Editorial

Alzheimer's Disease: Clinical Trials and the Amyloid Hypothesis

Jeffrey Cummings,[1] *MD*

Alzheimer's disease (AD) is a progressive fatal neurodegenerative disease whose numbers are approaching epidemic proportions as the world's population ages. There are currently 35 million victims worldwide with an anticipated 115 million by 2050 if effective treatments are not found.[1] There is an urgent need to identify treatments that will prevent or delay the onset, slow the progression, or improve the symptoms of AD and related neurodegenerative disorders affecting cognition and survival in the elderly.

Many of the agents currently in clinical trials and focusing on disease-modification of AD are based on the amyloid hypothesis[2] and target some aspect of amyloid metabolism. The agents include beta- and gamma-secretase inhibitors, alpha secretase enhancers, aggregation inhibitors, and plaque removing agents among others. Recent failures of drugs targeting amyloid pathways have raised questions about this approach and the validity of the amyloid hypothesis itself. No agent aimed at modifying the amyloid cascade has met prespecified efficacy outcomes. There is no treatment-based validation of the amyloid hypothesis or the centrality of amyloid to the etiopathogenesis of AD.

A review of the trials of amyloid-related drugs reveals that none have rigorously tested the amyloid hypothesis. Some trials failed because of issues related to trial conduct and methodology, others failed for pharmacokinetic or tolerability and safety-related problems. For example, it is now thought that tarenflurbil did not reach adequate concentrations in the brain,[3] and semagascestat had intolerable side effects and increased skin cancer.[4] Tramiprosate and rosiglitazone trials exhibited features suggesting methodologic flaws in trial conduct. Bapineuzumab appeared to be efficacious in patients who received all treatments for 18 months or who did not have the apolipoprotein E e4 AD risk gene but failed in the prespecified intent-to-treat (ITT) analysis required to support a claim for efficacy.[5] None of the trials tested the amyloid hypothesis, and the absence of trial successes does not constitute evidence against the amyloid hypothesis.

Autopsy and biomarker studies have provided new information on the role and timing of amyoid deposition in AD. Studies using stable isotope labeled kinetic (SILK) techniques have shown that the abnormality of amylolid beta-protein (Aβ) in late onset AD is reduced clearance;[6] this contrasts with the autosomal dominant form of AD where mutations in the amyloid precursor protein or presenilin component of gamma-secretase result in the overproduction of Aβ. Measurement of Aβ1-42 in cerebrospinal fluid (CSF) show reduced levels that begin before symptoms appear and remain low throughout the prodromal and dementia phases of AD.[7] Similarly, amyloid imaging has confirmed that amyloid deposition begins before significant cognitive symptoms occur and the Aβ burden in the brain remains approximately the same throughout the remainder of the disease.[8,9] Approximately 20% to 30% of cognitively normal elderly have substantial amyloid deposition in the brain comparable to the levels observed in AD dementia.[10] Amyloid levels in CSF and amyloid imaging do not correlate with cognitive decline or brain atrophy as shown by magnetic resonance imaging (MRI) during the stage of progressive AD dementia.[9] These observations have important implications for understanding the role of Aβ in AD and approaches to AD therapeutics. Documentation that Aβ is deposited early in AD— beginning before detectable cognitive decline occurs— and continues to be present throughout the course of AD confirms that Aβ abnormalities are central to AD and offers important support for the amyloid hypothesis. On the other hand, this new information indicates that some types of amyloid interventions might have to begin very early in the disease process to be effective; the brain can tolerate a high Aβ burden without cognitive dysfunction; and the total amount of amyloid in the brain may change little despite cognitive worsening and eventual death of the patient. Autopsy studies of patients in the AN1792 Aβ vaccination trial show that cognitive decline continues despite effective removal of Aβ plaques.[11] Together these new data suggest that while amyloid is one means of identifying AD and is characteristic of AD, its relationship to cell dysfunction and cognitive decline is uncertain and it may not be the optimal treatment target for arresting the progressive neurodegeneration leading to dementia.

Aβ deposition is the first detectible change in AD. What triggers the appearance of this protein in the brain? Studies of resting state MRI and default network activity suggest that sustained cerebral activity may provide local predisposing circumstances that lead to Aβ deposition and that these local

[1]Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada
Address for Correspondence: Dr Jeffrey Cummings, Cleveland Clinic Lou Ruvo Center for Brain Health, 888 W Bonneville Ave, Las Vegas, NV 89106.
Email: cumminj@ccf.org

changes are the "cause" of AD.[12] Aβ may be a result of these processes or, at least, they may comprise a predisposing cerebral ecology for the deposition of Aβ. If correct, these local changes may provide additional therapeutic targets for the treatment or prevention of AD.

Studies of autosomal dominant AD (ADAD) provide some of the most compelling data in support of the amyloid hypothesis. Mutations in the amyloid precursor protein (APP) gene, presenilin 1 (PS1) gene, or presenilin 2 (PS2) gene result in overproduction of Aβ1-42 and an alteration of the Aβ1-42/ Aβ1-40 ratio in favour of the form that oliogmerizes more readily.[13] The pathology and the clinical syndrome of progressive cognitive impairment is generally the same for ADAD and late onset AD, the causative mutation is known and the resulting pathophysiology is closely linked to Aβ abnormalities. The similarity of ADAD and sporadic AD supports the role of Aβ in the latter. There are important differences between these 2 forms of AD, however. SILK studies of Aβ show that the sporadic form of AD is a product of reduced clearance of AD whereas in ADAD, Aβ is overproduced.[6,14] ADAD generally occurs in those aged 40 to 55 years with little comorbidity and no age-related cerebral changes, whereas sporadic AD occurs in individuals aged 65 to 100 years where brain changes of ageing and comorbid cerebral pathology are the rule.[15] These differences in pathophysiology may create different roles for Aβ in the 2 conditions and may affect both treatment efficacy and side effect vulnerability.

Most trials of therapeutic agents for AD have been conducted in patients with mild-to-moderate dementia of the Alzheimer's type. Given the biomarker evidence that Aβ changes precede this stage of AD and begin prior to the onset of cognitive changes and also given the goal of minimising cognitive impairment by intervening at a time when cognitive and neuronal changes are limited, there is concern that treating at this stage may be too late. Trials are now beginning in prodromal AD defined as a syndrome of cognitive impairment without dementia and with biomarker evidence of the presence of an AD process.[16,17] The intent of targeting this stage is to limit the amyloid burden prior to major degeneration and progression of symptoms to AD dementia. Since there are no completed trials involving this disease stage, it is not proven that this approach will improve the chance of success. The logic of intervening early in AD may extend to trials of patients who are cognitively normal and have biomarker evidence of AD pathology or to patients who are at high risk for AD yet with no evidence of AD in the brain. Different agents might also have different optimal windows of time for intervention. Secretase inhibitors that reduce Aβ production, for example, might be most efficacious when administered during the period of amyloid deposition, whereas agents intended to remove plaques might have a role later in the disease course. Drugs such as PBT2 and the scyllo-inositol AZD-103 (ELND5000) targeting aggregation may be most effective in prodromal AD when MRI evidence suggests the onset of neurodegenerative changes. Secretase inhibitors that reduce monomer production would also be expected to reduce oligomer concentrations.

Aβ is thought to go through a process of progressive aggregation from monomers to oligomers through fibrillization to plaque formation.[18] There is growing evidence that Aβ oligomers are responsible for synaptic dysfunction and for initiating the process that leads to cell death and neurodegeneration.[19] An unresolved conundrum is why Aβ and Aβ oligomers can be resident in the brain for many years without producing sufficient cognitive dysfunction to be detected. Possibly, oligomers need to reach specific concentrations or be present in the brain for prolonged periods of time before neurotoxicity is triggered. The relationship between Aβ and cell death in the course of human AD requires clarification.

Existing evidence can also be interpreted to suggest that Aβ generation and Aβ-related neurobiological changes continue throughout the course of AD. Although Aβ1-42 levels are decreased and remain low beginning in the asymptomatic phase of AD and continuing through prodromal AD and AD dementia, Aβ levels are turned over at least twice daily suggesting that Aβ production continues throughout the disease course. Similarly, although amyloid imaging appears to suggest a stable amyloid burden across all stages of AD from the asymptomatic onset through severe dementia, these stable images may obscure dynamic changes in maturing and resolving plaques as suggested by observations in experimental animals.[20] Autopsy evidence indicates that plaque burden extends geographically during the course of AD,[21] and rare examples of cerebral biopsies early in the disease course and autopsy when the patient succumbs also support an increasing plaque burden.[22] Finally, amyloid imaging may be susceptible to saturation effects and the apparent absence of change in amyloid burden in the course of AD may not accurately reflect changes in plaque burden.[23] Until these issues are resolved, it is too early to abandon mild-to-moderate or even severe dementia of the Alzheimer's type as a suitable treatment target for anti-amyloid therapies.

With serious questions about the suitability of Aβ as a therapeutic target, the pharmacologic tractability of the complex pathways involved in Aβ metabolism, and the optimal timing of anti-Aβ therapies, what alternative treatment strategies might be adopted? The microtubule associated protein tau becomes hyperphosphorylated and aggregates in the form of neurofibrillary tangles in the course of AD.[24] Aggregated tau has an oligomeric form

with neurotoxic properties similar to the process noted for Aβ.[25] Tau therapeutics with microtubule stabilisers, phosphorylation inhibitors, and anti-aggregants represent an alternate therapeutic approach. Available evidence suggests that tau abnormalities are more closely related to neurodegeneration and to cognitive changes than Aβ.[26] Targets involving oxidative cellular injury, mitochondrial activity, membrane integrity, apoptosis or other related processes affecting cell function and survival are under consideration as viable pathways for therapeutic intervention. Combination therapies also deserve consideration since intervening in one pathway may be insufficient to meaningfully alter the disease course.[27]

Effective disease-modifying therapies for AD are urgently needed and the available data cast doubt on targeting Aβ as the most viable pathway to developing new treatments for AD. The chances of success in identifying new therapies will be enhanced by proliferating the disease pathways targeted and diversifying the drug development portfolio.

Acknowledgements

The author acknowledges Christine Moore of Cleveland Clinic for technical assistance in manuscript preparation.

Disclosure

The author has consulted for pharmaceutical and biotechnology companies regarding treatment for AD.

REFERENCES

1. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol 2011;7:137-52.
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353-6.
3. Wan HI, Jacobsen JS, Rutkowski JL, Feuerstein GZ. Translational medicine lessons from flurizan's failure in Alzheimer's disease (AD) trial: Implication for future drug discovery and development for AD. Clin Transl Sci 2009;2:242-7.
4. Cummings J. What can be inferred from the interruption of the semagacestat trial for treatment of Alzheimer's disease? Biol Psychiatry 2010;68:876-8.
5. Salloway S, Sperling R, Gilman S, Fox NC, Blennow K, Raskind M, et al; Bapineuzumab 201 Clinical Trial Investigators. A Phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 2009;73:2061-70.
6. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 2010;330:1774.
7. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, et al; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative. Ann Neurol 2009;65:403-13.
8. Sojkova J, Zhou Y, An Y, Kraut MA, Ferrucci L, Wong DF, et al. Longitudinal patterns of β–amyloid deposition in nondemented older adults. Arch Neurol 2011;68:644-9.
9. Villemagne VL, Pike KE, Chételat G, Ellis KA, Mulligan RS, Bourgeat P, et al. Longitudinal assessment of Aβ and cognition in aging and Alzheimer disease. Ann Neurol 2011;69:181-92.
10. Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol 2008;65:1509-17.
11. Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomized, placebo-controlled phase I trial. Lancet 2008;372:216-23.
12. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, HeddenT, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci 2009;29:1860-73.
13. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: back to the future. Neuron 2010;68:270-81.
14. Bateman RJ, Aisen PS, De Strooper B, Fox NC, Lemere CA, Ringman JM, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res Ther 2011;63:1.
15. Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, et al. The clinical course of advanced dementia. N Engl J Med 2009;361:1529-38.
16. Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, Barberger-Gateau P, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010;9:1118-27.
17. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734-46.
18. Ashe KH, Zahs KR. Probing the biology of Alzheimer's disease in mice. Neuron 2010;66:631-45.
19. Jin M, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ. Soluble amyloid beta-protein dimmers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. Proc Natl Acad Sci U S A. 2011;108:5819-24.
20. Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, et al. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. Nature 2008;451:720-4.
21. Gold G, Kovari E, Corte G, Herrmann FR, Canuto A, Bussiere T, et al. Clinical validity of A beta-protein deposition staging in brain aging and Alzheimer disease. J Neuropathol Exp Neurol 2001;60:946-52.
22. Di Patre PL, Read SL, Cummings JL, Tomiyasu U, Vartavarian LM, Secor DL, et al. Progression of clinical deterioration and pathological changes in patients with Alzheimer disease evaluated at biopsy and autopsy. Arch Neurol 1999;56:1254-61.
23. Cummings JL. Biomarkers in Alzheimer's disease drug development. Alzheimers Dement 2011;7:e13-44.
24. Pritchard SM, Dolan PJ, Vitkus A, Johnson GV. The toxicity of tau in Alzheimer Disease: turnover, targets and potential therapeutics. J Cell Mol Med 2011 Feb 23. doi: 10.1111/j.1582-4934.2011.01273.x.
25. Lasagna-Reeves CA, Castillo-Carranza DL, Jackson GR, Kayed R. Tau oligomers as potencial target for immunotherapy for Alzheimer disease and tauopathies. Curr Alzheimer Res 2011; in press.
26. Giannakopoulos P, Herrmann FR, Bussière T, Bouras C, Kövari E, Perl DP, et al. Tangle and neuron numbers, but not amyloid load, predict congnitive status in Alzheimer's disease. Neurology 2003;60:1495-500.
27. Mangialasche F, Solomon A, Winblad B, Mecocci P, Kivipelto M. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010;9:702-16.