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Rivaroxaban in Antiphospholipid Syndrome (RAPS)

Submission date
17/10/2012

Recruitment status
No longer recruiting

Registration date
18/10/2012

Overall study status
Completed

Last Edited
30/08/2016

Condition category
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Antiphospholipid syndrome (APS), in patients with or without lupus, causes blood clots (thrombosis); any blood vessel in the body is at risk but most commonly a deep vein thrombosis (DVT) occurs. If a clot dislodges from the DVT, it can travel to the lungs, causing life-threatening pulmonary embolism (PE). Long-term anticoagulation with warfarin is the established treatment following DVT and/or PE to prevent further thrombosis, which can be life-threatening. Treatment with warfarin, although effective, is problematic as it can interact with numerous drugs and dietary constituents. Its action can also be affected by alcohol, smoking, other illnesses and exercise. Patients therefore require frequent INR blood tests (INR = International Normalised Ratio, the test used to monitor warfarin), which is inconvenient for the patient and costly for the NHS. In thrombotic APS patients, warfarin effects can be more erratic, because these patients have antiphospholipid antibodies which recognise proteins that bind to the surface of blood cells/vessels as "the enemy". They cause thrombosis and can also interfere with the effects of warfarin. Rivaroxaban is a recently introduced oral anticoagulant (blood thinner), which is given as fixed-dose tablets once daily. Unlike warfarin, rivaroxaban does not require routine monitoring because it has a predictable anticoagulant effect. Also, unlike warfarin, rivaroxaban does not interact with food or alcohol and has few drug interactions. It is unlikely that antiphospholipid antibodies will interfere with rivaroxaban's effects on blood clotting as, unlike warfarin, it has a very targeted effect on blood. We plan to compare the anticoagulant (blood thinning) effect of rivaroxaban with that of warfarin in patients with thrombotic APS, with or without lupus. We will do this by assessment of a specialised and excellent measure of anticoagulation called the 'thrombin generation test' (TGT). We will also assess rates of bleeding and further thrombosis, and compare serious adverse events and quality of life in patients on rivaroxaban with those on warfarin. If we can demonstrate that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin, and that there is no increase in the rate of serious adverse effects (very unlikely - see below), we believe that this would provide good evidence to change practice for our patients, and make rivaroxaban the standard of care for patients with thrombotic APS, with or without lupus.

Who can participate?
Patients with thrombotic APS, with or without lupus, who have had a DVT and/or PE, and have been on warfarin at a target INR of 2.5 (range 2.0-3.0) for at least six months will be invited to take part in the study.

What does the study involve?
Patients will be randomly allocated to either remain on warfarin or to switch to rivaroxaban. Where possible, trial visits will be arranged to coincide with routine follow-up, and about three additional visits will be necessary. Trial visits will enable face-to-face contact with healthcare professionals to discuss any concerns and patients will be able to contact the Research Nurse to discuss any problems between visits. Two extra blood samples (each about four teaspoonfuls) will be taken prior to random allocation and six weeks later, in addition to routine blood tests. The trial treatment will last for six months and following this, patients will be offered appropriate anticoagulation.

What are the possible benefits and risks of participating?
Rivaroxaban is licensed in the UK and approved by NICE for the prevention of DVT/PE in patients undergoing hip and knee replacements and also for the treatment of DVT and prevention of recurrent DVT and PE following an acute DVT; and the prevention of stroke in patients with atrial fibrillation (an abnormal heart rhythm associated with an increased risk of stroke). Studies on tens of thousands of patients with DVT/PE or other conditions have shown that rivaroxaban is effective with a similar safety profile to warfarin. Indeed, to date in studies on a total of over 65,000 patients no major safety issues have emerged. It is likely that some patients with APS were included in the studies on DVT/PE, but there is no separate information available on this group.

Where is the study run from?
The study will take place at University College London Hospitals NHS Foundation Trust and Guys and St Thomas' NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
November 2012 to January 2015

Who is funding the project?
Arthritis Research UK and Bayer PLC

Who is the main contact?
RAPS Trial Manager
rapstrial@ucl.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-002345-38

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
13117

Study information

Scientific Title
A prospective randomised controlled phase II/III clinical trial of rivaroxaban versus warfarin in patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus

Acronym
RAPS

Study objectives
Antiphospholipid syndrome (APS) is an autoimmune disease that is caused by antibodies against normal blood proteins that bind to cell-membrane phospholipids that can provoke thrombosis. Patients with thrombotic APS experience venous and/or arterial thrombosis in association with persistent antiphospholipid antibodies. These thrombotic events are potentially fatal and patients require long-term anticoagulation therapy, with warfarin the mainstay. APS can also occur in patients with other autoimmune diseases, such as systemic lupus erythematosus (SLE).

Treatment with warfarin, although effective, is problematic as it can interact with numerous drugs and dietary constituents. Its action can also be affected by alcohol, smoking, intercurrent illness and exercise. Patients therefore require frequent monitoring, which is inconvenient for the patient and costly for the NHS. Rivaroxaban is a new, recently introduced fixed-dose oral anticoagulant with predictable anticoagulant effect, few reported drug interactions and no interactions with food or alcohol, and does not require routine anticoagulant monitoring.

156 patients with venous thromboembolism on warfarin for at least 6 months at a target INR (International Normalised Ratio; the test used to monitor the anticoagulant effects of warfarin) of 2.5, will be randomised to either continue with warfarin, or to switch to a daily 20 mg dose of rivaroxaban for 6 months. After the therapeutic phase of the trial, patients will be offered what is considered appropriate anticoagulation.

The primary aim of the trial is to assess the non-inferiority of the anticoagulant effects of rivaroxaban in comparison to warfarin. This will be achieved by comparing thrombin generation 42 days after randomisation in the two groups, assessed by the thrombin generation test (TGT), with the endogenous thrombin potential (ETP) a key parameter.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee South Central - Oxford A, 30/10/2012, ref: 12/SC/0566

Study design
Randomised interventional 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 below to request a patient information sheet

Health condition(s) or problem(s) studied
Thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus

Interventions
1. 20 mg rivaroxaban taken orally once daily for patient without renal impairment (creatinine clearance = 50 mL/min), for six months.
2. 15 mg rivaroxaban taken orally once daily for patients with moderate renal impairment (creatinine clearance of 30 - 49 mL/min), for six months.
3. Warfarin: This is the control arm where the treatment of patients with warfarin will remain unchanged. Warfarin will be prescribed and dispensed in accordance with national guidance and warfarin anticoagulant monitoring will be undertaken by the patient's usual anticoagulation clinic, which may be based at one of the trial sites or locally to the patient, either within a hospital or primary care anticoagulation clinic setting, or by patient self-monitoring under medical supervision.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Rivaroxaban, warfarin

Primary outcome measure
The percentage change in ETP from randomisation to day 42

Secondary outcome measures
1. Efficacy
2. Safety
3. Quality of life (QoL)
4. Laboratory assessment of compliance

Overall study start date
30/11/2012

Completion date
31/01/2015

Eligibility

Key inclusion criteria
Current inclusion criteria as of 02/10/2013:
1. Patients with thrombotic APS, with or without SLE, who have had either a single episode of VTE whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy
2. Patients with a target INR of 2.5 (range 2.0-3.0)
3. Treated with warfarin for a minimum period of three months since last VTE
4. Female patients must be using adequate contraception with the exception of postmenopausal or sterilised women

Previous inclusion criteria:
1. Patients with thrombotic APS, with or without SLE, who have had either a single episode of VTE whilst not on anticoagulation or recurrent episode(s) which occurred whilst off anticoagulation or on sub-therapeutic anticoagulant therapy.
2. Patients with a target INR of 2.5 (range 2.0-3.0)
3. Treated with warfarin for a minimum period of six months since last VTE
4. Female patients must be using adequate contraception with exception to postmenopausal or sterilised women

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
UK Sample Size: 156

Key exclusion criteria
Current exclusion criteria as of 02/10/2013:
1. Previous arterial thrombotic events due to APS
2. Recurrent venous thromboembolic events whilst on warfarin at a therapeutic INR of 2.0-3.0
3. Pregnant or lactating women
4. Severe renal impairment (creatinine clearance [calculated using the Cockcroft & Gault formula Appendix A] < 30 mL/min (i.e. 29 mL/min or less)
5. Liver function tests ALT > 2 x ULN
6. Cirrhotic patients with Child Pugh B or C
7. Thrombocytopenia (platelets < 75 x 10^9/L)
8. Non-compliance on warfarin (based on clinical assessment)
9. Patients on azole antifungals (e.g. ketoconazole, itraconazole, voriconazole and posaconazole)
10. Patients on Human Immunodeficiency Virus (HIV) protease inhibitors (e.g. ritonavir)
11. Patients on strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort)
12. Patients less than 18 years of age
13. Refusal to consent to the site informing GP and healthcare professional responsible for anticoagulation care, of participation

Previous exclusion criteria:
1. Previous arterial thrombotic events due to APS
2. Recurrent venous thromboembolic events whilst on warfarin at a therapeutic INR of 2.0-3.0
3. Pregnant or lactating women
4. Severe renal impairment (creatinine clearance [calculated using the Cockcroft & Gault formula Appendix A of the protocol] < 30 mL/min (i.e. 29 mL/min or less)
5. Liver function tests ALT > 2 x ULN
6. Cirrhotic patients with Child Pugh B or C
7. Thrombocytopenia (platelets < 75 x 10^9/L)
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12. Patients less than 18 years of age
13. Refusal to consent to CTU informing GP of participation

Date of first enrolment
30/11/2012

Date of final enrolment
31/03/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University College London
London
United Kingdom
WC1E 6BT

Sponsor information

Organisation
University College London (UK)

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WC1E 6BT

Sponsor type
University/education

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

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Arthritis Research UK (formerly ARC Arthritis Research Campaign) (UK)

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location

United Kingdom

Funder Name
Bayer PLC (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?
Protocol article	protocol	01/09/2015		Yes	No
Results article	results	01/09/2016		Yes	No
HRA research summary			28/06/2023	No	No