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PRedSS: Prednisolone in early diffuse systemic sclerosis

Submission date	Recruitment status	[X] Prospectively registered
19/06/2017	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
27/06/2017	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
28/07/2021	Musculoskeletal Diseases	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Systemic sclerosis (also termed 'scleroderma') is a rare, chronic disease affecting the connective tissues, blood vessels and immune system. The two most characteristic features of the disease are skin thickening and Raynaud's phenomenon (colour changes of the fingers and sometimes the toes, usually in response to cold exposure or emotional stress). However, the disease can also affect joints, tendons and internal organs, causing them to be unable to function normally. The diffuse cutaneous subtype of scleroderma, when skin thickening rapidly spreads from the hands and feet to involve the arms, legs and/or trunk, is associated with high mortality (death rates). Only around 60% of patients survive 10 years. As a result clinicians often focus on internal organ involvement. Yet on a day-to-day basis, the most distressing features of diffuse scleroderma are severe pain, itching, impaired upper and lower limb function, resulting in difficulty performing even simple tasks, and often a feeling of helplessness. These features of the disease often destroy the quality of life and, at present, there is no effective treatment. Prednisolone is a type of steroid medication that helps reduce inflammation (swelling) and could be helpful to treat this disease. The aim of this study is to see if the impact on a moderate dose of prednisolone is effective in reducing pain, disability, and skin thickening and if it is a safe therapy in patients with early diffuse scleroderma.

Who can participate?
Adults aged 18 and older who have diffuse cutaneous systemic sclerosis.

What does the study involve?
After a series of screening, eligible participants are randomly allocated to one of two groups. Those in the first group are given prednisolone taken daily by mouth for six months. Those in the second group receive a placebo (dummy) medication to take daily for six months. During this time, participants return to the clinics for monitoring at six weeks, three months and six months. Blood and urine samples are collected from participants. Participants are also given blood pressure monitors to take home and a study diary to record the readings in. After the six month visit, participants are informed of which treatment they received. Those who received the prednisolone can decide with their doctor if they would like to continue with the medication. Those who do not are advised to gradually lower their dose of the medication before stopping. Participants are recommended to see their usual doctor within 30 days of the trial. Participants

are assessed for their functional abilities and pain levels to see if the medication is safe and effective.

Added 05/11/2020:
From August 2020 the study re-opened following a halt due to COVID-19 under a new open-label design. Patients are still randomly allocated to one of two groups. Patients will still receive prednisolone if allocated to group one. If randomised to the second group, patients will no longer receive a placebo (dummy) medication. This group will receive no additional treatment but will continue to take the medication already prescribed by their clinician. At 6 months, all patients already know which treatment arm they have been on. For the patients receiving prednisolone, the treatment options following trial exit remain the same as detailed above. The number of visits remain the same but are now more flexible to allow the frequency of attending the hospital to be reduced if necessary. The screening, baseline and 3-month visits should take place at the hospital, but the screen and baseline visits can now take place on the same day. If necessary, the 6-week and 6-month visits can be conducted remotely over the telephone with the doctor.

What are the possible benefits and risks of participating?
Participants may benefit from experiencing relief in their symptoms and a reduction in pain, itching, skin function and improvements in function and quality of life. Participant's condition may worsen but this could happen whether they participate or not. There are side effects with prednisolone, such as risk of serious kidney problems. Participants have their blood pressure monitored during the study to monitor for this. This study may disrupt participant's normal routine as it required five extra hospital visits over six months. Participants may feel small discomfort when providing blood samples. It is very important that participants do not suddenly stop taking the study treatment. Abruptly stopping the medication will put individuals at risk of 'steroid withdrawal' symptoms and this is potentially dangerous. Suddenly stopping the study drug may require emergency medical treatment.

Where is the study run from?
This study is being run by the University of Manchester and takes place in Salford Royal NHS foundation trust (UK) and in 13 other hospitals in the UK.

When is the study starting and how long is it expected to run for?
March 2016 to February 2021 (updated 12/04/2021, previously: March 2021)

Who is funding the study?
Versus Arthritis (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-002651-25

ClinicalTrials.gov (NCT)
NCT03708718

Protocol serial number
34302

Study information

Scientific Title
A Phase II randomised study of oral prednisolone in early diffuse cutaneous systemic sclerosis (initially double-blind, then switched to open-label because of COVID-19)

Acronym
PRedSS

Study objectives
The aim of this study is to determine whether:
1. Moderate dose prednisolone is effective in reducing pain, disability and skin thickening in patients with early diffuse scleroderma
2. Moderate dose prednisolone is a safe therapy in patients with early diffuse scleroderma (with particular reference to kidney function)

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West – Great Manchester South, 26/06/2017, ref: 17/NW/0320

Study design
Randomised; Interventional; Design type: Treatment, Process of Care, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Systemic sclerosis

Interventions
Current interventions as of 27/04/2020:
Participants are asked to sign a consent form following a full explanation of the study. Before any treatment is given, individuals are asked to attend a screening visit. A doctor performs a physical examination and takes routine urine and blood samples. If the doctor thinks the study is suitable, participants are asked to return to the hospital a total of four more times. The next visit (baseline visit) is scheduled within 28 days of the screening visit, then again at six weeks, three months and six months. At every visit, the doctor performs a physical examination and a routine blood and urine sample are collected. At each visit, participants are also be asked to complete ten questionnaires. The questionnaires will take approximately 25 minutes to fill in.

Following screening, eligible participants are randomised at the baseline visit to receive either daily moderate dose prednisolone (as determined by body weight) or a matched placebo. To further eliminate subjective and unrecognised bias both the research team and participants are blind to the randomisation. A placebo control, as opposed to an active treatment control, is administered. Randomisation is conducted by the King's CTU Randomisation service. Once site have an eligible patient, the local research team will log on to this system and participants are randomised electronically.

Patients receive either the active therapy or placebo for a total of six months, administered at the baseline visit. During the treatment period, patients will return for monitoring on 3 further occasions (six weeks, three months and six months). To avoid the risk of an Addisonian crisis, arising from the abrupt discontinuation of corticosteroid therapy, the treatment code will be broken at the six month visit. At this stage the clinician will decide, for patients receiving prednisolone, whether to recommend remaining on active treatment at the current dose, whether to reduce the dose or whether to gradually taper the dose with a view to discontinuing treatment. Blood and urine samples are also be collected to be analysed for biomarkers (substances for measuring or predicting the progress of the disease) in future scleroderma research projects. The analysis of these samples will not be part of the results of the PRedSS study. Participants are under no obligation to take part in this sample collection. Individuals are free to decide to take part in the PRedSS study but decline to have these extra samples taken. If participants provide samples for the biomarker research, no extra visits to the hospital are required. The samples are taken at baseline, three months and six months.

Participants are also be given a blood pressure monitor to take home and a study diary to record the blood pressure readings in. The doctor will advise blood pressure is measured twice a week, but this is not compulsory. Both diaries are checked at every visit by the research nurse.

At the six month visit, once all the tests have been completed, the doctor will tell participants which study treatment was received. Individuals who have been taking prednisolone will decide with the doctor if taking this medication should be continued (perhaps at a reduced dose) or gradually reduce the dose with a view to stopping the medication. At this point, individuals are no longer taking part in the PRedSS study. The doctor will recommend that participants see their usual hospital consultant within 30 days. Individuals prescribed the placebo can stop taking the capsules immediately.

Added 05/11/2020:
From August 2020:
1. The screening and baseline visits can take place on the same day, but this decision will be made by the local clinician. Ideally patients will attend all five scheduled visits in person. If necessary, the 6-week and 6-month visit can be conducted over the phone.
2. A placebo will no longer be given. Patients randomised to this arm of the study will receive no additional trial treatment. Patients will continue to take their current prescribed medication.
3. Biomarker samples - these are no longer being collected for future scleroderma research projects under the open-label phase of the trial due to the risks associated with COVID-19.
4. At the 6-month visit, all patients will already know which treatment arm they have been following. For patients prescribed prednisolone, the continuing treatment options following trial exit remain the same.

Previous interventions:
Participants are asked to sign a consent form following a full explanation of the study. Before any treatment is given, individuals are asked to attend a screening visit. A doctor performs a physical examination and takes routine urine and blood samples. If the doctor thinks the study is suitable, participants are asked to return to the hospital a total of four more times. The next visit (baseline visit) is scheduled within 28 days of the screening visit, then again at six weeks, three months and six months. At every visit, the doctor performs a physical examination and a routine blood and urine sample are collected. At each visit, participants are also be asked to complete nine questionnaires. The questionnaires will take approximately 25 minutes to fill in.

Following screening, eligible participants are randomised at the baseline visit to receive either daily moderate dose prednisolone (as determined by body weight) or a matched placebo. To further eliminate subjective and unrecognised bias both the research team and participants are blind to the randomisation. A placebo control, as opposed to an active treatment control, is administered. Randomisation is conducted by the King's CTU Randomisation service. Once site have an eligible patient, the local research team will log on to this system and participants are randomised electronically.

Patients receive either the active therapy or placebo for a total of six months, administered at the baseline visit. During the treatment period, patients will return for monitoring on 3 further occasions (six weeks, three months and six months). To avoid the risk of an Addisonian crisis, arising from the abrupt discontinuation of corticosteroid therapy, the treatment code will be broken at the six month visit. At this stage the clinician will decide, for patients receiving prednisolone, whether to recommend remaining on active treatment at the current dose, whether to reduce the dose or whether to gradually taper the dose with a view to discontinuing treatment. Blood and urine samples are also be collected to be analysed for biomarkers (substances for measuring or predicting the progress of the disease) in future scleroderma research projects. The analysis of these samples will not be part of the results of the PRedSS study. Participants are under no obligation to take part in this sample collection. Individuals are free to decide to take part in the PRedSS study but decline to have these extra samples taken. If participants provide samples for the biomarker research, no extra visits to the hospital are required. The samples are taken at baseline, three months and six months.

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At the six month visit, once all the tests have been completed, the doctor will tell participants which study treatment was received. Individuals who have been taking prednisolone will decide with the doctor if taking this medication should be continued (perhaps at a reduced dose) or gradually reduce the dose with a view to stopping the medication. At this point, individuals are no longer taking part in the PRedSS study. The doctor will recommend that participants see their usual hospital consultant within 30 days. Individuals prescribed the placebo can stop taking the capsules immediately.

Intervention Type
Other

Primary outcome(s)
1. Functional ability is measured using the Health Assessment Questionnaire Disability Index (HAQ-DI) at baseline and three months
2. Pain is measured using the Health Assessment Questionnaire Disability Index (HAQ-DI) at baseline and three months
3. Skin score is measured using the modified Rodnan skin score (mRSS) at baseline and three months

Key secondary outcome(s))
Current secondary outcome measures as of 27/04/2020:
1. Functional ability and pain are measured using the HAQ-DI at six weeks and six months
2. Skin score is measured using the mRSS at six weeks and six months
3. Percentage change in skin score from baseline is measured using the mRSS at six weeks, three months and six months
4. Functional ability, to complement the HAQ-DI, will be measured by the 11 point scleroderma functional index at baseline, six weeks, three months and six months
5. Pain is measured using the visual analogue scale (part of the HAQ-DI) at baseline, six weeks, three months and six months
6. Pruritus is measured using the 5-D Itch questionnaire at baseline, six weeks, three months and six months
7. Hand function is measured using the Cochin Hand Function scale at baseline, six weeks, three months and six months
8. Fatigue is measured using the Functional Assessment of Chronic Illness Therapy (FACIT) questionnaire at baseline, six weeks, three months and six months
9. Anxiety and depression are measured using the Hospital Anxiety and Depression Scale at baseline, six weeks, three months and six months
10. Helplessness is measured using the Helplessness questionnaire at baseline, six weeks, three months and six months
11. Health-related quality of life is measured using the Short Form (36) Health Survey (version 2) (SF-36v2) and the EuroQol five dimensions questionnaire (EQ-5D) at baseline, six weeks, three months and six months
12. A patient global assessment and physician global assessment are measured using a visual analogue scale at baseline, six weeks, three months and six months
13. Digital Ulcer Count, Tendon Friction Rubs and joint count are measured at baseline, six weeks, three months and six months
14. Arthritis Index is measured using the Rheumatology Attitudes questionnaire at baseline, six weeks, three months and six months
15. Safety measures as defined by renal crisis are measured at baseline, six weeks, three months and six month

16. Health-related quality of life related to skin involvement as measured by the Scleroderma Skin Patient Reported Outcome questionnaire at baseline, six weeks, three months and six months

Previous secondary outcome measures:
1. Functional ability and pain are measured using the HAQ-DI at six weeks and six months
2. Skin score is measured using the mRSS at six weeks and six months
3. Percentage change in skin score from baseline is measured using the mRSS at six weeks, three months and six months
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Completion date
27/05/2021

Eligibility

Key inclusion criteria
1. Patients presenting with diffuse cutaneous systemic sclerosis with skin involvement extending to the proximal limb and/or trunk
2. Male or female age ≥ 18 years
3. Skin involvement of less than 3 years defined by patient report or clinician opinion
4. Patient is able and willing to follow the requirements of the study
5. Fully written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
35

Key exclusion criteria
Current participant exclusion criteria as of 27/04/2020:
1. Patients with significant uncontrolled Stage 1 Hypertension (clinic BP > 140/90mmHg). Patients with previous hypertension which is controlled (clinic BP < 140/90mmHg) for at least 4 weeks are considered eligible
2. Previous renal crisis or significant renal impairment (estimated Glomerular Filtration Rate (eGFR) < 40 ml/min)
3. Patients currently on steroid therapy, or previous steroid therapy within the last 4 weeks, with the exception of inhaled steroids for respiratory diseases or topical steroids for skin disease
4. Patients currently participating in another randomised controlled trial of an investigational agent or device, or previous participation within the last 30 days
5. Patients currently receiving an immunosuppressant or biologic therapy the dose of which has changed in the last 4 weeks prior to the baseline visit, or is likely to change during the first 3 months of study treatment
6. Patients with major myositis or inflammatory arthritis. Patients with low level myositis or inflammatory arthritis are eligible for inclusion (for example, in the case of myositis, a creatine kinase less than 4 times the upper limit of normal or myositis only demonstrable on magnetic resonance imaging).
7. Female patients who are pregnant at time of screening
8. Patients with significant inflammatory bowel disease as judged by the investigator
9. It is important that patients do not suddenly stop taking the study medication

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4. Patients currently participating in another randomised controlled trial of an investigational agent or device, or previous participation within the last 30 days
5. Patients currently receiving an immunosuppressant or biologic therapy the dose of which has changed in the last 4 weeks, or is likely to change during the first 3 months of study treatment
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Date of first enrolment
25/09/2017

Date of final enrolment
01/02/2021

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Salford Royal NHS Foundation Trust (Lead centre)
Department of Rheumatology
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Royal Free Hospital
University College London
Faculty of Medical Sciences
Division of Medicine
Centre for Rheumatology and Connective Tissue Diseases
Rowland Hill Street
London
United Kingdom
NW3 2PF

Study participating centre
Chapel Allerton Hospital
Leeds Institute of Rheumatic & Musculoskeletal Medicine (LIRMM)

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LS7 4SA

Study participating centre
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United Kingdom
BS10 5NB

Study participating centre
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NG7 2UH

Study participating centre
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BA1 1RL

Study participating centre
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Institute for Ageing and Chronic Disease
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Study participating centre
The Freeman Hospital
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Study participating centre
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Study participating centre
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Study participating centre
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DY1 2HQ

Study participating centre
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Study participating centre
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James Arrott Drive

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DD1 9SY

Sponsor information

Organisation
The University of Manchester

ROR
https://ror.org/027m9bs27

Funder(s)

Funder type
Charity

Funder Name
Versus Arthritis

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol article	protocol	17/09/2020	09/11/2020	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes