New Horizons in the Treatment of Alzheimer's Disease—Immunotherapeutics

a report by
Edward Tobinick, MD

Director, Institute for Neurological Research (INR)

DOI: 10.17925/USN.2008.04.01.34

The inability of pharmacologically based therapeutic molecules, such as the cholinesterase inhibitors and memantine, to effectively prevent clinical deterioration in Alzheimer's disease (AD) over the long term has stimulated the search for more effective therapeutic approaches that may have the ability to show significant disease-modifying activity. Immunotherapeutic approaches are perhaps the most exciting potential therapeutic options on the near horizon. The most closely watched therapeutic approaches falling into this class that may become available in the reasonably near term include: two experimental therapeutics designed to directly attack A-beta, AAC-001 and bapineuzumab; another immunotherapeutic whose mechanism of action is still being delineated, but which also contains anti-amyloid antibodies, namely intravenous immunoglobulin; and a fourth therapeutic, which, although it may address certain amyloid-mediated mechanisms, takes a completely novel therapeutic approach to treating AD, namely peri-spinal etanercept.

Active Anti-amyloid Immunotherapy with AAC-001

A-beta is widely hypothesized to be the major therapeutic target in AD. Unfortunately, there has not yet been a single agent designed to directly target amyloid that has been successfully brought through phase III clinical trials. One potential approach is active anti-amyloid immunotherapy. One preliminary clinical trial involving this approach studied 30 participants and found that those study participants immunized with A-beta peptide who actively generated anti-A-beta antibodies (20 of the participants) exhibited a slower rate of decline of certain cognitive functions over a study period of one year.[1] There has been considerable interest in AAC-001 (clinicaltrials.gov identifier NCT00498602), which is an active anti-amyloid vaccine undergoing clinical trial testing by Elan/Wyeth. It is a modified version of AN-1792,[2] a previous anti-amyolid vaccine tested several years ago by this same consortium, but whose clinical development was stopped because of severe meningoencephalitis that occurred in 18 of 300 study participants.[3]

Edward Tobinick, MD, is Director of the Institute for Neurological Research (INR), a private medical group, and directs the INR's active, patented, off-label, anti-tumor necrosis factor treatment program and its physician training program. He is also an Assistant Clinical Professor of Medicine at the University of California, Los Angeles (UCLA) and in 2007 was appointed to the Editorial Board of the *Journal of Neuroinflammation*. He invented and was the first to publish on the use of etanercept delivered by peri-spinal administration for the treatment of selected neurological disorders. Dr Tobinick completed medical school at the Univerity of California, San Diego School of Medicine in La Jolla, California, and post-graduate training at UCLA.

E: etmd@ucla.edu

The current AAC-001 trial was designed for patients with mild to moderate AD and a Mini-Mental State Examination (MMSE) score of 16–26. Because of the similarity of the mechanism of action of this agent to AN-1792 there remains significant concern regarding the safety of this vaccine. For this reason, the occurrence of severe skin lesions in a single patient receiving the vaccine has currently (May 2008) resulted in the halting of all clinical trials of this agent, but there is the possibility that testing will resume.

Passive Anti-amyloid Immunotherapy with Bapineuzumab

Bapineuzumab is a humanized monoclonal antibody to A-beta being developed by Elan/Wyeth.[4] The rationale is that passive A-beta antibodies may have the potential to bind and reduce brain A-beta. Bapineuzumab is currently being trialed in two separate studies in patients with probable AD: one for ApoE4-positive carriers and one for ApoE4-negative carriers. These studies are both for selected participants with mild to moderate AD with MMSE scores ranging from 16 to 26. The study of ApoE4-positive carriers (clinicaltrials.gov identifier NCT00575055) is planned to include 800 enrollees. The ApoE4 negative carrier study (clinicaltrials.gov identifier NCT00574132) is planned to include 1,250 enrollees at 200 study sites. Both trials were begun in December 2007 and are scheduled for completion in December 2010 (the final data collection date for the primary outcome measure).

These are placebo-controlled studies; the active comparator will consist of 0.5mg/kg infusions given over a period of 60 minutes every 13 weeks for a total of 18 months for the ApoE4-positive patients, and doses of 0.5, 1.0, or 2.0mg/kg (three groups) for the ApoE4-negative patients.

There is some concern regarding the risk of brain microhemorrhages, which have been seen in transgenic mice treated with passive A-beta vaccines.[5] In a 30-patient randomized, double-blind, placebo-controlled, single-ascending-dose trial of bapineuzumab treated with infusions ranging from 0.5 to 5mg/kg, three of 10 patients treated at the 5mg/kg dose developed magnetic resonance imaging abnormalities, consisting predominantly of high signal abnormalities on fluid attenuated inversion recovery sequences, which resolved by 12 weeks post-dose.[4] With multiple doses, one might be concerned that these effects could be augmented. The study designers were apparently more concerned about safety in the ApoE4 positive carriers, hence the reduced dosing levels in these patients. The phase III trials are currently recruiting study participants.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is used off-label for a variety of disorders involving neurological inflammation, including myasthenia gravis, certain forms

of multiple sclerosis, and chronic inflammatory demyelinating polyneuropathy.[6] In 2002, naturally occurring antibodies directed against A-beta were detected in IVIg preparations and found to be present in both serum and cerebrospinal fluid (CSF) after intravenous infusion.[7] These same investigators later conducted a pilot study utilizing monthly IVIg infusions in five patients with AD treated over six months. A-beta in the CSF decreased by 30% compared with baseline, and the Alzheimer's Disease Asssement Scale–cognitive subscale (ADAS-Cog) improved by 3.7±2.0 points.[8] Scores on MMSE did not show a significant change.[8] Most recently, at the just concluded American Academy of Neurology annual meeting, the results of a placebo-controlled, phase II clinical trial of IVIg for the treatment of 24 patients with probable AD (MMSE 14–26) was discussed. Subjects received infusions every two to four weeks at dosages ranging from 0.2g/kg/2weeks to 0.8g/kg/month, with assessment of ADAS-Cog and clinical global impression of change (CGIC).[9] IVIg resulted in increased anti-amyloid antibody levels and decreased CSF beta-amyloid.[9] Global outcomes, as measured by CGIC, were slightly improved (0.27 GCIC points for IVIg versus 1.25 for placebo), but ADAS-Cog, although favoring the active group, did not reach statistical significance.

> Acute renal failure, usually occurring in the first 10 days after intravenous immunoglobulin administration, is usually reversible, and thromboembolic complications are also a risk.

The results were interpreted as encouraging the initiation of a phase III clinical trial. In this trial, the only adverse event that was increased in the active group was skin rash. A review of IVIg therapy reports that most adverse events are mild and transient, but severe adverse reactions can occur.[10] Acute renal failure, usually occurring in the first 10 days after IVIg administration, is usually reversible, and thromboembolic complications are also a risk.[10] As a pooled blood product, there is a small risk of transmission of viral diseases, and hemolytic anemia, death, and transfusion-related acute lung injury have been reported.[10] A phase III clinical trial is scheduled to begin soon.

Peri-spinal Etanercept

Tumor necrosis factor-alpha (TNFα) is a cytokine that is well recognized as a key mechanism of disease.[11] In 1999, excess TNF in the CSF of patients with AD was found at a level 25 times that of controls.[12] Although initially it was thought by the group that made this discovery that TNF was playing a neuroprotective role, they later determined that excess TNF in patients with mild cognitive impairment was associated with progression to AD.[13] The present author conceived of the use of etanercept, a potent anti-TNF therapeutic, as a treatment for neurological disorders, including AD, in the late 1990s.[14,15] Etanercept is a recombinant dimeric fusion protein consisting of the extracellular ligand-binding portions of two human p75 TNFα receptors linked to the Fc fragment of human IgG1. Etanercept binds to TNF and blocks its interaction with cell surface TNF receptors, thereby reducing the biologic effect of excess TNF. The medical community now has more than one million patient-years of experience using etanercept for treatment of a variety of inflammatory disorders in which TNF plays a prominent role.[16] Accumulating basic science and epidemiological, genetic, and clinical data supports a central role of excess TNF in the pathogenesis of AD.[17–29]

Etanercept does not cross the blood–brain barrier when administered systemically.[30] A previous clinical trial utilizing systemically administered etanercept for the treatment of AD failed to show benefit.[31] Peri-spinal administration of etanercept, however, was hypothesized to have the ability to traverse the blood–dural barrier, as demonstrated by the ability of this novel treatment approach to reduce the symptoms of lumbar and cervical radiculopathy.[32,33] A prospective, open-label, six-month pilot study of peri-spinal etanercept administered weekly to a cohort of 15 patients with probable AD ranging in severity from mild to severe was performed.[34] The average age of the patient population was 76.7 years. The mean baseline MMSE was 18.2 (n=15), the mean baseline ADAS-Cog was 20.8 (n=11), and the mean baseline severe impairment battery (SIB) was 62.5 (n=5).

There was significant improvement with treatment, as measured by all of the primary efficacy variables, through six months: MMSE increased by 2.13±2.23, ADAS-Cog improved (decreased) by 5.48±5.08, and SIB increased by 16.6±14.52.[34] The methods used involving peri-spinal administration of etanercept were hypothesized to utilize the cerebrospinal venous system to enable therapeutically effective delivery of etanercept to the central nervous system.[35,36] Most recently, peri-spinal etanercept was demonstrated to result in rapid clinical improvement, beginning within minutes, in an 81-year-old physician with probable AD.[37,38] It was hypothesized that this rapid improvement may have been related to amelioration of the effects of excess TNFα on synaptic mechanisms and the role of TNF as a gliotransmitter.[25,37,39]

The proper use of peri-spinal etanercept for the treatment of AD requires that dosage and dosing intervals be individualized for each patient. This requires experience with the use of peri-spinal etanercept in the treatment of patients with dementia. At this point, until there is more widespread clinical experience utilizing this patented treatment approach, the proper performance of peri-spinal injection of etanercept, and disease management utilizing peri-spinal etanercept, both require specialized and specific physician training and experience and should not be attempted without such training.[40] Potential adverse effects of the use of peri-spinal etanercept for the treatment of AD (off-label use) include all of the risks inherent with the use of etanercept for its labeled indications, which include, but are not limited to, death, infection, decreased blood counts, congestive heart failure, lymphoma, demyelinating disease, and reactivation of tuberculosis. Purified protein derivative skin testing prior to initiation of etanercept treatment is mandatory, and a black box warning highlighting the risk of tuberculosis, sepsis, and severe infection has been added to the package insert. The initiation of randomized, placebo-controlled clinical trials will add much-needed additional clinical data. ■

> The proper use of peri-spinal etanercept for the treatment of Alzheimer's disease requires that dosage and dosing intervals be individualized for each patient.

1. Hock C, Konietzko U, Streffer JR, et al., Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease, *Neuron*, 2003;38(4):547–54.
2. Thatte U, AN-1792 (Elan), *Curr Opin Investig Drugs*, 2001;2(5):663–7.
3. Orgogozo JM, Gilman S, Dartigues JF, et al., Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization, *Neurology*, 2003;61(1):46–54.
4. Black RS, Sperling R, Kirby L, et al., A single ascending dose study of bapineuzumab, a humanized monoclonal antibody to A-beta, in AD, 9th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy, 2006, Geneva, Switzerland.
5. Pfeifer M, Boncristiano S, Bondolfi L, et al., Cerebral hemorrhage after passive anti-Abeta immunotherapy, *Science*, 2002;298(5597):1379.
6. Solomon B, Intravenous immunoglobulin and Alzheimer's disease immunotherapy, *Curr Opin Mol Ther*, 2007;9(1):79–85.
7. Dodel R, Hampel H, Depboylu C, et al., Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease, *Ann Neurol*, 2002;52(2):253–6.
8. Dodel RC, Du Y, Depboylu C, et al., Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease, *J Neurol Neurosurg Psychiatry*, 2004;75(10):1472–4.
9. Relkin R, Tsakanikas D, Adamiak B, et al., A double blind, placebo-controlled, phase II clinical trial of IVIG for treatment of Alzheimer's disease, American Academy of Neurology 60th Annual Meeting, 2008, Chicago, Illinois.
10. Katz U, Achiron A, Sherer Y, and Shoenfeld Y, Safety of intravenous immunoglobulin (IVIG) therapy, *Autoimmunity Reviews*, 2007;6(4):257–9.
11. Clark IA, How TNF was recognized as a key mechanism of disease, *Cytokine Growth Factor Rev*, 2007;18(3-4):335–43.
12. Tarkowski E, Blennow K, Wallin A, and Tarkowski A, Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia, *J Clin Immunol*, 1999;19(4):223–30.
13. Tarkowski E, Andreasen N, Tarkowski A, and Blennow K, Intrathecal inflammation precedes development of Alzheimer's disease, *J Neurol Neurosurg Psychiatry*, 2003;74(9):1200–5.
14. Tobinick E, TNF inhibitors for the treatment of neurological disorders, US patent 6,177,077, filed 1999.
15. Tobinick E, Tumor necrosis factor antagonists for the treatment of neurological disorders, US patent 6,015,557, filed 1999.
16. Amgen, Enbrel(R) package insert, 2005, Thousand Oaks, CA.
17. Chiarini A, Dal Pra I, Whitfield JF, and Armato U, The killing of neurons by beta-amyloid peptides, prions, and pro-inflammatory cytokines, *Ital J Anat Embryol*, 2006;111(4):221–46.
18. Laws SM, Perneczky R, Wagenpfeil S, et al., TNF polymorphisms in Alzheimer disease and functional implications on CSF beta-amyloid levels, *Hum Mutat*, 2005;26(1):29–35.
19. Lio D, Annoni G, Licastro F, Tumor necrosis factor-alpha -308A/G polymorphism is associated with age at onset of Alzheimer's disease, *Mech Ageing Dev*, 2006;127(6):567–71.
20. Medeiros R, Prediger RD, Passos GF, et al., Connecting TNF-{alpha} signaling pathways to iNOS expression in a mouse model of Alzheimer's disease: relevance for the behavioral and synaptic deficits Induced by amyloid {beta} protein, *J Neurosci*, 2007;27(20):5394–404.
21. Perry RT, Collins JS, Wiener H, et al., The role of TNF and its receptors in Alzheimer's disease, *Neurobiol Aging*, 2001;22(6):873–83.
22. Pickering M, Cumiskey D, and O'Connor JJ, Actions of TNF-alpha on glutamatergic synaptic transmission in the central nervous system, *Exp Physiol*, 2005;90(5):663–70.
23. Ramos, EM, Lin MT, Larson EB, et al., Tumor necrosis factor alpha and interleukin 10 promoter region polymorphisms and risk of late-onset Alzheimer disease, *Arch Neurol*, 2006;63(8):1165–9.
24. Ranaivo HR, Craft JM, Hu W, et al., Glia as a therapeutic target: selective suppression of human amyloid-beta-induced upregulation of brain proinflammatory cytokine production attenuates neurodegeneration, *J Neurosci*, 2006; 26(2):662–70.
25. Rowan MJ, Klyubin I, Wang Q, et al., Synaptic memory mechanisms: Alzheimer's disease amyloid beta-peptide-induced dysfunction, *Biochem Soc Trans*, 2007;35(Pt 5):1219–23.
26. Tan ZS, Beiser AS, Vasan RS, Inflammatory markers and the risk of Alzheimer disease: the Framingham Study, *Neurology*, 2007;68(22):1902–8.
27. Tweedie D, Sambamurti K, and Greig NH, TNF-alpha inhibition as a treatment strategy for neurodegenerative disorders: new drug candidates and targets, *Curr Alzheimer Res*, 2007; 4(4):375–8.
28. Van Eldik LJ, Thompson WL, Ranaivo HR, Proinflammatory cytokine upregulation as a therapeutic target for neurodegenerative diseases: function-based and target-based discovery approaches, *International Review of Neurobiology*, 2007;82:278–97.
29. Wang Q, Wu J, Rowan MJ, and Anwyl R, Beta-amyloid inhibition of long-term potentiation is mediated via tumor necrosis factor, *Eur J Neurosci*, 2005; 22(11):2827–32.
30. Banks, WA, Plotkin SR, and Kastin AJ, Permeability of the blood-brain barrier to soluble cytokine receptors, *Neuroimmunomodulation*, 1995; 2(3):161–5.
31. Bohac D, Burke W, Cotter R, et al., A 24-week randomized, double-blind, placebo-controlled study of the efficacy and tolerability of TNFR: Fc (etanercept) in the treatment of dementia of the Alzheimer type, *Neurobiol Aging*, 2002;23(1 Suppl. 1): S1–606, abstract 315.
32. Tobinick EL and Britschgi-Davoodifar S, Perispinal TNF-alpha inhibition for discogenic pain, *Swiss Med Wkly*, 2003;133(11–12): 170–7.
33. Tobinick E and Davoodifar S, Efficacy of etanercept delivered by perispinal administration for chronic back and/or neck disc-related pain: a study of clinical observations in 143 patients, *Curr Med Res Opin*, 2004;20(7):1075–85.
34. Tobinick E, Gross H, Weinberger A, and Cohen H, TNF-alpha modulation for treatment of Alzheimer's disease: a 6-month pilot study, *Medscape General Medicine*, 2006;8(2):25f.
35. Tobinick E, Perispinal etanercept for treatment of Alzheimer's disease, *Curr Alzheimer Res*, 2007;4(5):550–52.
36. Tobinick E and Vega C, The cerebrospinal venous system: anatomy, physiology, and clinical implications, *MedGenMed*, 2006;8(1):53.
37. Tobinick EL and Gross H, Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration, *J Neuroinflammation*, 2008;5:2.
38. Griffin WS, Perispinal etanercept: potential as an Alzheimer therapeutic, *J Neuroinflammation*, 2008;5(1):3.
39. Bains JS and Oliet SH, Glia: they make your memories stick!, *Trends Neurosci*, 2007;30(8):417–24.
40. Multiple pending and issued US patents issued to Edward Tobinick, assigned to TACT IP, LLC, including, but not limited to, US patents 6,982,089 and 7,214,658.

Impact of Increased Life Expectancy on Alzheimer's Disease Death Rate

More women than men have Alzheimer's/other dementias, primarily because on average women live longer than men and their longer life expectancy means females are more susceptible to developing neurological conditions.

Impact of Co-existing Medical Conditions

Most people with Alzheimer's/other dementias have one or more other serious medical conditions. For example, 30% of Medicare beneficiaries aged 65 years and over with Alzheimer's/other dementias also have coronary heart disease, while 28% have congestive heart failure.

However, deaths from diseases such as heart disease and cancer are declining, which, since 2000, has led to an increase in Alzheimer's disease death rates for the oldest age groups. For example, the death rate for those aged 75–84 increased from 139.6 per 100,000 in 2000 to 168.7 per 100,000 in 2004. People who may have died of the above-mentioned diseases live longer, and thus have an increased risk of dying of Alzheimer's disease.

Source: 2008 Alzheimer's Disease Facts and Figures, Alzheimer's Association.

Percentage of Medicare Beneficiaries Aged 65+ Years with Alzheimer's Disease/Other Dementias Who Had Specified Co-existing Medical Conditions