

Remembering what's new in Alzheimer's management

Sir,

Having read an article by Ghosh *et al*^[1] on the neuroprotective effects of aspirin on disorders, such as Alzheimer's disease (AD), I wanted to focus on the advances in AD management. Vaccines targeting amyloid-beta (A β) have shown to reduce amyloid burden, demonstrate plaque clearance, and improve cognitive function, but some of them (AN1792) were halted due to the development of meningoencephalitis.

Bapineuzumab, a humanized anti-beta-amyloid monoclonal antibody (to the N-terminus of A β), has shown considerable promise in reducing the cerebral A β burden in AD. It also works on tau protein (demonstrated lower CSF tau protein levels in patients with AD) which, on hyperphosphorylation, results in neurofibrillary tangles of paired helical filaments. It has shown beneficial cognitive effects in AD patients who did not have the ϵ 4 allele of the apolipoprotein E (*ApoE*) gene. Carbon-11-labeled Pittsburgh compound B (11C-PiB) PET (a marker of cortical fibrillar A β load

in vivo) demonstrated that bapineuzumab (0.5, 1, and 2 mg/kg intravenous infusion) for 78 weeks reduced cortical 11C-PiB retention.^[2] Bapineuzumab, however, is bogged down by a dose-limiting (2 mg/kg group) and potentially severe adverse reaction - vasogenic edema and especially in ApoE ϵ 4 carriers its benefit in slowing disease progression is not clear. Solanezumab, another monoclonal antibody (targeting A β 13-28), recognizes some variants of A β that are unrecognized by bapineuzumab and binds to soluble A β . It has documented benefit in neuritic plaques. Similarly ponezumab binds the A β peptide at the C-terminal end and has produced changes in CSF A β levels indicating beta-amyloid removal. Newer monoclonal antibodies targeting A β like gantenerumab, MABT-5102A, as well as an immunoglobulin G2 antibody are in the pipeline showing promise.^[3]

Another potential target is secretase (one of the enzymes required for production of A β from amyloid precursor protein-APP). Secretase inhibitors, nevertheless, interact with several neuronal factors including the notch receptor (involved in cell differentiation) and have poor side effect profile.

Two trials testing semagecestat were stopped because of significant cognitive decline in the control groups. Novel secretase inhibitors (begacestat, BMS-708163, PF-3084014) have shown to decrease A β burden with lesser harmful effects on the notch receptor. Inhibition of β -secretase (β -site APP-cleaving enzyme [BACE1]) is another approach accelerating A β removal. Other classes that stimulate α -secretase leading to non-amyloidogenic processing of APP, such as muscarinic agonists and GABA receptor modulators (etazolate) are currently being investigated.^[3]

NAP (NAPVSIPQ) is an octapeptide that binds to tubulin and prevents disruption of microtubules. It is shown to increase soluble tau, reduce tau hyperphosphorylation, and improve cognitive function in transgenic mice.^[4]

There is evidence that curcumin, a component of turmeric (high in Indian diet and may explain lower AD rate) decreases A β and tau related toxicity by decreasing oxidative stress and DNA damage, attenuating intracellular calcium levels and tau hyperphosphorylation.^[5]

A variety of other mechanisms, such as glycogen synthase kinase-3 inhibition (lithium, lovastatin, thiazolidinones, etc.), antibodies directed at tau, phosphodiesterase-5 inhibition, preventing cAMP-responsive element binding factor (CREB) phosphorylation and drugs, such as latrepirdine (nonselective antihistamine, acetylcholinesterase inhibitor, and NMDA receptor-blocker with mixed results), etanercept (TNF- inhibitor) are being investigated for therapeutic benefit in AD.

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