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Rituximab for the treatment of fatigue in primary biliary cirrhosis

Submission date	Recruitment status	[X] Prospectively registered
23/08/2012	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
23/08/2012	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
29/08/2019	Digestive System	

Plain English summary of protocol

Background and study aims:
Primary Biliary Cirrhosis (PBC) is a liver disease that predominantly affects females. PBC can arise for the first time at any age and develops over many years. It is caused by the immune system attacking the body's own tissues. People with PBC often feel tiredness (fatigue) which they describe as their 'batteries running down'. Although people still want to undertake normal activities, they lack the energy to be able to do them. This reduces quality of life, makes it difficult for people to work, and can end up with them becoming isolated in the community. At present we have no treatment for fatigue in PBC. We have found that that PBC patients with fatigue are unable to generate energy within their muscles correctly. This is associated with the presence of a component (antibody) in the blood which works against an important protein which normal cells in the body use to generate energy. The aim of this study is to examine the effects of a treatment (Rituximab) on severe fatigue in PBC to help us understand whether this will be a useful treatment. This information will tell us how energy generation changes in patients with PBC with and without the treatment and will also help us to develop new treatments for fatigue in other diseases.

Who can participate?
A total of 78 patients, males and females, aged 18 years and above diagnosed with PBC and severe fatigue.

What does the study involve?
Participants will be allocated at random to receive either Rituximab treatment or a salt solution (placebo). The study will take place over approximately one year and involve between 9 and 20 visits depending on the planning of some investigations. All participants will be asked to provide some extra blood (up to 6 teaspoonfuls) at the start of the study and after three, six, nine and twelve months for analysis of the cells and proteins in their blood and will collect normal clinical information about the severity of their liver disease. In addition, participants will have their activity levels monitored for a week using a small device, the size of a wrist watch, exercising twice on an exercise bike to measure their oxygen used and have two MRI scans.

What are the possible benefits and risks of participating?
The study has the potential to improve the quality of life of many patients with PBC, for whom

there is currently no hope of improvement. Blood sampling can sometimes cause bruising and soreness of the arms, or very rarely a blockage of the vein or a small nerve injury which can cause numbness and pain. Normally these problems resolve with time. Some people may faint while blood is being drawn.
Measurement of physical activity is a routine clinical investigation which involves wearing a small device like an armband to be worn on the back of the upper right arm for a week. This can be removed for showering etc. Participants will have two MR scans of their muscles whilst they perform gentle exercises by repeated flexion of the foot against a weight and the MRI scanner measures acid accumulation. MR scanning can be very noisy, and sometimes people feel more tired than normal after they have exercised in the scanner.

Where is the study run from?
The Clinical Research Facility, Royal Victoria Infirmary.

When is the study starting and how long is it expected to run for?
The start date is 1 October 2012, end date is 30 September 2015.

Who is funding the study?
Medical Research Council, National Institute of Health Research - Efficacy and Mechanism Evaluation Programme, Department of Health Subvention grant

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02376335

Clinical Trials Information System (CTIS)
2012-000145-12

Protocol serial number
12953

Study information

Scientific Title
Rituximab for the treatment of fatigue in primary biliary cirrhosis

Acronym
RITPBC

Study objectives
Primary Biliary Cirrhosis (PBC) is a liver disease that predominantly affects females, can present for the first time at any age and which develops over many years. It is caused by the immune system attacking the body's own tissues.

People with PBC frequently experience profound fatigue or tiredness which they liken to their 'batteries running down' and although people still want to undertake normal activities they simply lack the energy to be able to do them. This reduces quality of life, makes it difficult for people to work, and can end up with them becoming isolated in the community. At present we have no treatment for fatigue in PBC. Finding a treatment for fatigue in PBC is one of the highest research priorities identified by patient groups.

We have shown that PBC patients with fatigue have an abnormality in the way they generate energy within their muscles. This appears to be associated with the presence of an antibody in the blood which is directed against an important protein which normal cells in the body use to generate energy. In recent years new drug treatments have been developed which allow us to safely suppress the part of the immune system which produces antibodies of the type that seem to cause energy production problems in PBC. As yet, however, the extent to which these medicines can improve fatigue through removal of antibodies in PBC has not been tested.

The aim of this study is to undertake a clinical trial to examine the effects of this treatment (Rituximab) on severe fatigue in PBC to help us understand whether this will be a potentially useful treatment. This information will tell us how energy generation changes in patients with PBC with and without the treatment and will also help us to develop new treatments for fatigue in other diseases. The study has the potential to improve the quality of life of many patients with PBC, for whom there is currently no hope of improvement.

More details can be found here: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=12953

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North East - Newcastle & North Tyneside 1, 16/05/2012, ref: 12/NE/0095

Primary study design
Interventional

Study design
Randomised interventional trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Oral and gastrointestinal, hepatology

Interventions
This is a phase II, single-centre, randomised controlled, double-blinded trial comparing rituximab with placebo in fatigued Primary Biliary Cirrhosis patients over 12 months.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Fatigue severity in PBC patients and quality of life measured at baseline, 12 weeks, and three monthly thereafter up to 12 months

Key secondary outcome(s)
Added 25/11/2015:
1. Improvement in physical activity assessed using seven day physical activity monitoring (previously shown to be impaired in fatigued PBC patients with degree of impairment shown to associate with perceived fatigue severity)
2. Improvement in daytime somnolence (as assessed using the Epworth Sleepiness Scale (ESS)), vasomotor autonomic symptoms (assessed using the Orthostatic Grading Scale (OGS)), functional status (assessed using Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire (PROMIS HAQ) and the Cognitive Failure questionnaire (COGFAIL)). Reduction in depressive and anxiety-related symptoms will be assessed using the Hospital Anxiety and Depression Scale (HADS)
3. Reduction in serum anti-pyruvate dehydrogenase complex antibody levels assessed using ELISA and in numbers of peripheral blood B-cells specific for pyruvate dehydrogenase complex assessed using a novel tetramer-based technology (to confirm whether any clinical effect is directly related to antibody modulation)
4. Improvement in peripheral muscle bio-energetic function on exercise (to confirm whether any clinical effect is directly related to effects on muscle bioenergetic function)

The secondary outcomes will be measured at baseline and 12 weeks.

Completion date
01/10/2016

Eligibility

Key inclusion criteria
1. Age 18 years or over
2. Patient has capacity and provided written informed consent for participation in the study prior to any study specific procedures
3. Moderate or severe fatigue as assessed using previously designated cut-offs of the PBC-40 fatigue domain (i.e. fatigue domain score >33)
4. Presence of AMA (anti-PDH antibody) at a titre of >1:40
5. Adequate haematological function Hb >9g/L, absolute neutrophil count >1.5x109/L, platelet count > 50x109/L
6. Bilirubin = 50 µmol
7. INR = 1.5
8. Child-Pugh score < 7
9. ECOG performance status < 2
10. Adequate renal function Cockroft and Gault estimation > 40ml/min
11. Women of childbearing potential should have a negative pregnancy test prior to study entry AND be using an adequate contraception method, which must be continued for 3 months after completion of treatment
12. Male & female participants

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Advanced or decompensated disease (variceal bleed, hepatic encephalopathy or ascites)
2. History or presence of other concomitant liver diseases (including hepatitis due to hepatitis B or C or evidence of chronic viraemia on baseline screening), primary sclerosing cholangitis or biopsy proven non-alcoholic steatohepatitis)
3. Average alcohol ingestion >21 units/week (male) or >14 units / week (female)
4. Chronic sepsis or intercurrent condition likely to predispose to chronic sepsis during the study
5. Previous treatment with B-cell depleting therapy
6. Previous history of aberrant response or intolerance to immunological agents
7. Presence of significant untreated intercurrent medical condition itself associated with fatigue
8. Presence of significant risk of depressive illness (HADS score indicating caseness)
9. Current statin therapy or statin use within 3 months of enrolment
10. Ongoing participation in other clinical trials or exposure to any investigational agent 4 weeks prior to baseline or within <5 half lives of the investigational drug
11. Major surgery within 4 weeks of trial entry
12. Vaccination within 4 weeks of trial entry, patients requiring seasonal flu or travel vaccines will be required to wait a minimum of 4 weeks post vaccination to enroll in the trial

13. Pregnant or lactating women
14. Psychiatric or other disorder likely to impact on informed consent
15. Patient is unable and/or unwilling to comply with treatment and study instructions
16. Any other medical condition that, in the opinion of the investigator would interfere with safe completion of the trial
17. Hypersensitivity to the active substance (Rituximab) or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water (for infusion)) or to murine proteins
18. Active, severe infections (e.g. tuberculosis, sepsis or opportunistic infections)
19. Known HIV infection
20 .Clinical history of Latent TB infection unless the patient has completed adequate antibiotic prophylaxis
21. AST/ALT 4 x Upper Limit of Normal
22. Severe immune-compromised state
23. Severe heart failure (NYHA Class IV) or severe uncontrolled cardiac disease
24. Malignancy (other than basal cell carcinoma) within the last 10 years
25. Demyelinating disease
26. Previous participation in this trial
27. Any contraindication to Rituximab therapy not covered by other exclusions

Date of first enrolment
01/10/2012

Date of final enrolment
01/10/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Institute of Health and Society
Newcastle Upon Tyne
United Kingdom
NE2 4HH

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Department of Health (UK)

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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	01/04/2018		Yes	No
Protocol article	protocol	20/08/2015		Yes	No
HRA research summary			28/06/2023	No	No