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IL-6 inhibition in patients with depression and low-grade inflammation: the Insight study

Submission date
09/04/2018

Recruitment status
No longer recruiting

Registration date
16/04/2018

Overall study status
Completed

Last Edited
18/12/2024

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Research suggests inflammation may cause depression, but the precise mechanisms are unknown. The main aims of this study are to test whether interleukin 6 (IL-6), a pro-inflammatory protein, contributes to depression, and to examine the potential mechanisms by which IL-6 affects mood and cognition. A secondary aim is to compare depressed participants with and without evidence of low-grade systemic inflammation.

Who can participate?
Patients aged 20-65 who have depression with evidence of low-grade inflammation (n=50) and without evidence of inflammation (n=50)

What does the study involve?
Participants with evidence of inflammation (n=50) are randomly allocated into two groups to receive a single dose of normal saline (placebo) or tocilizumab (a drug that inhibits IL-6 signalling and is licensed in the UK for treatment of rheumatoid arthritis). Behavioural data and blood samples are collected at the start of the study and at day 7, 14 and 28 post-intervention. Cognitive tasks are performed at the start of the study and at day 14 post-intervention. Participants without low-grade inflammation undergo the same tests at the start of the study. Symptoms of depression are compared between the groups at follow-up. Depression severity, cognitive function and blood-based biomarkers are also measured.

What are the possible benefits and risks of participating?
By taking part, participants will find out whether there is evidence of low-grade inflammation in their body, which is not necessarily a cause for concern. Reasons could include obesity, smoking, alcohol use, and lack of exercise, so knowledge of the level of inflammation might prompt participants to adopt a healthier lifestyle. The most common side effects of treatment with tocilizumab are infections, followed by headache, high blood pressure, altered liver enzymes and nausea. The proportion of patients who stopped treatment due to any side effects in clinical trials was 5% for those taking tocilizumab and 3% for those taking placebo (dummy pill). The risk of infections will be minimised by excluding participants who have a history of repeated infections, recent serious infections or other serious physical illness (e.g. tuberculosis, HIV, Hepatitis B, Hepatitis C, VZV). Serious allergic reactions (anaphylactic reactions) such as

shortness of breath and swelling of lips can occur during or after infusion, but these are rare and unlikely after a single dose. Participants are required to give blood samples, which may cause discomfort and leave a temporary bruise. Every effort will be made to minimise this. As part of safety screening, participants have a chest X-ray to check that they do not have tuberculosis. This is part of the routine normal care for patients receiving tocilizumab. The X-ray uses ionising radiation, which can cause cell damage that may turn cancerous years or decade later. The dose of radiation received during X-ray is equivalent to that received, on average in the UK, from natural sources of radiation in the environment every three to ten days. However, all people are at risk of developing cancer: 50% of people do so at some point in their life. Taking part in the study will add an extremely small chance of this happening to participants (less than 1 in 1.5 million).

Where is the study run from?
1. Cambridge Biomedical Campus (UK)
2. Addenbrooke's Hospital (UK)
3. Fulbourn Hospital (UK)
4. Newmarket Community Hospital (UK)
5. West Suffolk Hospital (UK)
6. GP practices in Cambridgeshire and Suffolk – individual GP practices to be confirmed (UK)
7. Research activities could also take place at the participant's home address or any other location of the participant's choice (UK)

When is the study starting and how long is it expected to run for?
January 2017 to April 2022

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Prof. Golam Khandaker
golam.khandaker@bristol.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Golam Khandaker

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
238297

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 37724, IRAS 238297

Study information

Scientific Title
IL-6 inhibition in patients with depression and low-grade inflammation: the Insight study

Acronym
Insight

Study objectives
Research suggests inflammation may cause depression, but precise mechanisms are unknown. The main objectives of this study are to test whether interleukin 6 (IL-6), a pro-inflammatory protein, contributes to pathogenesis of depression, and to examine potential mechanisms by which IL-6 affects mood and cognition. A secondary objective is to compare depressed participants with and without evidence of low-grade systemic inflammation.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. South Central - Oxford B Research Ethics Committee, 24/04/2018, REC ref: 18/SC/0118
2. HRA Approval, 02/05/2018, IRAS ID 238297

Study design
Randomized; Both; Design type: Treatment, Drug, Cohort study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
GP practice, Home, Hospital, Other

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Depressive episode

Interventions
A proof-of-concept, randomized, double blind, placebo-controlled experiment based on approximately 50 depressed participants (intervention cohort) who have evidence of low-grade inflammation (i.e., serum/plasma high sensitivity C-reactive protein (hsCRP) level > = 3mg/L). Randomisation will be done by an external agency (i.e. Sealed Envelope). Participants will be randomly assigned to tocilizumab or normal saline group ensuring the two groups are comparable to each other on depression severity and sex using minimisation. Participants will receive a single intravenous infusion of normal saline (placebo) or tocilizumab (a drug that inhibits IL-6 signalling and is licensed in the UK for treatment of rheumatoid arthritis) (8 mg/kg; max 800 mg in total). Behavioural data and blood samples will be collected at baseline and after infusion around day 7, 14 and 28. Cognitive tasks will be performed at baseline and after infusion around day 14. Approximately 50 depressed participants without low-grade inflammation (serum/plasma hsCRP level < 3mg/L) will complete the same baseline assessments as the intervention cohort to fulfil the secondary objective of the study.

Intervention Type
Other

Primary outcome measure
Change in total somatic symptoms score from baseline assessment to around day 14 post-infusion. Somatic symptom score will be constructed by summing scores for seven relevant Beck Depression Inventory II (BDI-II) items (4=lack of pleasure, 15=loss of energy, 16=changes in sleeping pattern, 18=changes in appetite, 19=concentration difficulty, 20=tiredness or fatigue, and 21=loss of interest in sex). Somatic symptoms will be measured using BDI-II at baseline, day 7, 14 and 28 post-infusion.

Secondary outcome measures
Secondary outcome measure:
Change in total depression severity score from baseline assessment to around day 14 post-infusion assessed by BDI-II. Depression severity will be measured using BDI-II at baseline, day 7, 14 and 28 post-infusion.

Tertiary/exploratory outcome measures:

Behavioural measures:
1. Fatigue, assessed by Multi-dimensional Fatigue Inventory (MFI) at baseline, day 7, 14 and 28 post-infusion
2. Anhedonia, assessed by Snaith-Hamilton Pleasure Scale Questionnaire at baseline, day 7, 14 and 28 post-infusion

Cognitive measures:
1. Psychomotor speed, assessed by CANTAB Reaction Time (RTI) test or a similar test (computerised) and Digit Symbol Substitution Test (pen and paper) or a similar test at baseline and day 14 post-infusion
2. Attention, assessed by CANTAB Rapid Visual Information Processing (RVP) test or a similar test (computerised) at baseline and day 14 post-infusion
3. Memory, assessed by CANTAB Paired Associates Learning (PAL) test or a similar test (computerised) at baseline and day 14 post-infusion
4. Emotional processing, assessed by Emotional categorization and recall task or a similar task (computerised) at baseline and day 14 post-infusion

Blood biomarkers will be measured using appropriate tests at baseline and post-infusion follow-up. These include but are not limited to inflammatory markers, cortisol, cardio-metabolic markers, and phenotyping of peripheral blood mononuclear cell populations (PBMC).

Genetic analysis of blood samples will be carried out using appropriate methods at baseline and post-infusion follow-up.

Overall study start date
09/01/2017

Completion date
13/04/2022

Eligibility

Key inclusion criteria
Inclusion criteria for all participants:
1. Able and willing to give informed consent, including consent to share information with the participant's General Practitioner (GP) and to access GP records
2. Able to understand written and spoken English
3. Able to consent to blood sampling
4. Willing to abstain from strenuous exercise for 72 hours before the assessment visits
5. Age: 20-65 years (inclusive) at the time of eligibility assessment
6. Diagnosis of depression: meet ICD-10 criteria for diagnosis of depression at the time of eligibility assessment
7. Somatic symptom score: ≥7 at the time of eligibility assessment based on Beck depression inventory II (BDI-II) items 4=lack of pleasure, 15=loss of energy, 16=changes in sleeping pattern, 18=changes in appetite, 19=concentration difficulty, 20=tiredness or fatigue, and 21=loss of interest in sex
8. History of non/slow response to antidepressant: at the time of eligibility assessment receiving treatment with an antidepressant at adequate dose (according to BNF) for at least four weeks

Additional inclusion criteria for intervention cohort:
1. Inflamed: serum/plasma hsCRP level ≥3mg/L

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 100; UK Sample Size: 100

Total final enrolment
86

Key exclusion criteria
Exclusion criteria for all participants:
1. Current or lifetime diagnosis of bipolar disorder, psychotic disorder, personality disorder or eating disorder
2. Current suicidal thoughts (BDI II item 9=suicidal thoughts or wishes score 2 or more) or history of suicide attempt, deliberate self-harm, overdose within six months prior to eligibility assessment
3. History of alcohol or substance use disorder (abuse/dependence) within six months prior to eligibility assessment (nicotine and caffeine dependence are not exclusionary)
4. Pregnant or breastfeeding
5. History of serious allergic reaction after any infusion
6. Current use of medication likely to compromise interpretation of immunological data (including, but not limited to, antibiotics, non-steroidal anti-inflammatory drugs, oral/injectable corticosteroids – or any other substances to be determined by the Chief Investigator)
7. Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of eligibility assessment
8. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other opportunistic infections
9. Unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active infectious disease, including current or prior malignancy
10. Rheumatic autoimmune disease, mixed connective tissue disease, scleroderma, polymyositis, or significant systemic involvement secondary to rheumatoid arthritis
11. Uncontrolled hypertension defined as systolic blood pressure > 170 or diastolic blood pressure > 110
12. No history of chickenpox infection or no history of varicella zoster vaccination

Additional exclusion criteria for intervention cohort:
1. Current or past infection with TB, Hepatitis B, Hepatitis C, VZV or HIV confirmed by blood /other test. Chest X-ray will be also done to exclude TB
2. Pregnancy test (for female participants)
3. History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies

Date of first enrolment
01/06/2018

Date of final enrolment
31/12/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Clinical Suite
Herschel Smith Building
Cambridge Biomedical Campus
Robinson Way
Cambridge
United Kingdom
CB2 0SZ

Study participating centre
NIHR/Wellcome Trust Clinical Research Facility
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Windsor Research Unit
Fulbourn Hospital
Cambridge Road
Cambridge
United Kingdom
CB21 5EF

Study participating centre
Newmarket Community Hospital
56 Exning Road
Newmarket
United Kingdom
CB8 7JG

Study participating centre

Wedgwood House
West Suffolk Hospital
Hardwick Lane
Bury Saint Edmunds
United Kingdom
IP33 2QZ

Study participating centre
GP practices in Cambridgeshire and Suffolk (NIHR CRN: Eastern CCG) – individual GP practices to be confirmed
United Kingdom
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Study participating centre
Research activities could also take place at participant's home address or any other location of participant's choice
United Kingdom
-

Sponsor information

Organisation
Cambridgeshire and Peterborough NHS Foundation Trust

Sponsor details
c/o Stephen Kelleher
Elizabeth House
Fulbourn Hospital
Fulbourn
Cambridge
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United Kingdom
CB21 5EF
+44 (0)1223 217418
R&D@cpft.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.cpft.nhs.uk/

ROR

https://ror.org/040ch0e11

Organisation
University of Cambridge

Sponsor details
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Sponsor type
University/education

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust; Grant Codes: 201486/Z/16/Z

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan

The protocol will be published in a peer-review journal (BMJ Open). The protocol paper will include Informed Consent and Participant Information Sheet as online supplementary materials available from the BMJ Open website. The manuscript is currently being revised and it will be sent for publication shortly.

The main results will be published in high-impact peer-review journals approximately within one year of overall completion of the study. Findings will also be disseminated at conferences, departmental talks and other scientific meetings. Further dissemination will take place via social media, at public engagement events, and by using media channels.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Golam Khandaker (golam.khandaker@bristol.ac.uk).
Type of data: anonymised study data from the clinical trial part of the study
When available and for how long: after publication of main results and for up to 10 years
Access criteria, with whom, type of analysis and mechanism: data analysis/collaboration for research purpose, academic/scientific groups, secondary exploratory analysis of data/samples, sharing of data and study materials will be done by Data Transfer Agreement (DTA) and Material Transfer Agreement (MTA) or by other appropriate legal agreements
Consent: informed consent will be obtained so that study collaborators will be able to access anonymised data.
Anonymisation, any ethical or other comments: data will be anonymised – it will include Participant ID but no other personal identifiable information. Study biological samples will include Participant ID and date of birth. These will be covered by the ethical approval for the study.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V2	03/04/2018	16/04/2018	No	Yes
Protocol article	protocol	21/09/2018	31/10/2019	Yes	No
HRA research summary			28/06/2023	No	No
Other publications		05/08/2021	23/01/2024	Yes	No
Other publications		24/12/2021	23/01/2024	Yes	No