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Reducing pathology in Alzheimer's disease through angiotensin targeting

Submission date	Recruitment status	[X] Prospectively registered
10/09/2013	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/09/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
26/10/2021	Nervous System Diseases	

Plain English summary of protocol

Background and study aims
Alzheimer's disease profoundly affects memory and brain function in older individuals. The disease starts slowly and worsens to the extent that people eventually need 24-hour care - a heart-breaking, exhausting and often costly reality for family and health services. With an ageing population, Alzheimer's disease care provision needs will increase with an impact on NHS healthcare costs. In this study we will investigate whether losartan, a well-tolerated blood pressure drug, can complement current therapies for Alzheimer's disease. We believe losartan will slow down the progression of Alzheimer's disease by improving brain blood flow and altering chemical pathways that affect abnormal proteins that accumulate in Alzheimer's disease and cause brain shrinkage. This study tests the effect of losartan on brain tissue changes in patients diagnosed with Alzheimer's disease.

Who can participate?
Patients aged 55 and over who have mild to moderate Alzheimer's disease and are able to travel to one of 20-25 participating sites across the UK

What does the study involve?
Participants are randomly allocated to receive either losartan or a placebo (dummy tablet) once a day for 12 months. In addition to memory tests, brain imaging is used to measure whether losartan reduces shrinkage (atrophy) in brain areas that are strongly linked with reduced memory function and improves brain blood flow.

What are the possible benefits and risks of participating?
Losartan may help to slow the progression of Alzheimer's disease, but it must be stressed that there is no guarantee. Possible risks include experiencing side-effects from the study drug, which include dizziness, low blood pressure, feeling tired or weak, and too little sugar and too much potassium in the blood.

Where is the study run from?
The study is a collaborative project led by NHS North Bristol Trust, in collaboration with the University of Bristol, Bristol Randomised Trial Collaboration (UKCRC Registered Clinical Trials Unit).

When is the study starting and how long is it expected to run for?
March 2013 to May 2019

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Prof. Patrick Kehoe
Patrick.Kehoe@bristol.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Patrick Kehoe

Contact details
RADAR Coordinating Centre
School of Social and Community Medicine
Faculty of Health Sciences
University of Bristol
Oakfield House
Oakfield Grove
Bristol
United Kingdom
BS8 2BN
+44 (0)117 331 3317
Patrick.Kehoe@bristol.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2012-003641-15

Protocol serial number
15071

Study information

Scientific Title
Reducing pathology in Alzheimer's disease through angiotensin targeting - the RADAR trial: a phase II, two-arm, double-blind, placebo-controlled, randomised trial to evaluate the effect of losartan on brain tissue changes in patients diagnosed with Alzheimer's disease

Acronym
RADAR

Study objectives
Alzheimer's disease (AD) profoundly affects memory and brain function. It is a slow progressive disease that can last for a number of years - a heartbreaking, exhausting and often costly reality for family and health services. With an ageing population, AD health care provision needs will significantly rise. Existing treatments only temporarily treat specific imbalances in the brain but as yet there is no cure for AD. Losartan, a well-tolerated blood pressure drug, blocks a chemical pathway called angiotensin II which prevent the release of vital memory chemicals in the brain. Losartan improves memory problems in mice designed to have Alzheimer's features and in people given chemicals to temporarily affect their memories. People who have previously taken losartan, have lower risk of developing AD compared to other blood pressure drugs. These drugs may also slow the rate of deterioration in patients with Alzheimer's. This multi-centre clinical trial will investigate if losartan could complement current treatments for AD. We believe losartan will slow down the progression of AD by improving brain blood flow and altering chemical pathways that cause brain cell damage, brain shrinkage and memory problems in AD. Brain images will measure if losartan reduces brain shrinkage, which we know is strongly linked with reduced memory function. Blood samples taken within this study will be analysed to see whether losartan changed proteins that may be predictive of rates of disease progression. RADAR will offer great value for money if this cheap (3-4p per day) well tolerated drug is found to be beneficial in AD. RADAR will provide the requisite evidence needed to justify a much larger multicentre trial that will be needed to provide the final proof of losartan's benefit in AD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East Wales Research Ethics Committee C, 19/02/2013, ref: 12/WA/0338

Study design
Interventional phase II double-blind placebo-controlled randomised treatment trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Dementias and Neurodegenerative Diseases Research Network; Subtopic: Dementia; Disease: Dementia

Interventions
Group I: Placebo
Group II: Losartan

During the open-label phase losartan will be given at 25mg dose for 7 days and then 100mg for 7 days, followed by placebo for 4 days up to two weeks prior to the first MRI scan. Following the MRI, if suitable to proceed to the randomised phase, participants will be randomly allocated to receive either losartan at 25mg for 7 days followed by 100mg for the remainder of the trial, or placebo for the remainder of the trial. During the randomised phase patients will not know whether they are taking losartan or placebo.

Duration of intervention: Once a day for 12 months
The total follow up period is 12 months and at least 4 days (to allow a washout period after finishing the trial treatment before the final MRI).

The sample size will be recruited from at least 20 sites across the UK over 2 years which currently equates to approximately 12 patients per site at a monthly recruitment of 1 patient per month.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Losartan

Primary outcome(s)
Change in whole brain volume, measured using volumetric MRI (vMRI); Timepoint(s): after 12 months of treatment after randomisation

Key secondary outcome(s))
1. Rates of AD progression, assessed by changes in cognitive assessments, measures of activities of daily living and quality of life
2. Change to the level of CBF, measured by arterial spin labelling (ASL) techniques
3. Change to the level of white matter hyperintensities, measured by MRI
4. Change in BP
5. Measure of association between MRI measures of atrophy and rate of cognitive decline
6. Level of drug compliance and tolerability (particular consideration to non-hypertensive patients tolerability), although past studies report that drop out and side effects are not a major problem

Completion date
31/07/2019

Eligibility

Key inclusion criteria
1. Age ≥55 years
2. A Mini Mental State Examination (MMSE) score of 18-28 or Montreal Cognitive Assessment (MoCA) of 12-24
3. A modified Hachinski score (56) of 5 or less
4. A previous CT or MRI scan consistent with a diagnosis of AD
5. The presence of an informant who is willing to participate in the study
6. Capacity to consent for themselves as judged by a member of the research teamwith appropriate training and experience

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
55 years

Sex
All

Total final enrolment
261

Key exclusion criteria
Patients will be excluded/ineligible if they have any of the following:
1. Receiving ACE-Inhibitors; AT1RAs, aliskiren or potassium sparing diuretics
2. Known intolerance to sartans
3. Medically unsuitable for, or unwilling to have, an MRI scan
4. Consistent baseline BP of <115/70 mmHg or >160/110 mmHg
5. A fall in BP on standing of >20/10 mmHg associated with clinically significant symptoms or a fall >30/15 mmHg
6. Previous cerebrovascular accident (CVA), with significant residual impairment (Transient Ischaemic Attack (TIA) is NOT an exclusion)
7. Hypertrophic cardiomyopathy; or significant aortic valve stenosis
8. Estimated creatinine clearance of < 30 mL/min/1.73m2, or previous severe renal impairment with a sartan or ACE inhibitor
9. Evidence of liver disease or significant LFT derangement (Aspartate transaminase (AST)/ Alkaline Phosphatase (AP/ALP)/ Bilirubin greater than 2 x upper limit of normal) in the previous 12 months
10. Primary neurodegenerative diseases or potential causes of dementia other than AD.
11. Females who have not yet reached the menopause (defined as having a period in the previous 12 months) who test positive for pregnancy, are unwilling to take a pregnancy test prior to trial entry, or are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial
12. Any severe co-incident medical disease, or other factor inhibiting compliance with the study medication or follow up schedule e.g. participant unlikely to survive the trial follow up period due to a terminal comorbid condition
13. Participation in a previous CTIMP within 6 months of RADAR trial entry
14. Severe hippocampal atrophy as identified at baseline (or previous) MRI scan according to the Sheltens Scale

Date of first enrolment
31/10/2013

Date of final enrolment
17/05/2018

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Bristol
Bristol
United Kingdom
BS8 2BN

Sponsor information

Organisation
North Bristol NHS Trust (UK)

ROR
https://ror.org/036x6gt55

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		20/11/2021	26/10/2021	Yes	No
Protocol article	protocol	01/05/2018		Yes	No
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes