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The Imperative for Disease Modifying Treatments in Alzheimer's Disease

It is estimated that there are currently as many as 38,000 people with dementia in Ireland and that this figure may exceed 70,000 by 2026.[1] Indeed the prevalence of dementia is rising worldwide and it is not surprising therefore, that Alzheimer's disease (AD), which accounts for 50 - 60% of all cases of dementia is the focus of a great deal of scientific endeavour.[2] The current trend towards increasing numbers of patients in the moderate to severe stages of AD who require substantial residential and community healthcare resources is particularly worrying. Existing therapies have limited effects on the underlying disease pathobiology and the need for the disease modifying therapies that act at an earlier stage of the disease process is overwhelming. The failure to either delay disease onset or progression will have stark implications for the demands placed on healthcare resources, patients and their informal caregivers.[3]

The exact cellular mechanisms leading to neuronal cell death in AD remain uncertain. The amyloid cascade hypothesis holds that the Beta amyloid protein (Abeta) plays a central role in AD. Abeta is derived from the much larger transmembrane protein, amyloid precursor protein (APP) by the action of two proteases referred to as beta and gamma secretase. The initial cleavage of APP is mediated by beta secretase and then, depending on the exact point of cleavage by gamma secretase, three principle forms of Abeta comprising 38, 40 or 42 amino acid residues respectively are produced. At a certain critical concentration Abeta monomers associate to form neurotoxic oligomers which then further associate into insoluble fibrils and are deposited as amyloid plaques. The relative amount of Abeta42 formed is important as this longer form of Abeta is far more prone to oligomerise and form amyloid fibrils.[4] This cascade may be disrupted at a number of key points and several agents which either inhibit Abeta production or facilitate its clearance are currently under investigation. The central significance of amyloid in the pathogenesis of AD has recently been called into question given negative outcomes from trials of certain agents targeting this pathway.[5] Tarenflurbil, an agent which modulates gamma secretase activity, failed to achieve significance on its primary endpoints in a phase III trial and another agent,Tramiprosate, which binds soluble Abeta thus preventing amyloid deposition, was equally disappointing.[6,7]

Immunotherapy forms another potential strategy in anti-amyloid therapy. Research into this area began in earnest when it was found that it was possible to prevent or reverse Abeta accumulation in the brain of an animal model by active immunization with Abeta42.[8] A phase two trial utilizing this method demonstrated effective removal of Abeta plaques but was stopped prematurely because 6% of patients developed meningoencephalitis. The specificity of Abeta antibodies has since been investigated and active immunization therapies targeting different regions of Abeta42 are currently investigation. It was similarly found that passive immunization by peripheral infusion of Abeta antibodies facilitated Abeta clearance in animal models[9] and subsequent clinical trials have yielded variable results. One phase II trial utilising a humanized monoclonal antibody demonstrated efficacy on a cognitive endpoint in a subgroup of patients who were non ApoE4 carriers but failed to achieve statistical significance in the overall study population.[10] Other investigators have utilized intravenous immunoglobulin, which contains naturally derived human antibodies against Abeta, and have presented promising results.[11] Phase III trials of passive immunization techniques are currently underway. A number of differing hypotheses have been proposed to explain how immunotherapy may result in Abeta clearance. It has been proposed that microglial activation with resulting endocytosis andphagocytosis of Abeta neuritic plaques facilitates clearance while alternately it has been suggested that circulating antibodies may draw soluble Abeta across the blood brain barrier thus preventing detrimental binding within the CNS.[12]

Although amyloid has received much attention with regard to halting the progression of AD it is not the only target for disease modifying therapies. Neurofibrillary tangles which consist of aggregations of hyperphophorylated Tau protein are another pathologic hallmark of AD. Tau binds to and stabilises microtubules which are elongated polymers intrinsic to axonal structure and function. When Tau is hyperphosphorylated it aggregates into tangles with resulting destabilization of microtubules and compromised neuronal function. It is unclear whether neurofibrillary tangles are a cause or consequence of AD but their formation may be a critical link to AD related cell death.[13] Tau phosphorylation is regulated by a balance between multiple kinases and phosphatases and agents which target the kinases responsible for Tau phosporylation are currently under investigation. Glycogen synthase kinase 3 (GSK-3) is a key tau kinase and the use of specific GSK-3 inhibitors, like lithium, could have therapeutic potential in Alzheimer's disease.[14] Several other hypotheses have been proposed to explain the pathogenesis of AD and a number of alternate disease modifying therapies are currently under investigation.

There is also evidence to suggest cerebrovascular disease and AD may have converging pathogenic mechanisms given that many variables traditionally considered as vascular risk factors have now been associated with AD.[15] This, together with laboratory evidence of links between cholesterol and Abeta, has triggered enquiry into the possible usefulness of statins for AD. A small randomised trial of atorvastatin in patients with mild to moderate AD concluded that further investigation with larger multicentre studies was warranted[16] and a recent study which randomised 400 patients between simvastatin and placebo was reported as negative.[17] Additional mechanisms that have been proposed include; abnormalities in proteins regulating the cell cycle, inflammatory mechanisms, oxidative stress, and mitochondrial dysfunction with disruption in neuronal energy metabolism.[6] Neurotrophic factors, critical to the regulation of cell survival and death, are an area of therapeutic interest in AD and strategies to both increase and potentiate nerve growth factor signalling are currently under investigation.[18] Certain compounds postulated to have neuroprotective properties have yielded promising trial data[19] while others have not.[20] Anti-inflammatories remain a focus of interest although interventional studies to date have failed to show significant benefits. The putative advantages of HRT based on observational data has equally not been borne out in randomised controlled trials.[21]

Pathological changes in the brains of AD patients are believed to start 20-30 years before symptomatic disease onset and the increasing use of biomarkers combined with established clinical and neurocognitive risk factors should aid more accurate detection of patients in early and preclinical stages. Concentrations of Tau and Abeta42 in CSF are strongly predictive of the development of AD in patients with Mild Cognitive Impairment (MCI).[22] Radiological advances equally allow earlier evaluation of characteristic structural and functional cerebral changes in areas such as the hippocampus and entorhinal cortex. Detection of AD in these early clinical stages is likely to be of increasing importance as research into disease modifying therapies continues to progress.[23] In the interim the burden of dementia and dementia related illness is set to rise markedly and the implications for the healthcare sector generally and old age psychiatry and geriatric services in particular are significant. Considerable forward plannning and adequate resourcing of services which reflect the needs of our ageing population are required and the time for action is now.

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