Losartan to slow the progression of mild-to-moderate Alzheimer's disease through angiotensin targeting: the RADAR RCT

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Declared competing interests of authors: Patrick G Kehoe has previously undertaken advisory work for Novartis in the development and use of dual-acting inhibitors of angiotensin receptors and neprilysin for the treatment of different forms of cardiovascular disease. He is also an unfunded co-investigator of the ongoing Alzheimer's Association (USA)-funded HEART Phase 1b study of telmisartan and its use as an intervention against the renin–angiotensin system in non-dementia African Americans at risk of developing dementia by parental history. Carole H Sudre was a recipient of an Alzheimer's Society Junior Fellowship (AS-JF-17–011) during the conduct of the study.

J Athene Lane is a co-director of a Clinical Trials Unit (CTU) that receives National Institute for Health Research (NIHR) CTU infrastructure support and is a member of the NIHR CTU Standing Advisory Committee. Peter Passmore received honoraria for talks on a variety of antihypertensive medications over a number of years. This included losartan (losartan potassium; Teva Pharmaceuticals Industries Ltd, Petah Tikva, Israel) and similar medications. Nick Fox reports personal fees from Biogen Inc. (Cambridge, MA, USA), GE Healthcare (Chicago, IL, USA) and Lilly (Hampshire, UK) and Roche (Roche Diagnostics, Hertford, UK), outside the submitted work. Yoav Ben-Shlomo has received funding from the NIHR HTA programme as a co-investigator of the CHolinesterase Inhibitors to prEvent Falls in Parkinson's Disease (CHIEF-PD) trial. He is a member of the NIHR Parkinson's Portfolio Development Group (PDG) and the Care, Implementation and Public Health Grant Advisory Board for the Alzheimer's Society and is the cohort representative for the Caerphilly Prospective Study (CaPS) that is part of the Dementia Platform UK collaboration.

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Scientific summary

The RADAR RCT

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Scientific summary

Background

Despite the predicted rise and the huge social impact of Alzheimer's disease, there are still only limited symptomatic treatments and no disease-modifying interventions. Clinical trials over the past 20 years, which have focused almost exclusively on reducing the production of or clearing amyloid-β, have unfortunately not met with any success. The hypothesis of these studies is that interventions against amyloid-β will serve as means to slow or halt the progression of numerous pathological processes that contribute to neurodegeneration and progressive cognitive decline. Improvements to health care worldwide have contributed greatly to improved welfare and longevity in many countries. However, this observed increased life expectancy globally has meant that the numbers of people who are at increased risk of developing dementia has also increased. There is therefore an urgent need to better understand and identify the disease processes that accelerate the disease pathology of and the cognitive decline involved in dementia, and particularly so in Alzheimer's disease, which represents the largest cause of dementia. This should include consideration of other biochemical mechanisms, beyond, but not to the exclusion of, what has been the traditional thinking of the importance of amyloid-β and tau protein pathology in the development and progression of Alzheimer's disease.

Mid-life hypertension is a modifiable risk factor for Alzheimer's disease. Vascular dysfunction, including reduced cerebral blood flow and blood–brain barrier breakdown, is a major but as yet less well-researched facet of disease pathology associated with cognitive decline in Alzheimer's disease. Cerebrovascular damage is also present in the majority of patients with neuropathologically confirmed Alzheimer's disease. Disease progression modelling, based on clinical imaging and recent longitudinal clinical observation studies, namely the Alzheimer's Disease Neuroimaging Initiative, has more recently indicated that vascular dysfunction is one of the earliest pathological features of Alzheimer's disease. Furthermore, vascular dysfunction maps to regional changes in disease pathology, while also serving as a strong independent marker of cognitive decline in Alzheimer's disease.

The conceptualisation of the renin–angiotensin system wherein this project is based has also evolved in recent years, particularly in relation to its likely involvement in the development and pathogenesis of Alzheimer's disease. Currently, what is now more commonly called the classical renin–angiotensin system, the main mechanism attributed to blood pressure regulation and vascular function through the action of angiotensin II signalling, has repeatedly been shown to be relevant to the pathogenesis of Alzheimer's disease. Since our original research with human post-mortem brain tissue that showed that the classical renin–angiotensin system was significantly overactive and is closely associated with disease pathology and cognitive decline in Alzheimer's disease, we have found that the regulatory renin–angiotensin system, which works to counter angiotensin II signalling by enzyme-mediated degradation of angiotensin II, is also significantly inhibited in Alzheimer's disease. Several studies have also now shown that antihypertensive medications that directly target the classical renin–angiotensin system delay the onset and reduce the incidence of Alzheimer's disease, as well as reducing disease pathology, to a greater extent than other anti hypertensive treatments that do not act on this system. Moreover, of the two common groups of renin–angiotensin system-acting medications, those that inhibit the signalling of angiotensin II (via angiotensin II type 1 receptors) rather than its synthesis (angiotensin I converting enzyme inhibitors) have consistently been shown to perform better.

These findings have also been supported in several in vivo studies involving murine models of Alzheimer's disease cognitive and neurodegenerative pathology, where various angiotensin II type 1 receptor antagonists, also known as sartans, have consistently improved cognitive impairment and neuropathological hallmark outcomes. Indeed, the importance of the classical renin–angiotensin system

and excessive angiotensin II signalling has also been supported indirectly by a recent number of studies in murine models of Alzheimer's disease and various forms of central nervous system injury. These studies also show that the loss of the regulatory renin–angiotensin system, namely angiotensin I converting enzyme 2 activity [which degrades angiotensin II and converts it to angiotensin (1–7)], or angiotensin (1–7) signalling via the Mas receptor (that has functions that oppose those of angiotensin II type 1 receptor), is associated with disease pathology and overactivity in the classical renin–angiotensin system. Together, this growing body of evidence has continued to reinforce the need to investigate the detrimental role of angiotensin II in the development and progression of Alzheimer's disease. This detrimental role, attributed to angiotensin II signalling, has been suggested to adversely affect vascular function in Alzheimer's disease and contribute unfavourably to numerous pathological processes commonly reported in Alzheimer's disease (e.g. inflammation, oxidative stress, reduced cholinergic function, increased amyloid-β and tau-related pathologies). Furthermore, this study is designed to explore the possibility of intervening in angiotensin II signalling through the use of existing 'repurposable' sartans, whereof losartan is the prototype, that are more commonly used to treat hypertension and some other peripheral forms of cardiovascular dysfunction.

Objectives

The Reducing Pathology in Alzheimer's Disease through Angiotensin TaRgeting (RADAR) trial investigated whether or not taking the antihypertensive drug angiotensin II type 1 receptor antagonist losartan, in addition to normal care, would slow the progression of Alzheimer's disease when compared with a placebo. This study intended to investigate this in people with a diagnosis of mild-to-moderate Alzheimer's disease who, as per the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria, either had hypertension and had not been previously exposed to the intervention or were normotensive. Normotensive participants were included to explore whether or not the inhibition of angiotensin II signalling might have effects that were independent of any prior hypertension and hence widen the potential treatment benefits to all Alzheimer's disease patients.

Design

This was an individually randomised, multicentre randomised controlled trial with follow-up from randomisation (baseline) at 14 days and at 3, 6, 9 and 12 months. Participants underwent a RADAR-specific magnetic resonance imaging protocol at baseline and at 12 months, having successfully completed a preceding open-label pre-randomisation phase of 4 weeks. Various secondary outcome data were also collected from participants and their study companions at baseline and at 6 and 12 months, whereas secondary outcome magnetic resonance imaging data were also collected on a subset of the study population at baseline and 12-month follow-up.

Patient and public involvement

The original design of the study was explored with participants and carers, who provided feedback that prompted the inclusion of the open-label phase. Similarly, feedback was sought on the study information sheets to be shared with participants and study partners at the outset of the study. In addition, later in the study, as part of a more defined qualitative study among a wider group of representatives, feedback was sought on, and endorsement subsequently given of, further proposed revisions to the study information sheets, which were made to aid final recruitment for the study.

Setting

Twenty-three NHS hospital trusts in England, Scotland and Northern Ireland where people with Alzheimer's disease are routinely diagnosed and treated.

Participants and study criteria

Participants with a diagnosis of mild-to-moderate Alzheimer's disease were required to meet all of the following conditions to be eligible:

- aged $\geq$ 55 years
- have the capacity to consent for themselves as judged by a member of a recruiting research team with appropriate training and experience
- have a Mini Mental State Examination score of 15–28 at the consented eligibility assessment
- have a modified Hachinski Ischaemic Score of $\leq$ 5
- have had a previous computerised tomography, single-photon emission computed tomography, or magnetic resonance imaging scan that was consistent with a diagnosis of Alzheimer's disease
- have a study companion who was willing to participate in the study.

Participants were ineligible if any of the following conditions were met:

- They were currently receiving angiotensin I converting enzyme 1 inhibitors; angiotensin II type 1 receptor antagonists (e.g. losartan), the renin inhibitor aliskiren or potassium-sparing diuretics; or had a known intolerance or renal problems with angiotensin I converting enzyme 1 inhibitors or sartans from previous use.
- They were medically unsuitable for, or unwilling to undergo magnetic resonance imaging or had a primary neurodegenerative disease or potential cause of dementia other than Alzheimer's disease.
- They had clinically significant low blood pressure (systolic < 115 and diastolic < 70 mmHg) or had uncontrolled or untreated high blood pressure (systolic > 160 and diastolic > 110 mmHg), or experienced at the eligibility assessment visit a fall in blood pressure on standing of > 20/10 mmHg associated with clinically significant symptoms or a fall > 30/15 mmHg.
- They had a previous cerebrovascular accident and had resultant clinically significant residual impairment; however, transient ischaemic attack was not an immediate basis for exclusion.
- In addition, pre-existing hypertrophic cardiomyopathy, clinically significant aortic valve stenosis, impaired renal function (measured by estimated glomerular filtration rate of < 30 ml/minute/1.73 m^2), and evidence of liver disease or significant liver function test derangement (aspartate transaminase/alkaline phosphatase/bilirubin more than two times the upper limit of normal) were excluding factors, as were levels of potassium > 6.0 mmol/l taken from a non-haemolysed sample at the eligibility visit.
- Because of the known properties of the intervention, women who had not yet reached the menopause (defined as not having had a menstrual period in the previous 12 months), tested positive for pregnancy or were unwilling to take a pregnancy test prior to trial entry, or were unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial, were not eligible.
- Furthermore, participants who had any severe coincident medical disease (e.g. a severe comorbidity or terminal condition) or other factors that would inhibit their compliance with the study medication or adherence to study follow-up schedule were ineligible. In addition, there needed to be a period of 6 months before commencing RADAR if they had participated in a previous clinical trial of an investigational medicinal product study.

Intervention

Participants were randomised to either overencapsulated 100 mg of losartan (Teva Pharmaceuticals Industries Ltd, Petah Tikva, Israel) daily or encapsulated placebo to match for 12 months. The therapeutic dose was achieved in both the open-label and the randomised phase after a 1-week upwards titration on 25 mg of losartan (Teva Pharmaceuticals Industries Ltd).

Main outcome measures

The primary outcome was based on assumption of therapeutic benefit being a clinically meaningful attenuation of brain atrophy with an absolute difference between trial arms of at least 3.8 ml/year in total brain volume between baseline and 12 months post randomisation, measured using volumetric magnetic resonance imaging [T1-weighted magnetisation-prepared rapid-gradient echo (T1 MPRAGE)]. Secondary outcomes included (1) rates of Alzheimer's disease progression as assessed by the Alzheimer's Disease Assessment Scale – Cognitive Subscale, Mini Mental State Examination and Neuropsychiatric Inventory; where facilities allowed, additional magnetic resonance imaging sequences to allow the measurement of (2) white matter hyperintensity volume [T2-weighted – fluid-attenuated inversion recovery (T2-FLAIR MRI)] and (3) cerebral blood flow by arterial spin labelling; (4) change in blood pressure; (5) association between magnetic resonance imaging measures of atrophy and measures of cognitive decline; and (6) level of drug compliance and tolerability.

Results

A total of 261 participants entered the open-label study, of whom 211 (81% of those consented) were entered into the main study and randomised to the intervention arm ($n = 105$) or the placebo ($n = 106$) arm. The baseline characteristics were similar in both trial arms. A total of 197 participants completed the study (93% retention) and primary outcomes were recovered from 171 participants (81% recovery rate), resulting in a statistical power of 82%, which is a negligible difference from the 84% that the original design of the study aiming to recruit 228 participants was intended to have. There was no therapeutic benefit with respect to the primary outcome. The difference in brain volume was consistent with chance (–2.79 ml, 95% confidence interval –6.46 to 0.89 ml; $p = 0.19$). There were no obvious benefits recorded in the secondary outcome measures, including the Alzheimer's Disease Assessment Scale – Cognitive Subscale, the Neuropsychiatric Inventory and measures of quality of life (Dementia Quality of Life Measure) and activities of daily living (Bristol Activities of Daily Living Scale). There were no indications of intervention-based differences in the subsets of the participants from whom it was possible to collect magnetic resonance imaging data on cerebral blood flow and white matter hyperintensities.

Conclusions

Interest in the involvement and role of the renin–angiotensin system in Alzheimer's disease continues to grow. Yet, to our knowledge, the RADAR trial is the first randomised controlled intervention trial to formally test the angiotensin hypothesis in a formalised population of clinically diagnosed Alzheimer's disease participants. This robustly designed study, which had demonstrably effective randomisation and a favourable participant retention rate, unambiguously shows that the prototype angiotensin II type 1 receptor antagonist losartan did not alter brain atrophy by at least 3.8 ml/year in Alzheimer's disease, a finding that we deemed a priori to be clinically meaningful and indicative of progression. We also found no significant evidence from any of the secondary outcome measures that losartan offered a therapeutic benefit. Our study does not exclude the possibility that the duration of treatment, the greater severity of disease among the participants, or the extent to which the drug penetrates the

brain are factors in not detecting an effect on our primary and secondary outcomes. Future studies that are undertaken could note these limitations, either using losartan once more or using another related angiotensin II type 1 receptor antagonist about which there may be less doubt as to its penetration of the blood–brain barrier. Similar consideration could be given to the suitability of including milder diagnostic groups such as those with mild cognitive impairment, who may be followed up for at least 18–24 months, as is now recommended by the regulatory bodies, to investigate disease modification. These may help to ensure that the angiotensin hypothesis can be tested more comprehensively and not prematurely discounted on the basis of this study.

Trial registration

This trial is registered as ISRCTN93682878 and EudraCT 2012-003641-15.

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