ISRCTN77854383 https://doi.org/10.1186/ISRCTN77854383

Pain reduction with oral methotrexate in knee osteoarthritis

Submission date	Recruitment status	[X] Prospectively registered
25/10/2013	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
25/10/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
30/07/2024	Musculoskeletal Diseases	

Plain English summary of protocol

Background and study aims
Osteoarthritis (OA) is the most common form of arthritis and is an increasingly common problem in our aging society. In the UK an estimated 8.5 million people are affected by OA, causing an enormous burden to health authorities, as well as considerable pain and disability to these individuals. A recent study by Arthritis Care reported that 81% of people with OA experience constant pain and 72% have important related conditions, such as high blood pressure or depression. Current treatments for knee OA are limited as they often only work for short periods and are not effective for all patients. As a result people with OA often live with severe pain and have significant difficulty in carrying out their normal day-to-day activities. There is therefore an urgent need to find new and better ways to manage pain for people with OA. Methotrexate has been used very successfully to treat inflammation in rheumatoid arthritis, and it is now the drug used most often to treat that type of arthritis. Recent studies suggest that inflammation is also important in OA, and that by reducing inflammation, pain will also be reduced. The aim of this study is to find out whether methotrexate is an effective treatment for reducing inflammation in knee OA and whether this leads to a reduction in pain.

Who can participate?
Patients aged 18 and over with knee OA

What does the study involve?
Participants are randomly allocated to take either methotrexate or a placebo (dummy drug), in combination with drugs licensed for use in pain management of OA. Knee pain and function, pain in other joints, quality of life, anxiety, depression, and health service resource use are measured at the start of the study, and after 3, 6, 9 and 12 months.

What are the possible benefits and risks of participating?
Not provided at time of registration

Where is the study run from?
1. Leeds Teaching Hospitals Trust (UK)
2. Aintree University Hospital NHS Trust (UK)
3. Staffordshire and Stoke-on-Trent Partnership NHS Trust (UK)

4. Northumbria Healthcare NHS Foundation Trust (UK)
5. NHS Fife (UK)
6. Cannock Chase Hospital (UK)
7. New Cross Hospital (UK)
8. Guy's and St Thomas's NHS Foundation Trust (UK)
9. King's College Hospital (UK)
10. Ashford & St Peter's Hospitals NHS Foundation Trust (UK)
11. NIHR Wellcome Trust Southampton Clinical Research Facility (UK)
12. Harrogate and District NHS Foundation Trust (UK)
13. York Teaching Hospital NHS Foundation Trust (UK)
14. Salford Royal NHS Foundation Trust (UK)
15. Oxford University Hospitals NHS Foundation Trust (UK)
16. West Suffolk NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2014 to January 2019

Who is funding the study?
Arthritis Research UK

Who is the main contact?
Sarah Kingsbury
S.R.Kingsbury@leeds.ac.uk

Contact information

Type(s)
Scientific

Contact name
Ms Sarah Kingsbury

Contact details
LIRMM
Level 2 Chapel Allerton Hospital
Chapeltown Road
Leeds
United Kingdom
LS7 4SA
+44 (0)113 392 4878
S.R.Kingsbury@leeds.ac.uk

Additional identifiers

EudraCT/CTIS number
2013-001689-41

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
15495

Study information

Scientific Title
Pain Reduction with Oral Methotrexate in knee Osteoarthritis: a pragmatic phase III trial of Treatment Effectiveness

Acronym
PROMOTE

Study objectives
Osteoarthritis (OA) is the most prevalent form of arthritis and is an increasingly common problem in our aging society. In the UK an estimated 8.5 million people are affected by OA, causing an enormous burden to health authorities, as well as considerable pain and disability to these individuals. A recent study by Arthritis Care reported that 81% of people with OA experience constant pain and 72% have important related conditions, such as hypertension or depression.

Current treatments for knee OA are limited as they often only work for short periods and are not effective for all patients. As a result people with OA often live with severe pain and have significant difficulty in carrying out their normal day-to-day activities. There is therefore an urgent need to find new and better ways to manage pain for people with OA. Methotrexate has been used very successfully to treat inflammation in rheumatoid arthritis; it is now the commonest drug used to treat that type of arthritis. Recent studies suggest that inflammation is also important in OA, and that by reducing inflammation, pain will also be reduced. The trialists believe that methotrexate may be an effective treatment for reducing inflammation in knee OA and that this reduction in inflammation will lead to a reduction in pain.

Ethics approval required
Old ethics approval format

Ethics approval(s)
First MREC approval date 23/09/2013; 13/YH/0279

Study design
Randomised interventional treatment trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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
Topic: Primary Care Research Network for England; Subtopic: Not Assigned; Disease: All Diseases

Interventions
Patients will be randomised on a 1:1 basis to the intervention (Methotrexate, up to 25 mg per week) or placebo, used in combination with drugs licensed for use in pain management of OA

Follow Up Length: 13 months

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
Average overall knee pain severity over the 1-week period prior to measurement; Timepoint(s): 6 months

Secondary outcome measures
Added 25/08/2016:
Clinical endpoints:
1. Patient-reported knee pain
2. Disease activity and knee function
3. Pain in other joints
4. Number of withdrawals due to total knee replacement in the signal knee
Measured at baseline, 3, 6, 9 and 12 months

Quality of life endpoints:
1. Quality of life
2. Anxiety and depression
Measured at baseline, 6 and 12 months

Resource use endpoints:
1. Health service resource utilisation
2. Imaging/MRI endpoints (MRI sub study)
3. Synovitis and cartilage scores
Measured at baseline, 6 and 12 months

Overall study start date
01/01/2014

Completion date

08/01/2019

Eligibility

Key inclusion criteria

Current inclusion criteria as of 25/08/2016:
1. Fulfil clinical American College of Rheumatology (ACR) Criteria for knee OA
2. Knee pain on most days in the last 3 months
3. Insufficient pain relief from, inability to tolerate, or contra-indication to oral and/or topical Non-steroidal anti-inflammatory drugs (NSAIDs) and/or opioids and/or Paracetamol. Moderate to severe pain of the signal knee as defined by a score of ≥40mm on a Visual analogue scale (VAS) (0-100mm) using the question "On average, how would you rate your knee pain during the last 3 months?"
4. Knee pain is the predominant pain condition
5. Patient able to identify a 'signal' painful knee (either the most painful knee or selected from equally painful knees)
6. A radiograph (X-Ray) of the signal knee within the last 2 years, with changes consistent with tibio-femoral OA
7. No change in the average weekly dose of oral/topical analgesics (including NSAIDs and Paracetamol) for at least 4 weeks
8. Has used chondroitin or glucosamine for at least 3 months with no change to the average weekly dose, is not using, or is willing to stop using if recently started
9. All male and female participants biologically capable of having children must agree to use a reliable method of contraception for the duration of the study and 24 weeks after the end of the study period. Acceptable methods of contraception are surgical sterilisation, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives. If female and have potential for child bearing then a negative pregnancy test must be performed prior to starting treatment
10. The patient must be able to adhere to the study visit schedule and other protocol requirements
11. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures
12. All patients must have had a chest radiograph (X-Ray) within the last 6 months
13. Aged ≥ 18 years

Previous inclusion criteria:
1. Fulfil clinical ACR Criteria for knee OA.
2. Knee pain on most days in the last 3 months.
3. Insufficient pain relief from, inability to tolerate, or contra-indication to oral and/or topical NSAIDs and/or opioids. Moderate to severe pain of the signal knee as defined by a score of ≥40mm on a VAS (0-100mm) using the question On average, how would you rate your knee pain during the last 3 months?.
4. Knee pain is the predominant pain condition.
5. Patient able to identify a signal painful knee (either the most painful knee or selected from equally painful knees).
6. A previous radiograph (X-Ray) of the signal knee with changes consistent with tibiofemoral OA.
7. No change in the average weekly dose of oral/topical analgesics (including NSAIDs) for at least 4 weeks.
8. Has used chondroitin or glucosamine for at least 3 months with no change to the average weekly dose, is not using or is willing to stop using if recently started.
9. Men and women must use adequate birth control measures (e.g. abstinence, oral

contraceptives, Intra-uterine device, barrier method with spermicide, or surgical sterilisation) for the duration of the study and should continue such precautions for 6 months after receiving the last dose of MTX. If female and have potential for child bearing then a negative pregnancy test must be performed prior to starting treatment.
10. The patient must be able to adhere to the study visit schedule and other protocol requirements.
11. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures.
12. All patients must have had a chest radiograph (X-Ray) within the last 6 months.
13. Target Gender: Male & Female ; Lower Age Limit 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
UK Sample Size: 160

Total final enrolment
155

Key exclusion criteria
Current exclusion criteria as of 25/08/2016:
1. The presence of any inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriatic arthritis, seronegative spondylarthropathy, previous diagnosis of pseudogout in target joint with proven crystals on joint aspiration or elevated CRP at time of knee arthritis flare) or fibromyalgia.
2. Use of intra-articular (IA) hyaluronic acid in the signal knee within the 4 months preceding enrolment in the study.
3. Use of IA, IM or oral corticosteroids in the 3 months preceding enrolment.
4. Use of other anti-synovial agents (e.g. hydroxychloroquine or sulphasalazine) in the 2 months preceding the study.
5. Significant knee injury or any knee surgery within the 6 months preceding enrolment in the study.
6. A history of partial or complete joint replacement surgery in the signal knee at any time, listed for knee surgery, or anticipating knee surgery during the study period.
7. Commencement of physiotherapy or non-pharmacological knee OA treatment in the 2 months preceding the study.
8. The presence of non-OA causes of pain in the signal knee e.g. referred hip pain, osteonecrosis.
9. Women who are pregnant, breast-feeding, or men or women planning pregnancy within 18 months after screening (i.e. approximately 6 months following last study medications).
10. Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.

11. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral disease, or active current infection.
12. Uncontrolled disease states, such as moderate/severe asthma, Chronic Obstructive Pulmonary Disease (COPD) or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids, or recurrent infections.
13. Unwilling to keep alcohol intake to below the recommended maximum daily limit during the trial (2 units per day for women, 3 units per day for men).
14. Planned need for live vaccination during 12 months of study (e.g. for foreign travel) with exception of Zostavax® which is permissible.
15. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
16. Melanoma, squamous cell carcinoma or non-skin cancer in the past 3 years.
17. Intolerance to lactose.
18. Significant haematological or biochemical abnormality
18.1. Haemoglobin =<8.5 g/dL
18.2. WCC =<3.5 x 109/L
18.3. Neutrophils =<1.5 x 109/L
18.4. Platelets =<100 x 109/L
18.5. ALT >2 times ULN for the laboratory conducting the test.
18.6. Creatinine > 1.5 times ULN for the laboratory conducting the test
18.7. eGFR <30ml/minute

Subjects with the following contra-indications to MRI scanning will not be included in the MRI substudy but may still be enrolled into the main study:
1. Pacemakers
2. Surgical clips within the head
3. Certain inner ear implants
4. Neuro-electrical stimulators
5. Metal fragments within the eye or head

Previous exclusion criteria:
1. The presence of any inflammatory arthritis (e.g. gout, reactive arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, seronegative spondylarthropathy) or fibromyalgia.
2. Use of intra-articular (IA) hyaluronic acid in the signal knee within the 4 months preceding enrolment in the study.
3. Use of IA, IM or oral corticosteroids in the 3 months preceding enrolment.
4. Use of other anti-synovial agents (e.g. hydroxychloroquine or sulphasalazine) in the 2 months preceding the study.
5. Significant knee injury or any knee surgery within the 6 months preceding enrolment in the study.
6. A history of partial or complete joint replacement surgery in the signal knee at any time, listed for knee surgery or anticipating knee surgery during the study period.
7. Commencement of physiotherapy or non-pharmacological knee OA treatment in the 2 months preceding the study.
8. The presence of non-OA causes of pain in the signal knee e.g. referred hip pain, osteonecrosis.
9. Women who are pregnant, breast-feeding, or men or women planning pregnancy within 18 months after screening (i.e. approximately 6 months following last study medications).
10. Use of any investigational (unlicensed) drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
11. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease.

12. Uncontrolled disease states, such as moderate/severe asthma, COPD or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids, or recurrent infections.
13. Intake of alcohol above the recommended government guidelines (2 units per day for women, 3 units per day for men).
14. Planned need for live vaccination during 12 months of study (e.g. for foreign travel) or lack of immunity to chicken pox.
15. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
16. Melanoma or non-skin cancer in the past 3 years.
17. Intolerance to lactose.
18. Significant haematological or biochemical abnormality
18.1. Haemoglobin =<8.5 g/dL
18.2. WCC =<3.5 x 109/L
18.3. Neutrophils =<1.5 x 109/L
18.4. Platelets =<100 x 109/L
18.5. ALT >2 times ULN for the laboratory conducting the test.
18.6. Creatinine > 1.5 times ULN for the laboratory conducting the test
18.7. eGFR <30ml/minute

Subjects with the following contra-indications to MRI scanning will not be included in the MRI substudy but may still be enrolled into the main study:
1. Pacemakers
2. Surgical clips within the head
3. Certain inner ear implants
4. Neuro-electrical stimulators
5. Metal fragments within the eye or head

Date of first enrolment
01/05/2014

Date of final enrolment
31/08/2016

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Leeds Teaching Hospitals Trust
Chapel Allerton Hospital
Chapeltown Road

Leeds
United Kingdom
LS7 4SA

Study participating centre
Aintree University Hospital NHS Trust
Longmoor Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Staffordshire and Stoke-on-Trent Partnership NHS Trust
Haywood Hospital
High Lane
Burslem
Stoke-On-Trent
United Kingdom
ST6 7AG

Study participating centre
Northumbria Healthcare NHS Foundation Trust
Rake Lane
North Shields
United Kingdom
NE29 8NH

Study participating centre
NHS Fife
Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Study participating centre
Cannock Chase Hospital
Brunswick Road
Cannock
United Kingdom
WS11 5XY

Study participating centre
New Cross Hospital
Wolverhampton Road
Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Guys and St Thomas's
Guy's Hospital
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
King's College Hospital
King's College London
Suite 3, Golden Jubilee Wing
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Ashford & St Peter's Hospitals NHS Foundation Trust
Guildford Road
Chertsey
United Kingdom
KT16 0PZ

Study participating centre
NIHR Wellcome Trust Southampton Clinical Research Facility
Southampton Centre for Biomedical Research
C Level West Wing
Mailpoint 218
Southampton General Hospital
Tremona Road
Southampton

United Kingdom
SO16 6YD

Study participating centre
Harrogate and District NHS Foundation Trust
Lancaster Park Road
Harrogate
York
United Kingdom
HG2 7SX

Study participating centre
York Teaching Hospital NHS Foundation Trust
Wigginton Road
York
United Kingdom
YO31 8HE

Study participating centre
Salford Royal NHS Foundation Trust
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Oxford University Hospitals NHS Foundation Trust
Nuffield Orthopaedic Centre
Windmill Road
Headington
Oxford
United Kingdom
OX3 7HE

Study participating centre
West Suffolk NHS Foundation Trust
Hardwick Lane
Bury St Edmunds
United Kingdom
IP33 2QZ

Sponsor information

Organisation
University of Leeds (UK)

Sponsor details
Faculty Research Office
Room 10.110, Level 10 Worsley Building
Clarendon Way
Leeds
England
United Kingdom
LS2 9NL

Sponsor type
University/education

Website
http://www.leeds.ac.uk/

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan
Fully anonymised datasets generated during the current study will be available upon request from Prof. Torgerson (e-mail, david.torgerson@york.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	04/03/2015		Yes	No
HRA research summary			28/06/2023	No	No
Results article		30/07/2024	30/07/2024	Yes	No