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A study of pre-clinical joint disease in psoriasis and the imaging response to ustekinumab

Submission date
26/07/2012

Recruitment status
No longer recruiting

Registration date
19/09/2012

Overall study status
Completed

Last Edited
31/12/2019

Condition category
Skin and Connective Tissue Diseases

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

Plain English summary of protocol

Background and study aims
We know that some people with psoriasis will develop psoriatic arthritis, but is not fully understood why some people do and some do not. Before patients develop joint symptoms of pain, swelling and/or stiffness, early changes take place within the bones, joints and tendons, although it is not known to what extent this can be picked up and best treated in patients with skin psoriasis. In theory, early, targeted treatment has the potential to reduce the physical, emotional and financial burden of future disabling joint disease, a concept that has been demonstrated in patients with rheumatoid arthritis.
We hope to develop a simple scanning technique for use in clinic, to identify early arthritis in patients with psoriasis before they develop joint symptoms. To do this involves the use of several imaging techniques (old and new) in patients with skin psoriasis. These include:
Ultrasound (USS) A widely used, pain-free and safe technique that can be used to look at any organ within the body with a hand-held probe held against the skin. We will use ultrasound to look at tendons, ligaments, joints and fingernails.
Optical Coherence Tomography (OCT) A newer technique, similar to ultrasound that provides more detailed images of the fingernails.
Magnetic Resonance Imaging (MRI) A safe technique frequently used to image the tendons, ligaments, bones and joints in finer detail, commonly used in the assessment of patients with arthritis.
In addition to identifying early arthritis (i.e. before it is severe enough to cause symptoms), these techniques will also be used to monitor response to treatment. This will help to determine if the drugs currently used to treat moderate or severe psoriasis can decrease these changes, and to what extent.

Who can participate?
New patients (male and female, aged 18-80 years) from the dermatology clinics held at Chapel Allerton Hospital, Leeds, may be considered for participation if they have a diagnosis of moderate or severe skin psoriasis for at least 12 months, and have only ever been treated topically (i.e. with creams/ointments). Participants should not have any symptoms of joint disease (i.e. morning stiffness >30 minutes, joint tenderness or swelling). Their skin disease should be bad enough that they have been referred to the hospital by their General Practitioner because they now need a form of systemic therapy, usually given in tablet form. Female patients

must not be pregnant or wish to become pregnant during the study, or for at least three months after the study has ended.

What does the study involve?
The study requires patients to take one of two treatments (after randomisation) for their skin psoriasis. These are:
1. Methotrexate - the current first-line standard tablet treatment for moderate to severe psoriasis
2. Ustekinumab - an injection therapy used in the treatment of moderate to severe psoriasis, but usually reserved for patients who have not responded to methotrexate and at least one other systemic treatment. This means that this drug is being given off-licence.
Both of these medicines will be given at the same dose and frequency as they would be in routine clinical practice for skin psoriasis. Participants will be examined and screened (with a small number of blood tests, a chest x-ray and a heart tracing/ECG) at the start of the study for their safety (as would be the case if they were not taking part in the study). Both treatments will be given for six months as part of the study. Methotrexate is taken in tablet form once weekly, in addition to a vitamin tablet (folic acid) taken on the other six days of the week. Ustekinumab is given by a single injection into a fatty part of the body on three occasions (at the start, after four weeks and after twelve weeks). This will be administered by the doctor in clinic.
Participants will need to attend Chapel Allerton Hospital for regular review visits with a dermatologist (typically every 4-8 weeks). This occurs in the same place, at the same time, and at the same frequency as it would if they were not taking part in the study. Blood tests are usually performed at these visits to monitor the effects of the drug on the blood, liver, kidneys and heart /blood vessels, and participants will also be asked to provide an additional 10-20ml of blood for research into the genetics of psoriasis.
The main outcome of the study is the effect of these medicines on the bones, joints and tendons. Participants will be required to have an ultrasound scan of their hands, wrists, ankles and feet and a similar scan called Optical coherence tomography (or OCT) of their fingernails, at the start, after twelve weeks and after 24 weeks of treatment. Some may also be asked to have a whole-body MRI scan at these time points. These investigations are essential to see if participants have any signs of asymptomatic joint disease, and what the response of this is to the two drugs. This will prolong the length of each visit from the norm, but will not result in any additional visits. None of these investigations requires any exposure to radiation (x-rays).
All research studies are always completely voluntary, and participants are free to withdraw at any time, without providing a reason. This will not affect the standard of their routine care.

What are the possible benefits and risks of participating?
There is good evidence that treating arthritis as early as possible is beneficial and can significantly reduce longer-term pain, joint destruction and disability. We know that methotrexate can help to reduce the changes seen on Ultrasound, OCT and MRI scans by approximately 10-20%. We believe that ustekinumab may be even better. As we are seeing eligible study participants regularly in our clinic for their psoriasis, we would like to extend our assessment beyond their skin by looking for early, symptom-free joint disease, and monitor this closely to see if their skin treatment also helps to improve any early arthritis. It cannot be guaranteed that participants will gain any other personal benefit from this study. However, beneficial information may be acquired for future patients with psoriasis. This will enable us to understand who is more likely to develop psoriatic arthritis and treat future patients more effectively.
The MRI scan involves lying still within the scanner for up to one hour. It can very rarely cause a sensation of muscle twitching. The scanner is quite noisy, and so participants will be given ear defenders to wear. Some people experience claustrophobia (fear of enclosed spaces) during the scan if this should happen, they will be able speak to let us know and we will stop the scan. They

do not need to have any needles or injections for this scan.
Like any drug, both methotrexate and ustekinumab can have side effects. Both of these treatments have been extensively studies in humans and are prescribed around the world on a daily basis without harm. Participants will be monitored closely for any adverse effects and will be given a detailed explanation of the potential side effects at the start. They will also be given a written information sheet produced by the British Association of Dermatologists about their drug.
At the end of six months, participants taking ustekinumab will stop treatment. If needed, they will be started on an alternative by their dermatologist. They will remain eligible for this treatment on the NHS once they satisfy the licence (i.e. failed two systemic therapies). Patients taking methotrexate may continue if needed, or switched to an alternative at their dermatologists discretion.

Where is the study run from?
The study is taking place in one centre Chapel Allerton Hospital. All visits and tests will be done at this site.

When is the study starting and how long is it expected to run?
The study will start in autumn 2012 and will run for twelve months, or until the required number of 60 participants have been recruited. Each patient will participate in the trial for six months.

Who is funding the study?
The funding for this study has been granted in part by the Leeds Foundation for Dermatology Research (LFDR) and in part by Janssen-Cilag Pharmaceuticals, who manufacture Ustekinumab.

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
RR12-10234

Study information

Scientific Title
A prospective, single-centre, open-label, feasibility study evaluating the prevalence of diagnostic clinical imaging features of subclinical enthesitis in patients with moderate to severe plaque psoriasis and the impact on the MUSculoskeletal system of skin-directed therapy with usTEKinumab

Acronym
MUSTEK

Study objectives
Patients with psoriasis develop imaging changes within their joints, bones and tendons consistent with early psoriatic arthritis before they develop symptoms of pain, swelling and/or stiffness, and these changes can be reduced or resolved with standard ustekinumab treatment when given primarily to improve their skin disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Phase IV prospective open-label feasibility study

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 the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied

Psoriatic disease (psoriasis and psoriatic arthritis)

Interventions
Participants are randomised to:

Methotrexate - the current first-line standard tablet treatment for moderate to severe psoriasis

Ustekinumab (IMP) anti-IL12/23 p40 monoclonal antibody

Intervention Type
Other

Phase
Phase IV

Primary outcome measure
To assess the change in subclinical enthesitis from baseline in patients with psoriasis treated for 24 weeks with ustekinumab for their skin disease

Secondary outcome measures
1. To assess the feasibility of a full randomized controlled trial (RCT) comparing ustekinumab with first line systemic therapies for the management of subclinical psoriatic joint disease in patients with moderate or severe psoriasis.
2. To estimate the baseline prevalence of peripheral subclinical enthesitis in systemic and biologic treatment-naïve patients with plaque psoriasis, recruited from a new-patient psoriasis clinic, with a PASI score greater than 10 and no symptoms of joint disease (as assessed by the CASPAR criteria) at presentation.
3. To estimate the baseline prevalence of subclinical axial arthropathy in systemic and biologic treatment-naïve patients with plaque psoriasis, recruited from a new-patient psoriasis clinic, with a PASI score greater than 10 and no symptoms of joint disease (as assessed by the CASPAR criteria) at presentation.
4. To assess the change in subclinical peripheral and axial inflammatory joint disease from baseline in patients with psoriasis treated for 24 weeks with ustekinumab for their skin disease
5. To establish if a relationship exists between the change from baseline in any routine clinical scoring measures and the change in subclinical enthesopathy on ultrasound after treatment with ustekinumab:
5.1. Skin disease severity: PASI score
5.2. Skin disease extent: BSA measurement (expressed as a percentage)
5.3. Psychosocial impact: DLQI score
5.4. Nail disease severity: NAPSI score
6. To evaluate whether there is an association between the pattern of plaque psoriasis (e.g. scalp disease) in systemic and biologic naïve patients and the severity of subclinical enthesopathy before treatment.
7. To validate the utility of optical coherence tomography in the assessment of subclinical nail disease in patients with psoriasis, compared to ultrasound, in terms of:
7.1. Efficacy/level of detection of abnormalities
7.2. Variability/Reproducibility
8. To investigate the prevalence and severity of the OCT changes seen in subclinical psoriatic nail disease in patients with moderate or severe psoriasis (PASI >10) prior to treatment with systemic and biologic therapies.
9. To evaluate whether there is an association between the severity of subclinical psoriatic nail

disease and the severity of subclinical joint disease in patients with moderate or severe psoriasis (PASI >10) who are systemic and biologic-treatment naïve.
10. To assess the change in subclinical psoriatic nail disease from baseline in patients with psoriasis treated for 24 weeks with ustekinumab for their skin disease (open label).
11. To investigate which, if any, serological abnormalities exist in our psoriasis cohort (particularly in relation to the metabolic system and cardiovascular risk) and to quantify the change in these biomarkers from baseline after 24 weeks of treatment with ustekinumab.

Overall study start date
01/10/2012

Completion date
01/10/2014

Eligibility

Key inclusion criteria
1. Male and female patients aged 18-80 years
2. Diagnosis of plaque psoriasis (dermatologist confirmed)
3. Duration of psoriasis greater than twelve months
4. Moderate or severe disease [Psoriasis Area and Severity Index (PASI score >10)]
5. No prior treatment with systemic or biologic agents
6. No current or prior symptoms of psoriatic arthritis (or arthralgia/ articular symptoms)
7. Evidence on screening ultrasound of subclinical enthesitis (GUESS score >12)
8. All male and female subjects biologically capable of having children must agree to use at least one reliable method of contraception for the duration of the study and for 24 weeks after the end of the study. Acceptable methods of contraception are surgical sterilization, oral, implantable or injectable hormonal methods, intrauterine devices or barrier contraceptives

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
80 Years

Sex
Both

Target number of participants
30

Total final enrolment
73

Key exclusion criteria
1. Patients aged 17 or under, or 81 and over
2. Psoriasis of mild to moderate psoriasis (PASI<10)
3. Previous treatment with any systemic or biologic agents (for psoriasis or any other indication)
4. Patients unable or not willing to attend all imaging, serological and clinical assessments
5. Any contraindication to MRI (e.g. pacemaker, aneurysm coil)
6. Patients not willing to use adequate contraception
7. Pregnancy or breast feeding
8. Any contraindication to systemic or biologic therapy:
8.1. Active infection, including open leg ulcers, HIV, hepatitis B or C carriers
8.2. Active or latent tuberculosis
8.3. Malignancy current, or previous within the last ten years (except basal cell carcinoma)
8.4. Severe heart failure (NYHA grade 3 or more)
8.5. Demyelinating disorders
8.6. Uncontrolled diabetes
8.7. Chronic lung disease (pulmonary fibrosis or bronchiectasis)
8.8. Previous PUVA phototherapy (>1000 joules)
9. History of other significant medical conditions, including:
9.1. Severe pulmonary disease (defined as requiring previous hospital admission or supplemental oxygen)
9.2. Active or severe cardiovascular disorders: uncontrolled hypertension, myocardial infarction within the previous twelve months, unstable angina within the previous six months)
9.3. Any immunodeficiency disorder
9.4. Connective tissue diseases (e.g. primary Sjogrens syndrome, systemic sclerosis, systemic lupus erythematosus, polymyositis)
9.5. Renal impairment (creatinine clearance <45ml/min)
9.6. Abnormal liver function tests (alanine transferase >3x upper limit of normal)
9.7. Blood disorders, i.e. thrombocytopenia (platelets <125x109/l), neutropenia (neutrophils <2.0x109/l) or anaemia (haemoglobin <8g/dl).
10. Any forthcoming event that may interrupt participation (e.g. a holiday, elective hospital admission) lasting longer than 14 days

Date of first enrolment
01/10/2012

Date of final enrolment
01/10/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

Section of Musculoskeletal Disease
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Sponsor information

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Sponsor type
University/education

Website
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ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Industry

Funder Name
Janssen Cilag Ltd (UK)

Funder Name
Leeds Foundation for Dermatology Research (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

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	results	01/04/2019		Yes	No