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# A study examining the effect of etanercept on inflammation in the brain

**Submission date**
07/05/2015

**Recruitment status**
No longer recruiting

**Registration date**
23/06/2015

**Overall study status**
Completed

**Last Edited**
11/08/2022

**Condition category**
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Mild cognitive impairment (MCI) is a condition where there has been a decline in emotional and intellectual (cognitive) abilities such as memory or thinking, but these changes are not severe enough to interfere with normal daily life. Some patients with MCI will go on to develop Alzheimer's disease (AD), a type of dementia which causes problems with memory, thinking and behavior due to the gradual death of brain cells. It is not known what causes a person with MCI to go on to develop AD because the cause of AD is unknown. There is some evidence to suggest that inflammation occurs in the brain of people with AD, which damages the brain cells and may be responsible for some of the symptoms of AD. It is possible that the presence of inflammation in the brain may play a role in the progression of MCI to AD. Etanercept is a drug commonly used to treat inflammation in certain diseases, such as rheumatoid arthritis and other inflammatory diseases of the joints. Etanercept works by blocking the action of a certain protein in the body that causes inflammation. Etanercept may indirectly reduce inflammation in the brain by reducing inflammation in the body, which may help to prevent damage and death of brain cells and progression to AD. The aim of this study is to see whether etanercept can reduce the amount of inflammation in the brain of a person with MCI. The study will also see whether reducing inflammation in the brain decreases the likelihood that a person with MCI will progress to having AD within a set time period.

Who can participate?
Adults aged 50-90 diagnosed with MCI due to AD.

What does the study involve?
Participants are randomly allocated into one of two groups. Those in group 1 (intervention group) are given a 50mg injection of etanercept once a week for 1 year. Those in group 2 (control group) are given a 'dummy' (placebo) injection once a week for 1 year. All participants have positron emission tomography (PET) scans of their brain, provide blood samples and complete questionnaires.

What are the possible benefits and risks of participating?
This study will enable patients with MCI, through the use of a type of brain scanning not currently available on the NHS, to get a more accurate prognosis on the likelihood of them

developing AD within the next 18 months. Also, this study is using a treatment intervention that is already licensed and is in widespread clinical use in an elderly population, therefore there are no specific risks associated with participating in this study.

Where is the study run from?
1. Memory Assessment & Research Centre (UK)
2. Memory Clinic (UK)

When is the study starting and how long is it expected to run for?
September 2015 to November 2017

Who is funding the study?
1. European Union
2. Alzheimer’s Society (UK)
3. Alzheimer's Drug Discovery Foundation (USA)

Who is the main contact?
Prof C Holmes
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# Contact information

### Type(s)
Scientific

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# Additional identifiers

### EudraCT/CTIS number
2015-002145-63

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers

INMiND-02

# Study information

### Scientific Title
A double-blind, placebo-controlled study of the effect of a TNFα a inhibitor, etanercept (Enbrel), on microglial activation in amyloid PET positive patients with mild cognitive impairment due to Alzheimer's disease-intermediate likelihood

### Study objectives
Study hypothesis:
In mild cognitive impairment (MCI) due to Alzheimer's disease (AD), systemic inflammation and elevated systemic levels of TNFα cause partially activated, or primed, microglial cells, to become fully activated, which can be modulated by the administration of a peripheral TNFα inhibitor, etanercept.
Study question:
Will the administration of a peripheral TNFα inhibitor, etanercept, over a 12 month treatment period, reduce microglial activation in patients with MCI due to AD-intermediate likelihood, and reduce cognitive and behavioural decline?

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
NRES Committee South Central - Hampshire A, 26/08/2015, ref: 15/SC/0435

### Study design
Multi-centre randomised double blind placebo controlled study

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

### Study setting(s)
Community

### Study type(s)
Prevention

### Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

### Health condition(s) or problem(s) studied
Mild cognitive impairment (MCI) due to Alzheimer’s disease (AD).

### Interventions

Participants in the study will be given either:
1. A 50mg once weekly subcutaneous injection of etanercept for 52 weeks
2. A subcutaneous injection of the placebo

## Intervention Type
Drug

## Phase
Phase II

## Drug/device/biological/vaccine name(s)
Etanercept

## Primary outcome measure
Ascertain the change in microglial activation on [11C] (R)-PK-111-95 PET scans from base-line to the final imaging visit in the treatment group compared to the placebo group. The imaging related outcome measures (microglial activation and cortical amyloid load) will be done at the screening image visit and at the final imaging visit, one week before the end of the treatment period.

## Secondary outcome measures
The neuro-psychological testing related outcome measures will be done at base-line, Visit (V) 1, and repeated at V3 (13 weeks into treatment period), V4, (26 weeks), V5 (39 weeks), V6, (52 weeks on treatment, end of treatment period). Procedures carried out: PET scans x 4; MRI scans x 2; CXR x 1; blood tests x 10; urine tests x 8; ECG x 1, and as required; optional LP x 1; study injection, sub-cutaneous, x 53; physical examination x 8; neuro-psychological testing x 6:
1. Ascertain the change in the primary cognitive outcome measure, the Montreal Cognitive Assessment (MOCA) from baseline to final treatment visit
2. Ascertain the change in cortical amyloid load on AMYVID PET scans from base-line to the final imaging visit
Exploratory objectives:
1. Ascertain the change in the first of the exploratory cognitive outcome measures, the Repeatable Battery for the Assessment of Neuro-psychological Status, (RBANS), from baseline to final treatment visit
2. Ascertain the change in the second of the exploratory cognitive outcome measures, the Free and Cued Recall Selective Reminding Test with Immediate Recall (FCSRT-IR), from baseline to final treatment visit
3. Ascertain the change in the Cornell Scale score from base-line to final treatment visit
4. Ascertain the change in the behavioural assessment the Apathy Inventory from baseline to final treatment visit
5. Ascertain the change in the behavioural assessment the Apathy Clinicians Diagnostic Criteria from baseline to final treatment visit
6. Ascertain the change in the levels of plasma markers of neuro-inflammation (pro and anti-inflammatory cytokines: IL-1; IL-6, TNF-α, IFN-γ, IL-4, IL-10, IL-12, IL-13; CRP, and TGF-β). The neuro-inflammatory markers for the neuro-inflammatory explorative outcome measures will be taken at the two imaging visits and at V3, V4, and V5.
7. Study the relationship between the changes in the levels of plasma markers of neuro-inflammation (IL-1; IL-6, TNF-α, IFN-γ, IL-4, IL-10, IL-12, IL-13; CRP, TGF-β) and changes of microglial activation on PK1195 PET scan, and clinical outcomes
8. Study the relationship between the changes in the levels of plasma markers of neuro-

inflammation (IL-1; IL-6, TNF-α, IFN-γ, IL-4, IL-10, IL-12, IL-13; CRP, TGF-β) and changes of microglial activation on [11C] (R)-PK-111-95 PET scan, the change in cortical amyloid load on AMYVID PET scans and clinical outcomes
9. Examine the penetration of etanercept across the blood brain barrier in patients with mild cognitive impairment due to AD
10. Optional lumbar puncture to examine the effects of etanercept on inflammatory markers in the cerebrospinal fluid (CSF) of patients with mild cognitive impairment due to AD, and the relationship with clinical outcomes. CSF will be collected from 4 to 10 patients at V4, +/- two weeks. Tests will be done on the cerebro-spinal fluid samples to measure levels of etanercept, to determine cytokine levels (Cytokine assays using MESOSCALE elisa's), and possibly to determine levels of amyloid protein

### Overall study start date
01/04/2015

### Completion date
28/02/2018

# Eligibility

### Key inclusion criteria
1. Capacity to make an informed decision as to whether they would like to take part in this specific clinical research trial
2. Male or female aged between 50-90
3. Minimum 7 years formal education
4. Be able to hear, read, write and perform study neuro-psychological tests in English
5. Adequate visual and auditory acuity to allow neuro-psychological testing, based on the research clinician’s judgement
6. Fulfil the NIA-AA criteria for the diagnosis of MCI due to AD at the screening visit. Participants must have a MOCA score of 19 to 25 inclusive at screening, at the discretion of the Principal Investigator
7. Have a study partner who spends at least eight hours a month with the subject. The study partner may be a close friend or a neighbour and not necessarily a close relative, spouse, son or daughter, and should be present at all visits. Every effort should be made to ensure that the study partner will be the same throughout the study. If it becomes necessary for the study partner to change, the new study partner must satisfy the requirements of this criterion and the change of study partner must be clearly documented
8. Been on a stable medication regime for more than 3 months prior to screening
9. Women of child bearing potential must use adequate contraception to prevent pregnancy and continue its use for at least four weeks after the last study dose

### Participant type(s)
Patient

### Age group
Adult

### Sex
Both

### Target number of participants

## Key exclusion criteria

1. Inability or refusal to provide informed consent from subject or study partner
2. Absence of study partner
3. Unlikely to cooperate in the study, not able to attend scheduled examinations and visits, or not able to follow study instructions
4. Participation in another study with administration of any investigational drug in the previous 3 months or already enrolled in another study

Medical and therapeutic criteria:

1. Parkinson's disease, Dementia with Lewy Bodies or clinically significant Parkinsonian symptoms
2. Vascular disorder (modified Hachinski Ischaemic Scale score >4)
3. Recent Transient Ischaemic Attack (TIA) (within the last 3 months)
4. Signs of major cerebrovascular disease on MRI or CT scan prior to entry into study (i.e. evidence of an established cortical or basal ganglia infarct)
5. Signs of major cerebrovascular disease on the MRI performed at the screening imaging visit prior to the amyloid and microglial PET scans
6. Any other previous or ongoing chronic or recurrent disease of the central nervous system, including demyelinating disease or psychiatric diseases, that may have an impact on cognitive performance
7. Any of the following laboratory abnormalities at the screening visit:
7.1. Clinically significant Vitamin B12 levels less than the lower limit of normal
7.2. Clinically significant folate levels less than the lower limit of normal
7.3. Clinically significant thyroid-stimulating hormone (TSH) levels greater than the upper limit of normal and a clinically significant free thyroxine (FT4) level lower than the lower limit of normal (participants who are successfully treated for folate, vitamin B12 or thyroxine deficiencies may be re-screened after 3 months)
8. Subjects with a previous or present history of severe medical conditions, or medical conditions which are poorly controlled, such as hypertension or diabetes
9. History of alcohol or drug dependence or abuse within the last 2 years. Current alcohol >35 units/week for men or >28 units/week for women, or drug abuse
10. Surgical intervention planned during the study period
11. Treatment with immunosuppressive drugs including any systemic corticosteroid drugs (topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted)
12. Treatment with benzodiazepines within a period of three days prior to [11C] (R)-PK-111-95 PET scans imaging
13. Vaccination or immunisation with any live vaccine (e.g. polio, rubella, yellow fever) within the past 30 days
14. Pregnancy or breast feeding
15. Severe hepatic, renal or cardiac disease
16. Previous use of a TNFα agent
17. Known skin photosensitivity
18. Infection in past 4 weeks or active infection
19. Heart failure: New York Heart Association (NYHA) Grade 3-4
20. History of blood disorders or current WCC ≤ 3.5 x 109/l; platelet count ≤ 100x109/l; Hb ≤ 10g /dl
21. Active or latent tuberculosis
22. Rheumatoid arthritis; psoriasis; psoriatic arthritis or ankylosing spondylitis
23. Septic arthritis in past 12 months
24. Sepsis of prosthesis in past 12 months

25. Chronic leg ulcers
26. Indwelling urinary catheter
27. Pulmonary fibrosis
28. History of neoplasms/malignancies in past 5 years
29. Pre-malignant conditions including Barrett's oesophagus, cervical dysplasia and large bowel polyps
30. Other clinically significant abnormality on physical, neurological, ECG or laboratory examination that could compromise the study evaluations or be detrimental to the patient during the course of the study
31. Use of experimental medications for AD, or any other investigational medication or device, within 60 days. Patients who have been involved in a monoclonal antibody study are excluded unless it is known that they were receiving placebo in that trial
Imaging exclusion criteria:
33. Significant cortical or basal ganglia infarct or other significant pathology found on MRI brain scan
34. Negative amyloid PET scan. NB: Subjects with a positive amyloid PET scan or a border-line positive PET scan will be included in the study

### Date of first enrolment
01/09/2015

### Date of final enrolment
01/08/2016

## Locations

### Countries of recruitment
England

United Kingdom

### Study participating centre
**Memory Assessment & Research Centre**
Tom Rudd Unit
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Botley Rd
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### Study participating centre
**Memory Clinic**
North Manchester General Hospital
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# Sponsor information

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### Sponsor type
University/education

### ROR
https://ror.org/01ryk1543

# Funder(s)

### Funder type
Other

### Funder Name
European Union

### Funder Name
Alzheimer’s Society (UK)

### Funder Name
Alzheimer's Drug Discovery Foundation (USA)

# Results and Publications

## Publication and dissemination plan

### Intention to publish date
01/06/2019

### Individual participant data (IPD) sharing plan
The data arising from the study will be made available to the INMiND consortium, but the data will remain the property of the University of Southampton and the publication of the data will be the responsibility of the Chief Investigator, who will be free to place any information from the study into the public domain.

### IPD sharing plan summary
Not expected to be made available

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Basic results | | 12/11/2020 | 16/06/2022 | No | No |
| Protocol file | version 2.0 | 25/09/2015 | 11/08/2022 | No | No |
| HRA research summary | | | 28/06/2023 | No | No |