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Cardiovascular events and mortality in systemic sclerosis (SSc): a study of the effect of iloprost on these and on disease progression

Submission date
13/07/2005

Recruitment status
No longer recruiting

Registration date
07/09/2005

Overall study status
Completed

Last Edited
30/04/2020

Condition category
Musculoskeletal Diseases

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

Plain English summary of protocol

Background and study aims
Systemic sclerosis is a long-term condition that causes thickening and hardening of the skin and can also affect the internal organs. Death from cardiovascular (heart) disease is a significant problem for patients with systemic sclerosis, accounting for one third of all deaths in this population. The drug iloprost, delivered into a vein (intravenous), will be a familiar treatment to many patients with systemic sclerosis. It is used as a prophylactic (preventative) treatment for Raynaud's phenomenon (spasm of the small blood vessels in the fingers and toes). However, its effect as a blood vessel dilator may also prevent patients with systemic sclerosis from developing cardiovascular disease. The aim of this study is to find out whether oral iloprost treatment is effective at reducing systemic sclerosis disease progression.

Who can participate?
Patients over 40 years of age with systemic sclerosis

What does the study involve?
Participants take a placebo (dummy drug) for one month to ensure that they are compliant with the study medication in that period. Following this phase, all participants are reviewed first at three months (to ensure stability on treatment and absence of serious side effects); at six months; and then six monthly until their final visit at the end of the study. Participants are randomly allocated to take either iloprost or placebo as one tablet (50mcg) daily for one week. This is then increased to one tablet twice daily for a further week, then one tablet three times daily for a further week and, if tolerated, then increased to the maximum desired dose of 200mcg daily (100mcg twice daily) and kept at that dose for the duration of the study. Participants are then followed up to assess disease progression for a period of 4 to 7 years based on when they joined the study.

What are the possible benefits and risks of participating?
This study is important as it takes a medication known to be of use for some aspects of systemic sclerosis and investigates whether it may prevent cardiovascular disease which may result in death. This study involves the collaboration of medical, nursing and other staff with expertise in

this area throughout the UK and Eire. It also provides a further opportunity to follow up patients for over 4 years to look at other important aspects of this disease, namely heart, lung and kidney function, to find out whether this treatment is protective of other organs as well. There may be risks involved with participation in this study related to possible side effects of the drug iloprost, which may include flushing, light-headedness, dizziness, faintness or low blood pressure, nausea, and headache. Although iloprost has been used and tested before, side effects may occur which have not been seen previously.

Where is the study run from?
1. Ninewells Hospital (UK)
2. Foresterhill Hospital (UK)
3. Woolmanhill Hospital (UK)
4. Western General Hospital (UK)
5. St John's Hospital (UK)
6. Glasgow Royal Infirmary (UK)
7. Freeman Hospital (UK)
8. Chapel Allerton Hospital (UK)
9. Royal St James Hospital (UK)
10. Northampton General (UK)
11. Royal Free Hospital (UK)
12. St Vincent's Hospital (Ireland)

When is the study starting and how long is it expected to run for?
February 2002 to December 2008

Who is funding the study?
Raynaud's and Scleroderma Association (UK)

Who is the main contact?
1. Prof. Jill Belch
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2. Dr Stephen McSwiggan
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title
Cardiovascular events and mortality in systemic sclerosis (SSc): a study of the effect of iloprost on these and on disease progression

Acronym
SSTEP: Systemic Sclerosis Trial of Events and Progression

Study objectives
That oral iloprost therapy is more effective than placebo in reducing SSc disease progression, and coronary and cerebrovascular events in patients with SSc.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scotland ‘A’ REC, 08/11/2001, ref: MREC 01/0/70

Study design
Randomised placebo-controlled parallel-group 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 the contact details to request a patient information sheet

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

Interventions
Oral iloprost or placebo

Added 11/08/2017:
The study was a randomised, placebo-controlled clinical trial with a one month placebo run in to ensure patients were compliant with study medication in that period. Following this placebo run in phase, all patients enrolled in the study were reviewed first at three months (to ensure stability on treatment and absence of serious side effects); at six months; and then six monthly until their final visit at the end of the study period. Block randomisation was done for each site in blocks of six (three active versus three placebo) to ensure even distribution, where possible, of active and placebo allocation at each site. Investigators and participants were blinded to treatment. Study drugs and placebo were in small identical capsules of 50 mcg doses. Participants were advised to continue on one tablet (50mcg) daily for one week. This was then increased to one tablet twice daily for a further week, then one tablet three times daily for a further week and, if tolerated, then titrated to the maximum desired dose of 200mcg daily (100mcg bd) and maintained at that dose for the duration of the trial. Participants were then followed up for a period of 4 to 7 years dependent on time of enrolment.

Iloprost and placebo composition
Active ingredient in the Iloprost capsules was 0.38 mg Iloprost β-cyclodextrin clathrate (50µg Iloprost and 0.33mg β-cyclodextrin) with the following inactive ingredients:
1. Lactose monohydrate
2. Microcrystalline cellulose
3. Methacrylic acid copolymer (Eudragit NE 3OD)
4. Magnesium stearate
5. Titanium dioxide
6. Polyethlene glycol 6000
7. Polysorbate 80
8. Silicon dioxide
9. Hard gelatin capsule (containing titanium dioxide, iron oxide (red) and gelatin)
The matched placebo was identical to the Iloprost capsule but lacked the active ingredient, Iloprost β-cyclodextrin clathrate.

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome measure
A composite primary endpoint is sought for this study.
1. Fatal coronary and stroke events plus non fatal myocardial infarction and stroke
2. Vascular disease death
3. SSc disease progression to include:
3.1. Deteriorating renal function as measured by 24-hour urine and blood sampling for creatinine clearance
3.2. Deteriorating lung function as measured by changes in DLCO total lung capacity
3.3. Increase in pulmonary artery pressure measured in millimetres in mercury by echocardiogram
3.4. Skin score assessed using the modified Rodnan Skin Score
These will be monitored and percentage change from baseline calculated. If deterioration is indicated by an increasing figure then 30% change will be required. If deterioration is based on a decreasing number then 20% change from baseline will be required. Additionally the Medsger categories will be evaluated. A final decision regarding the primary endpoints will be carried out by the Data and Safety Monitoring Committee approximately 8 months into the study. The definition of the above cardiovascular (CV) events will be made according to the World Health Organisation (WHO) Criteria for the diagnosis of coronary events and stroke (fatal and non-fatal).

Secondary outcome measures
The main secondary endpoints are:
1. All cause mortality
2. Non-fatal myocardial infarction and stroke
3. Occurrence of other vascular events including requirement of coronary or peripheral arterial bypass surgery and/or angioplasty, development of angina, claudication or development of critical limb ischaemia
4. Severity of Raynaud's Phenomenon

Overall study start date
07/02/2002

Completion date
31/12/2008

Eligibility

Key inclusion criteria
Subjects will be patients with both limited and diffuse SSc, as our pilot work has shown atherosclerotic vascular disease to occur in both groups. The patients considered for this study will be as follows:
1. Any patient fulfilling Arthritis Research Campaign (ARC) criteria for SSc
2. Any patient with Raynauds Phenomenon and at least 3 other features of limited SSc
3. Any patient with Raynauds Phenomenon and the presence of an SSc-related autoantibody (e.g. anticentromere, antitopo1 [scleroderma 70], anti-U1RNP, anti-ThRNP, anti-U3RNP, anti-PmScl)

All will be >40 years of age. These patients will be recruited from Connective Tissue Disease clinics throughout Tayside, Fife, Strathclyde, Lothian, Grampian, Yorkshire, Bath, Northamptonshire and Ireland. Patients with SSc will be invited to attend the clinics to have their vascular risk factors assessed. Volunteers will then be asked to give informed consent and if that consent is given, enter the screening phase of the study

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
215

Key exclusion criteria
1. Suspected serious physical illness such as cancer which may be expected to curtail life expectancy
2. Psychiatric illness (reported by GP)
3. Congenital heart disease
4. Any patient who is pregnant or who wishes to become pregnant within the time course of the study

Date of first enrolment
07/02/2002

Date of final enrolment
28/02/2005

Locations

Countries of recruitment
England

Ireland

Scotland

United Kingdom

Study participating centre
Ninewells Hospital
Dundee
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DD1 9SY

Study participating centre
Foresterhill Hospital
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AB25 2ZG

Study participating centre
Woolmanhill Hospital
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AB25 1LD

Study participating centre
Western General Hospital
United Kingdom
EH4 2XU

Study participating centre
St John's Hospital
United Kingdom
EH54 6PP

Study participating centre
Glasgow Royal Infirmary
United Kingdom
G4 0SF

Study participating centre
Freeman Hospital
United Kingdom
NE7 7DN

Study participating centre
Chapel Allerton Hospital
United Kingdom
LS7 4SA

Study participating centre
Royal St James Hospital
United Kingdom
LS9 7TF

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Northampton General Hospital
United Kingdom
NN1 5BD

Study participating centre
Royal Free Hospital
United Kingdom
NW3 2QG

Study participating centre
St Vincent's Hospital
United Kingdom
D04 Y8V0

Sponsor information

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University of Dundee (UK)

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Sponsor type
University/education

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

ROR
https://ror.org/03h2bxq36

Funder(s)

Funder type
Charity

Funder Name
Raynaud's and Scleroderma Association

Alternative Name(s)
RSA

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Protocol and statistical plan are available direct on request. The trialists plan to publish the protocol if possible. Planned publication in a high-impact peer reviewed journal of 10-year follow-up data.

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository - the local Safe Haven, the Tayside Health Informatics Centre: https://www.dundee.ac.uk/hic.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic		09/08	24/08		

results		/2017	/2017	No	No
Results article	results	01/01 /2019	17/01 /2019	Yes	No
Results article	results	01/11 /2016	17/01 /2019	Yes	No
Results article	results of a parenting program among women who began childbearing as adolescents and young adults	01/11 /2017	17/01 /2019	Yes	No
Results article	results of promoting child development through group-based parent support within a cash transfer program	01/02 /2017	17/01 /2019	Yes	No
Results article	results of stimulating parenting practices in indigenous and non-indigenous Mexican communities	25/12 /2017	17/01 /2019	Yes	No