting phospho-Ser422 by active Tau Immunotherapy in the THYTau22 mouse model: a suitable therapeutic approach. Curr Alzheimer Res. 2012; 9:397–405. [PubMed: 22272619]

16. Lasagna-Reeves CA, Castillo-Carranza DL, Jackson GR, Kayed R. Tau oligomers as potential targets for immunotherapy for Alzheimer's disease and tauopathies. Curr Alzheimer Res. 2011; 8:659–65. [PubMed: 21605039]

17. Hughes RA, Dalakas MC, Cornblath DR, Latov N, Weksler ME, Relkin N. Clinical applications of intravenous immunoglobulins in neurology. Clin Exp Immunol. 2009; 158(Suppl 1):34–42. [PubMed: 19883422]

18. Kaveri SV. Intravenous immunoglobulin: exploiting the potential of natural antibodies. Autoimmun Rev. 2012; 11:792–4. [PubMed: 22349620]

19. Dodel R, Hampel H, Depboylu C, Lin S, Gao F, Schock S, et al. Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease. Ann Neurol. 2002; 52:253–6. [PubMed: 12210803]

20. Szabo P, Mujalli DM, Rotondi ML, Sharma R, Weber A, Schwarz HP, et al. Measurement of anti-beta amyloid antibodies in human blood. J Neuroimmunol. 2010; 227:167–74. [PubMed: 20638733]

21. Relkin N. Clinical trials of intravenous immunoglobulin for Alzheimer's disease. J Clin Immunol. 2014; 34(Suppl 1):74–9.
22. Magga J, Puli L, Pihlaja R, Kanninen K, Neulamaa S, Malm T, et al. Human intravenous immunoglobulin provides protection against Abeta toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. J Neuroinflammation. 2010; 7:90. [PubMed: 21138577]
23. Sudduth TL, Greenstein A, Wilcock DM. Intracranial injection of Gammagard, a human IVIg, modulates the inflammatory response of the brain and lowers Abeta in APP/PS1 mice along a different time course than anti-Abeta antibodies. J Neurosci. 2013; 33:9684–92. [PubMed: 23739965]
24. Puli L, Tanila H, Relkin N. Intravenous immunoglobulins for Alzheimer's disease. Curr Alzheimer Res. 2014
25. Gong B, Levine S, Barnum SR, Pasinetti GM. Role of complement systems in IVIG mediated attenuation of cognitive deterioration in Alzheimer's disease. Curr Alzheimer Res. 2014
26. Lahiri DK, Ray B. Intravenous immunoglobulin treatment preserves and protects primary rat hippocampal neurons and primary human brain cultures against oxidative insults. Curr Alzheimer Res. 2014
27. Counts SE, Perez SE, He B, Mufson EJ. Intravenous immunoglobulin reduces tau pathology and preserves neuroplastic gene expression in the 3xTg mouse model of Alzheimer's Disease. Curr Alzheimer Res. 2014
28. Counts SE, Ray B, Mufson EJ, Perez SE, He B, Lahiri DK. Intravenous immunoglobulin (IVIG) treatment exerts antioxidant and neuropreservatory effects in preclinical models of Alzheimer's disease. J Clin Immunol. 2014; 34(Suppl 1):80–5.
29. Joly-Amado A, Brownlow M, Pierce J, Ravipati A, Showalter E, Li Q, et al. Intraventricular human immunoglobulin distributes extensively but fails to modify amyloid in a mouse model of amyloid deposition. Curr Alzheimer Res. 2014
30. Lemere CA. Immunotherapy for Alzheimer's disease: hoops and hurdles. Mol Neurodegener. 2013; 8:36. [PubMed: 24148220]
31. Castillo-Carranza DL, Sengupta U, Guerrero-Munoz MJ, Lasagna-Reeves CA, Gerson JE, Singh G, et al. Passive immunization with Tau oligomer monoclonal antibody reverses tauopathy phenotypes without affecting hyperphosphorylated neurofibrillary tangles. J Neurosci. 2014; 34:4260–72. [PubMed: 24647946]