Alzheimer’s disease in England and Wales, for whom antidepressant drugs are now unavailable on the NHS after the pronouncement from NICE?

Third, is dimebon a drug looking for an indication? Testing readily available drugs makes economic sense, and drugs developed in this way will probably be cheaper than newly developed compounds. Other drugs with a sound rationale for use in Alzheimer’s disease should be trialled and the most made of existing technologies. For instance, the tetracycline minocycline has several biological actions that affect amyloid and attenuates learning and memory deficits in animal models of Alzheimer’s disease.8

Current treatments for Alzheimer’s disease are moderately effective, but not for every patient. Addition of treatment options is good news for patients and clinicians—it promotes choice and offers the possibility of bespoke treatment packages which maximise the chances of a response. Doody and colleagues’ trial shows that dimebon is better than placebo (which is no mean feat considering the positive placebo responses in dementia). Further work will establish its efficacy (or otherwise) in addition to, or compared with, established treatments, and indeed a second phase III trial has recently been announced.9

*Alistair Burns, Robin Jacoby

Will anti-amyloid therapies work for Alzheimer’s disease?

In today’s Lancet, Clive Holmes and co-workers1 report a 6-year prospective follow-up of 80 patients entered into the first phase I clinical trial of active immunisation against amyloid-β42 (Aβ) as a treatment for Alzheimer’s disease. Their report contains both expected and unexpected results. As had been widely predicted from the initial animal studies,2,3 cortical Aβ loads were lower in patients who were immunised than in the control group. Equally predictably, patients with the biggest antibody response had more extensive Aβ removal. Unexpectedly, however, there was no statistically significant evidence for improvement in cognitive function or survival, even in patients with high antibody titres. Indeed, several of those who had near complete plaque removal at autopsy had clinically deteriorated to severe dementia.

This study will undoubtedly evoke concern that anti-amyloid therapies will be ineffectual, and that two decades of experimental work supporting their development were spent barking up the wrong tree. Indeed, the theory that the accumulation of Aβ in the brain is central to the pathogenesis of Alzheimer’s disease has been controversial since Glenner first expounded it in 1984.4 Several important observations can be drawn from the present study. The conclusions do not lead to complete abrogation of a major role for Aβ in the pathogenesis of Alzheimer’s disease, nor should they lead to the premature abandonment of research into therapies directed against Aβ.

The first observation is that the vaccine clearly had a biological effect (on brain amyloid). This provides proof of principle that anti-amyloid therapies can influence cerebral Aβ deposition.

The second observation is that the continued clinical deterioration and eventual death of patients after...
effective vaccination clearly diminishes the hope that anti-amyloid therapies will bring symptomatic Alzheimer’s disease to a dramatic halt. However, to conclude that the vaccine had no effect would be premature. The study was not powered to detect small differences in the rates of progression. There were also many drop-outs during follow-up. Finally, whether vaccination changed the concentrations of the putatively neurotoxic Aβ oligopeptides is unclear.5

The third observation, which the authors have reported previously, is that other features of the disease (eg, the accumulation of tau) remain even in areas of amyloid clearance. Data from familial cases, in which people who are at risk can be identified, reveal that the accumulation of Aβ precedes the onset of symptoms by decades6,7 but sets in motion a series of downstream events that also injures neurons. The present report therefore raises concern that these secondary events (which include upregulation of inflammatory responses, misprocessing of tau, and changes in free-radical and calcium metabolism) cause a self-perpetuating injury. Once started, these secondary processes might be unaffected by the removal of the primary injury induced by Aβ accumulation. If so, there may be only a narrow window of opportunity for anti-Aβ monotherapies.

Four lines of experimental evidence support the hypothesis of an Aβ-mediated initiation and then exacerbation and propagation by other factors. First, in human beings genetically at risk for Alzheimer’s disease (eg, carriers of PS1 mutations, patients with trisomy 21),8 the earliest feature is the cerebral accumulation of Aβ, which begins years before symptoms.6,9 Second, animal models reveal that co-expression of mutant amyloid precursor protein and tau transgenes augments both neuronal dysfunction and pathology,10 and these can be attenuated by reducing tau expression.11 Third, under certain circumstances tau pathology is self-propagating.12 Finally, studies in human beings and animals reveal that inflammation is a feature of Alzheimer’s disease, and that inflammation damages neurons.13

What are the next steps? Although the current study suggests that anti-Aβ vaccination (and perhaps other anti-Aβ therapies) may not completely cure symptomatic Alzheimer’s disease, removal of the initial motor for the disease might slow progression. Further clinical trials are therefore necessary, and must be powered to detect even small changes in rates of progression. More importantly, it may be time to change treatment models from curative to preventive. Perhaps the correct use of anti-amyloid monotherapies will be as a prophylactic given long before the onset of symptoms in people at risk of the disease (as determined by exposure to genetic and environmental factors). Additionally, researchers need to better characterise the secondary neuron-damaging pathways, and devise new therapies to address them. As with many chronic disorders, future treatment of Alzheimer’s disease will probably need a pluralistic approach.

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References

Dementia: psychosocial interventions for family caregivers

Caring for a family member with dementia increases the caregiver’s risk for depression, chronic illness, and even death. In addition to the physical and emotional tolls, families incur significant monetary costs, which increase with the progression of functional and cognitive impairment and contribute to the strain experienced by caregivers.

Over the past 25 years, evidence-based interventions to decrease the burden of caring for a person with dementia have been identified. The most promising approaches combine education, skills training, treatment of depression, and family support, but the costs versus benefits and long-term outcomes of these interventions remain largely unknown. Two recent articles address these issues.

The first is a groundbreaking randomised investigation by Linda Nichols and colleagues of the incremental cost-effectiveness ratio of a psychosocial intervention delivered to caregivers in the Resources for Enhancing Alzheimer’s Caregivers Health (REACH II) project. Cost-effectiveness was analysed in individuals from the Memphis REACH site: 46 participants were randomised to receive a caregiver intervention of nine individual in-home counselling sessions followed by three telephone calls, and 46 were randomised to receive a control condition of two brief check-in telephone calls. Detailed costs of providing the intervention were tracked over 6 months, and benefits were calculated on the basis of hours spent by the family caregiver providing direct care. After 6 months, participants in the intervention group had decreased their caregiving hours by 1·5 h per day, while the caregiving hours in the control group were unchanged (the result was statistically significant). The total cost for this outcome was less than US$5 per caregiver per day, and the incremental cost-effectiveness ratio was financially positive. Furthermore, the REACH II global-outcome assessment (which included evaluation of burden, emotional wellbeing, self care, social support, and care-recipient behavioural problems) was significantly better in the intervention group than in the controls, which indicates additional non-monetary benefits of the intervention in terms of the caregivers’ and recipients’ quality of life.

The second article is from a pioneering investigation, the New York University Caregiver Intervention (NYUCI), which began in 1987. Over the past 20 years, this randomised trial of a psychosocial family-support programme to a usual-treatment control group has shown that six sessions of individual and family counselling, followed by weekly availability of a support group, and ad-hoc counselling are significantly more effective than usual care in decreasing caregivers’ depression, improving self-rated health, and delaying care-recipient institutionalisation. The latest findings

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