BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-007985
Article Type:	Protocol
Date Submitted by the Author:	17-Feb-2015
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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Hepatobiliary disease < GASTROENTEROLOGY, IMMUNOLOGY, Clinical trials < THERAPEUTICS

RITPBC: B-Cell Depleting Therapy (Rituximab) as a Treatment for Fatigue in Primary Biliary Cirrhosis: study protocol for a randomised controlled trial

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Abstract

Background

Primary Biliary Cirrhosis (PBC) is an autoimmune liver disease with approximately 50% of patients experiencing fatigue. This can be a particularly debilitating symptom, affecting quality of life and resulting in social isolation. Fatigue is highlighted by patients as a priority for research and patient support groups were involved in designing this trial. This is the first randomised controlled trial to investigate a treatment for fatigue in PBC. The trial protocol is innovative as it utilises novel Magnetic Resonance Spectroscopy (MRS) techniques as an outcome measure. The protocol will be valuable to research groups planning clinical trials targeting fatigue in PBC and also transferrable to other conditions associated with fatigue.

Methods/Design

RITPBC is an MRC and NIHR Efficacy and Mechanism Evaluation Programme (EME) funded project. It is a phase II, single-centre, randomised controlled, double blinded trial comparing rituximab with placebo in fatigued PBC patients. 78 patients with PBC and moderate to severe fatigue will be randomised to receive two infusions of rituximab or placebo. The study aims to assess whether rituximab improves fatigue in patients with PBC, the safety and tolerability of rituximab in PBC and the sustainability of its beneficial actions. The primary outcome will be an improvement in fatigue domain score of the PBC-40, a disease-specific quality of life measure, evaluated at 12 week assessment. Secondary outcome measures include novel MRS techniques to assess muscle bio-energetic function, physical activity, anaerobic threshold and symptom and quality of life measures.

The trial started recruiting in October 2012 and is open to recruitment until April 2015.

Ethics and dissemination

The trial has ethical approval from the NRES Committee North East, has Clinical Trial Authorisation from MHRA and local R&D approval. The trial findings will be presented at international conferences and in peer-reviewed journals.

Trial registration number: ISRCTN03978701

Strengths and Limitations of this study

Strengths

- RITPBC is the first randomised controlled trial of a treatment for fatigue in Primary Biliary Cirrhosis.
- The trial describes novel mechanistic outcome measures using magnetic resonance spectroscopy
- Novel recruitment strategies utilising the UK-PBC trials platform are described.

Limitations

- The main limitation is the responsivity of the primary outcome measure to meaningful improvement in fatigue. Responsivity is one of the 6 psychometric properties of any measure and determines its ability to measure meaningful change in a symptom in response

to effective therapy. It is the untested one for the PBC-40 fatigue domain for the obvious reason that there is no therapy able to improve fatigue to allow us to test it. We have mitigated against this by having both an objective measure as well (activity) and biomarkers (MRS).

Keywords

Primary Biliary Cirrhosis

Fatigue

Rituximab

Anti-mitochondrial Antibody

Anti-PDH Antibody

Randomised Controlled Trial

Health related quality of life

Background

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with a prevalence of 30 per 100,000(1). It affects approximately 20,000 people in the UK, predominantly females (10:1)(2). PBC has an autoimmune aetiology with the majority of patients expressing autoantibodies directed against mitochondrial and nuclear antigens(3) and has strong associations with other autoimmune diseases(4). PBC is characterised by inflammation and subsequent loss of the small intrahepatic bile ducts. Despite its name only a small number of patients will progress to cirrhosis and end-stage liver disease and a number of these will require liver transplantation(5). There is only one licensed treatment, ursodeoxycholic acid (UDCA) which slows progression of liver disease(6).

PBC is associated with a number of symptoms including fatigue, cognitive impairment and pruritus. There are treatments available for PBC associated pruritus but at present there are no licensed treatments for fatigue or cognitive dysfunction. Fatigue, which patients describe as physical exhaustion or their "batteries running down" can be a very debilitating symptom. Fatigued patients are often unable to carry out normal day to day activities and frequently are unable to work resulting in a negative impact on quality of life(7). Recent data suggests that when patients have social isolation in combination with fatigue this has a negative impact on quality of life(8). One patient with PBC has very eloquently described the impact of fatigue in PBC and the loneliness, frustration and despair that can result(9). In addition to the impact on the patients and their friends and family, fatigue is associated with economic costs (loss of earning, paying for assistance). Interestingly, fatigue is not related to the severity of liver disease(10) and is unresponsive to UDCA therapy(11), suggesting that the processes responsible for fatigue in PBC are linked to the condition but not directly to liver injury.

There have been many advances in our understanding of fatigue over the years, starting initially with recognising it as a symptom associated with PBC, and then appreciating the scale of the problem(10) and the impact it has on patient's quality of life(8). Fatigue is a subjective symptom and not particular easy to study in clinical trials, and therefore the development and validation of the PBC-40, a disease-specific quality of life questionnaire, provides a key tool for studying fatigue in PBC(12). Studies have improved our understanding of the potential mechanisms driving fatigue in PBC and culminated in this clinical trial of rituximab. Magnetic Resonance studies point to an abnormality in muscle bio-energetic function as a potential cause of fatigue in PBC. Using the methods of phosphorous magnetic resonance spectroscopy (31P-MRS) they have demonstrated excessive intra-muscular acidosis during and in the recovery from exercise. The severity of fatigue that patients describe is associated with the length of time that the acidosis is present and the recovery time back to the baseline pH(13). As a result of these observations we hypothesise that the anti-mitochondrial antibodies which are seen in over 90% of people with PBC lead to over-utilisation of anaerobic pathways through their activity against pyruvate dehydrogenase (PDH). This is supported by MRS studies which have shown that mitochondrial dysfunction in directly related to AMA levels(14). Unpublished data from the Newcastle group have demonstrated significantly lower anaerobic threshold (AT) values compared with age and sex matched Primary Sclerosing Cholangitis (PSC) patients and sedentary controls, again supporting a muscle bio-energetic abnormality contributing to the fatigue seen in PBC. These findings support a trial to investigate rituximab, an anti-CD20, B cell depleting monoclonal antibody as a potential treatment for fatigue in PBC.

To date there have been two pilot studies of rituximab in PBC(15, 16). Neither had fatigue as a primary outcome measure, and instead focussed on UDCA-unresponsive disease and biochemical outcomes. Both studies found that rituximab resulted in an improvement in liver biochemistry and is safe and well tolerated in PBC. The pilot study in Canada reported a clinically significant reduction in fatigue but the trial was not optimised for the study of fatigue and didn't include fatigue in the inclusion criteria, therefore potentially underestimating the clinical effect of rituximab on fatigue(16).

The RITPBC trial aims to investigate rituximab as a treatment for fatigue in PBC. RITPBC will provide important data on the efficacy, safety and tolerability of rituximab in PBC, as the pilot studies have suggested there may be a role for rituximab in treating UDCA unresponsive disease. The second and important aspect of the trial will be the mechanistic data which aims to gain a better understanding of the mechanisms underpinning fatigue in PBC, and if a benefit is seen, to establish the mechanism of action. The novel MRS techniques used as a secondary outcome measure are unique to this trial. Given that fatigue is not specific to PBC, any advances in the understanding of the mechanisms of this symptom are likely to be transferrable to other conditions associated with fatigue.

Research has been moving forward over the past 20 years to improve our understanding of the impact of fatigue and identify potential mechanisms but clinical trials of therapeutic agents have been lacking. Patients highlight fatigue as a priority for research and close working with the patient support groups re-iterates that trials and subsequent treatments for fatigue are much needed. RITPBC is the first randomised controlled trial of a therapeutic agent to target fatigue in PBC. RITPBC also pilots novel recruitment techniques through utilisation of the UK-PBC stratified medicine trials platform. If this recruitment strategy proves successful it has the potential to revolutionise trials in PBC and provide an approach for trial recruitment transferrable to any rare disease. This article discusses the protocol design and methodology and will hopefully aid further trials to target fatigue in PBC as well as being transferrable to the many other conditions that have fatigue as a prominent symptom.

Methods/Design

Study Design

RITPBC is a phase II, single-centre, randomised controlled, double-blinded trial comparing rituximab with placebo in fatigued Primary Biliary Cirrhosis patients. A total of 78 patients (39 per arm) with definite or probable PBC and moderate-severe fatigue (PBC-40 fatigue domain score >33) will be recruited. The primary outcome is improvement in fatigue severity, assessed using the PBC-40, a disease-specific quality of life measure(12) which will be evaluated at baseline and 12 weeks.. The secondary objectives will be to explore the extent to which any such improvement in fatigue is related to a reduction in the level of anti-PDH antibody and any associated effect on biomarkers of bio-energetic function assessed using novel MRS protocols. Other secondary outcome measures are improvement in anaerobic threshold, physical activity levels, liver biochemistry, daytime somnolence, autonomic symptoms, functional status, cognitive dysfunction and anxiety and depressive symptoms. The safety of rituximab in PBC will be explored and the sustainability of any beneficial actions evaluated.

Screening, Recruitment and Consent

Recruitment will principally be from the large clinical cohort under follow-up at the Joint Autoimmune Liver Disease Clinic in the Newcastle upon Tyne Hospitals NHS Foundation Trust (>500, the largest clinical PBC service in the UK). Participant Identification Centres (PICs) in hospital trusts in the North of England will be opened to aid recruitment. Articles will be written for the patient support group LIVErNORTH and PBC Foundation and published in their newsletters and magazines. This trial is unique as it was the first trial to utilise the UK-PBC platform for recruitment to trials. UK-PBC is a £5 million MRC stratified medicine trials platform which holds genetic, symptom and biochemical data on over 3,000 PBC patients in the UK. Patients recruited to UK-PBC are consented to be contacted about trials and can therefore be easily accessed and recruited. The UK-PBC database can be searched for patients with a PBC-40 fatigue domain score >33. The clinicians looking after these patients can then be contacted and can approach the patients to see if they would be interested in taking part in the trial. This recruitment strategy targets patients with moderate to severe fatigue on a national level that would be impossible to do usually in a single centre trial.

Potentially eligible participants are given a study Participant Information Sheet (PIS) after which they will have a minimum of 48 hours to consider this information before written informed consent is obtained.

Participants will have a diagnosis of definite or probable PBC established using recognised epidemiological criteria (17, 18).

Eligibility Criteria

Inclusion Criteria

- Age ≥ 18 years
- Patient has capacity and provided written informed consent for participation in the study prior to any study specific procedures
- Moderate or severe fatigue as assessed using previously designated cut-offs of the PBC-40 fatigue domain score (i.e. fatigue domain score >33)
- Presence of AMA at a titre of >1:40
- Adequate haematological function Hb>9g/L, neutrophil count >1.5x10^9/L, platelet count >50x10^9/L
- Bilirubin <50µmol
- INR ≤ 1.5
- Child-Pugh score <7
- ECOG performance status <2
- Adequate renal function; Cockcroft and Gault estimation >40ml/min
- Women of child bearing potential should have a negative pregnancy test prior to study entry and be using an adequate contraceptive method which must be continued for 12 months after completion of treatment

Exclusion Criteria

- 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)
- Average alcohol ingestion >21 units/week (male) or >14 units/week (female)
- Chronic sepsis or intercurrent condition likely to predispose to chronic sepsis during the study
- Previous history of aberrant response or intolerance to immunological agents
- Presence of significant untreated intercurrent medical condition itself associated with fatigue
- Presence of significant risk of depressive illness (HADS score indicating caseness)
- Current statin therapy or statin therapy within 3 months of enrolment
- 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
- Major surgery within 4 weeks of study entry
- Vaccination within 4 weeks of study entry; patients requiring seasonal flu or travel vaccines will be required to wait a minimum of 4 weeks post vaccination to enrol in the study
- Pregnant or lactating women
- Psychiatric or other disorder likely to impact on informed consent
- Patient is unable and/or unwilling to comply with treatment and study instructions
- Any other medical condition that, in the opinion of the investigator would interfere with safe completion of the study
- Hypersensitivity to the active substance (Rituximab) or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water (for injection)) or to murine proteins
- Active, severe infections (e.g. tuberculosis, sepsis or opportunistic infections)

Known HIV infection
Clinical history of latent TB infection unless patient has completed adequate antibiotic prophylaxis
AST/ALT 4x upper limit of normal
Severe immune-compromised state
Severe heart failure (NYHA Class IV) or severe uncontrolled cardiac disease
Malignancy (other than basal cell carcinoma) within the last 10 years
Demyelinating disease
Previous participation in this study
Any contraindication to Rituximab therapy not covered by other exclusions

Intervention

Patients in the study will be randomised on a 1:1 ratio to receive either:

- Rituximab 1g on days 1 and 15 - study drug
- 100mls 0.9% sodium chloride on days 1 and 15 - placebo

Experimental Intervention: Rituximab

The investigational medicinal product used in the clinical trial is rituximab, 1000 mg IV. This product has been approved with the European Commission decision (MA number: EU/1/98/067/002). Patients randomised to receive rituximab therapy will be given treatment at the infusion rates recommended for rheumatoid arthritis patients as per the Newcastle upon Tyne Hospitals NHS Foundation Trust protocol.

Control Intervention: Placebo

Patients randomised to receive placebo will receive a control infusion of normal saline. The control infusion will be delivered in a double blinded manner to participants using the same protocol.

Conditioning

In line with recommendations for the administration of rituximab in other conditions, all patients will receive a conditioning regimen prior to the infusions of study medication on days 1 and 15 to maintain double-blinding. The conditioning regimen compromises paracetamol 1g PO and chlorpheniramine 4mg PO to be administered 1 hour prior to infusion and methylprednisolone 100mg IV to be administered 30 minutes prior to infusion.

Concomitant Medications

For patients who are on ursodeoxycholic Acid (UDCA), the dose will not be changed during the period of study. No other disease modifying agents should be introduced during the duration of the trial. Therapy aimed at reducing pruritus can be introduced if unavoidable at the discretion of the investigators.

Live vaccines must not be given during the study.

Randomisation and blinding

Randomisation will be conducted by the Newcastle Clinical Trials Unit (NCTU) web based system on a 1:1 ratio and random-permuted blocks with random block length. The treatment allocation will be kept blind from the subjects, study assessors and investigators until study completion. The randomisation system will generate a treatment number for each participant that links to the corresponding allocated study drug (blinded). A code-break list will be kept in the pharmacy department.

Study procedures and outcome measures

The schedule of events which includes completion of study questionnaires and collection of mechanistic data is described in Figure 1.

Quality of Life and symptom questionnaires

The primary outcome measure if the fatigue domain of the PBC-40. Severity of other symptoms will be assessed in terms of numerical change for the relevant domain of the PBC-40 (itch, cognitive symptoms, social and emotional symptoms). The PROMIS HAQ(19) measures the functional and physical ability of the participants (washing, dressing, arising, eating, walking, hygiene, reach, grip and activity). The score is on a 0-100 scale with higher scores indicating worse functional ability. Anxiety and Depression will be assessed by the Hospital and Anxiety and Depression Scale (HADS)(20). Improvement in daytime somnolence will be assessed using the Epworth Sleepiness Scale (ESS) (21). Vasomotor autonomic symptoms will be assessed using the Orthostatic Grading Scale (OGS)(22).Cognitive function will be assessed with the COGFAIL questionnaire. (23)

Fatigue Diary

Participant held diaries will be used to gather qualitative information as to symptoms and functional ability. We will use diaries that include both structured (quantitative) and unstructured (qualitative) methods of data collection. The diaries measure fatigue using a scale of 1 to 6 (1 – no fatigue and 6 – extreme fatigue). Participants will be asked to complete the diaries six times during the study. They will complete the diaries for a period of a week at the beginning of each month at baseline, 1, 3, 6, 9 and 12 months. They will return the diaries at the final visit.

Muscle Acidosis

Magnetic resonance data will be acquired at baseline and at 12 weeks using a 3T Intera Achieva scanner (Philips, Best, NL) which is equipped with additional specialist hardware to perform phosphorous-31 MRS. The protocol used for acquisition and analysis has been described elsewhere but in summary, involves controlled plantar flexion using a purpose-built exercise apparatus developed for operation within the MRI scanner(14). Participants will perform 2 x 180s bouts of plantar flexion contractions at 25% and then 35% of maximal voluntary contraction, with each bout preceded by 60s of rest and followed by 390s of recovery. Phosphorous spectra will be collected at 10s intervals.

Anaerobic Threshold

Participants will cycle on a stationary ergometer (Corival, Lode, Nederland) at between 60-70rpm. The test will be terminated voluntarily by the participant or when they were unable to maintain a pedal frequency of 60rpm. Expired air will be collected at rest and during exercise using a breathing mask and analysed online using a gas analysis system (MetaLyzer II, CORTEX, Germany). Anaerobic threshold will be assessed using the computerised v-slope method and values compared at baseline and 12 week follow up.

Physical Activity Levels

Physical activity will be measured objectively using two activity monitors which will be worn for 7 days at baseline and week 12. The first is a validated multi-sensor array (SenseWear Pro$_3$, Bodymedia Inc, PA, USA) which measures 4 key metrics; skin temperature, galvanic skin response, heat flux and motion via a 3-axis accelerometer. The sensors combined with algorithms, calculate the average daily energy expenditure relative to baseline metabolism (metabolic equivalent: MET per day,

1MET=resting metabolic rate), total energy expenditure (calories per day), active energy expenditure (total calories expended over 3METS per day), physical activity duration (min over 3METS per day) and average daily number of steps walked. Patterns of sedentary behaviour will be assessed by power law analyses of the lengths of sedentary bouts fitted from raw sedentary data. Outcome measure for study evaluation will be mean number of steps/24 hours. The second, the GENEActiv (ActivInsights, Ltd) is a waterproof, lightweight (16 grams) triaxial accelerometer. Raw accelerations are collected at a range of +/- 8g with a recording frequency of 40Hz.

B cell biology

Quantification and phenotyping of total B-cell populations and B-cell subsets will be carried out using a FACS-based approach with a well-described protocol utilising markers other than CD20(24). Outcome measure will be change in individual parameters with therapy. Total and activated B-cells in peripheral blood will be evaluated using a direct immune-fluorescence reagent (Fast Immune CD19/CD69/CD45, BD Biosciences). B cell subsets will be analysed to assess naïve, memory (CD27) and plasma cell (CD38) populations. Finally, activation status of the B cell populations will be analysed using CD80, CD86 and CD268.

Anti-PDH antibody total and individual isotype levels and antibody functional inhibitory capacity will be studied on day 0 and at the primary end point (12 weeks after therapy). Antibody levels will also be correlated with long term fatigue status during the secondary follow-up period to 12 months. Anti-PDH levels and isotype patterns will be assessed using a well established ELISA developed within our research group(25). In the analysis phase impact of rituximab on fatigue in PBC will be correlated with changes in individual autoantibody isotype responses and with PDH-inhibitory capacity of serum.

Liver Biochemistry

We will collect data on a reduction in serum alkaline phosphatase level and attainment of the previously identified positive outcome measure of drop in baseline alkaline phosphatase of >40% or normalisation (Barcelona Criteria)(26).

Data Analysis

Sample size calculation

A total sample size of 78 participants (39 per arm) will be recruited and randomised; this includes an assumption of 10% attrition at 12-week follow-up (based on experience in clinical trials in PBC). The primary outcome is the PBC-40 fatigue domain score (range 11-55) after 12 weeks of intervention. The standard deviation of fatigue scores is 8 units (based on the PBC-40 derivation studies utilising >1000 patients(12)), with a correlation of 0.6 between baseline and follow-up time points based on previous studies. The study is powered to detect a mean change in PBC-40 fatigue domain score of 5 units (equating to an average of 0.5 point change per question; a difference in PBC-40 score demonstrated in our population-based studies to be associated with significantly higher levels of social function and which was therefore deemed to be clinically significant for the purposes of the study design) with a power of 90% and a 5% significance level. This equates to 35 participants in each group providing data on the primary outcome (PBC-40 fatigue score at 12 weeks): incorporating an assumption of a 10% attrition gives a total of 78. The number of participants lost to follow-up, or withdrawing consent prior to initial treatment is expected to be minimal.

Analysis of outcome measures

Analysis will be on the basis of intention to treat.

Primary Outcome

Differences between intervention and control groups at 12 weeks on PBC-40 fatigue domain scores will be analysed by analysis of covariance (ANCOVA) using baseline scores as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

Secondary Outcome

Secondary outcomes, covering comparison of other clinical symptom and functional capability scales at 12 weeks will also be analysed by ANCOVA using baseline values as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

The analysis of the mechanistic variables will be more descriptive in nature, and will involve comparison of means or proportions between intervention groups, as appropriate, and the use of correlation coefficients to explore the relationship between physiological/immunological measurements and fatigue. For the secondary outcome measures the variables will be compared at baseline and 12 week assessment. Physical activity levels will compare mean number of steps per 24 hours measured over a seven day period. Anaerobic threshold will be measure during cardio-pulmonary exercise testing. MRS will compare the minimum pH seen in the exercise and recovery period, the time required post-exercise for pH to return to within 0.01 units of baseline levels (calculated as the sum for each individual for the two bouts to form a total pH recovery time) and the mean “area under the curve” for pH for the 2 exercise episodes which reflects total acid exposure. A change in the number of B cells and B cell subsets will be reported and a change in anti-PDH titres. The safety and tolerability of rituximab in PBC will also be reported as a secondary outcome measure.

There are no planned interim analyses for efficacy, however if the data Monitoring and Ethics Committee (DMEC) requires interim analysis for safety it will be performed. Final analyses will be carried out when all participants have completed follow up.

Data monitoring, quality control and quality assurance

Withdrawal of participants

Study drug must be discontinued if:

- the participant develops elevated serum Alanine Transaminase (ALT)/Aspartate Transaminase (AST) 4 times above the upper limit of normal
- the participant decides she/he no longer wishes to continue
- cessation of study drug is recommended by the investigator

Discussion

Over recent years there have been many advances in gaining a better understanding of fatigue in PBC. We now appreciate what a significant problem it is, both in terms of the prevalence of fatigue as a symptom as well as the impact that it can have on patient's lives. Although the pathophysiology of fatigue is not entirely understood research has enabled us to have a much better understanding of the potential causes of fatigue in PBC and possible targets for treatment. Given the recent increases in our understanding of fatigue the next step was to design and deliver a trial of a therapeutic agent aimed to improve fatigue in PBC which would also improve our understanding of the mechanisms of fatigue.

The trial is designed to provide useful information about the physiological effects of fatigue, the pathophysiology of fatigue as well as assessing the role of rituximab in treating fatigue.

Fatigue is a subjective symptom and is not always an easy symptom to study in a trial which is why the protocol of this trial has been published with the hope of aiding others who may wish to design and deliver trial on fatigue in PBC as well as the many other conditions that have fatigue as a key symptom. The trial also incorporates novel techniques that can provide objective data on fatigue (MRS, anaerobic threshold and physical activity monitoring) as well as describing new recruitment techniques using national disease-specific databases. 40 patients have now received either rituximab or placebo infusions as part of the trial which make it the largest biological trial in PBC. We believe the high number of patients recruited to this trial is because we are addressing fatigue which is the issue that matters most to patients.

Trial Status

Recruitment to RITPBC opened in October 2012 and will close in April 2015.

At the time of manuscript submission the trial is open to recruitment.

Lists of abbreviations used

ALT	Alanine Transaminase
AMA	Anti-mitochondrial Antibody
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
COGFAIL	Cognitive Failure Questionnaire
DMEC	Data Monitoring and Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ESS	Epworth Sleepiness Scale
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
INR	International Normalised ratio
IV	Intravenous
MRS	Magnetic Resonance Spectroscopy
MRC	Medical Research Council
NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
NYHA	New York Heart Association
OGS	Orthostatic Grading Scale
PBC	Primary Biliary Cirrhosis
PDH	Pyruvate Dehydrogenase
PIC	Participant Identification Centre

PO	Per oral
PROMIS	Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire
TB	Tuberculosis
UDCA	Ursodeoxycholic Acid

Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

DJ and JN designed and developed the trial protocol. JW and JQ developed the trial protocol and manage the trial. DH, as the trial statistician did the sample size calculation and analysis plan. JP and AF designed the B cell experiments. AB developed the MRS protocol. MT developed the cardio-pulmonary exercise testing protocol to measure anaerobic threshold. LJ is involved in the coordination of the trial and drafted the manuscript for this publication.

Acknowledgements

The authors would like to thank LIVErNORTH for their ongoing support of trials in PBC and for their input in the trial design and assistance in raising awareness of the trial and recruiting patients.

This Research was supported by the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals NHS Foundation Trust and Newcastle University. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Funding and Ethical Approval

This is an MRC and NIHR Efficacy and Mechanism Evaluation Programme (EME) funded project. The trial has received Ethical Approval from the NRES Committee North East – Newcastle & North Tyneside, has Clinical Trial Authorisation from the MHRA and Newcastle upon Tyne Hospitals Foundation Trust Research and development (R&D) approval. The study has been included in the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio with co-adoption to the Hepatology Specialty Group. (NIHR CLRN study ID: 12953). The study has also been registered with ISRCTN as part of the portfolio adoption. (ISRCTN03978701).

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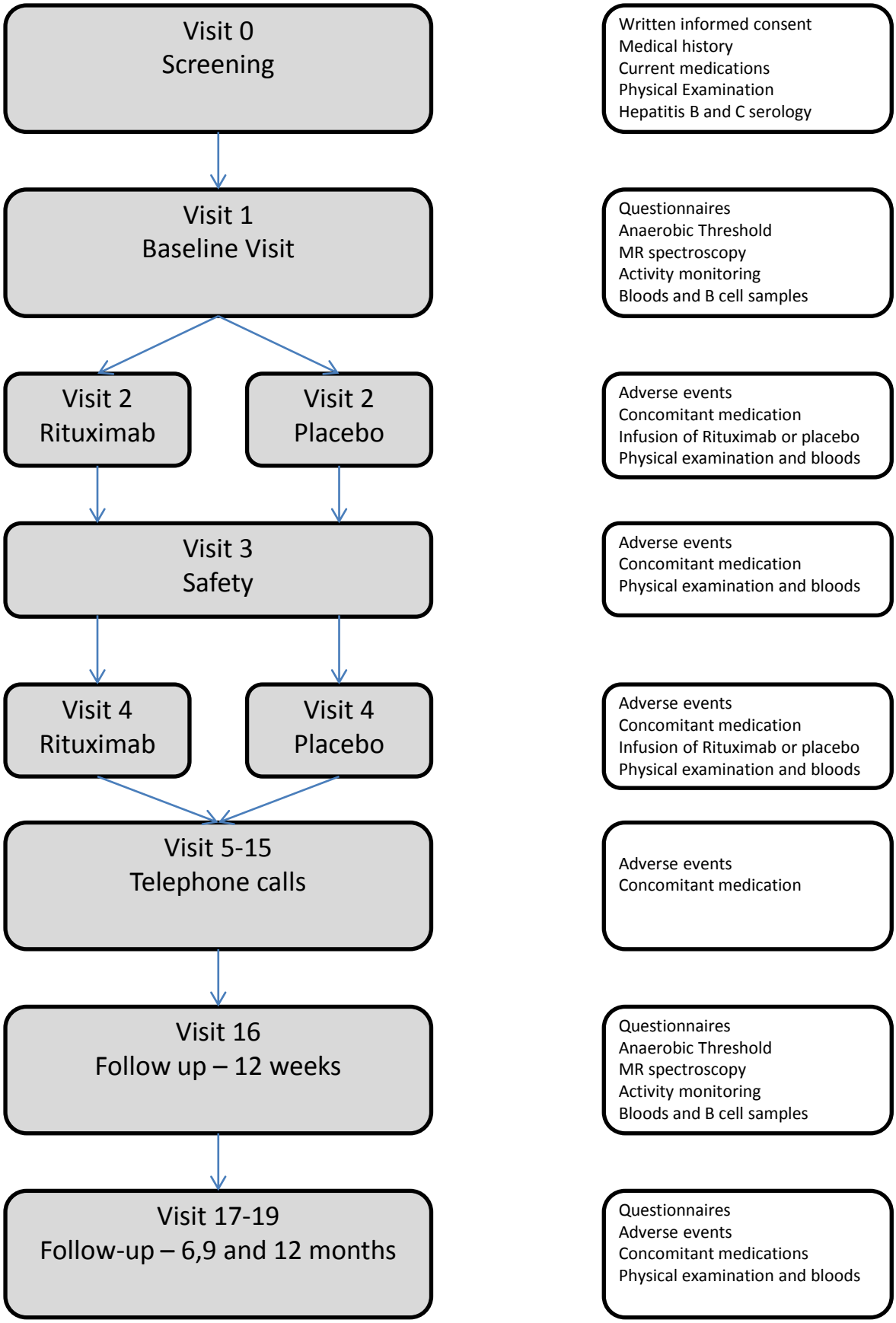
Figure 1


Visit 0
Screening
Written informed consent
Medical history
Current medications
Physical Examination
Hepatitis B and C serology
Visit 1
Baseline Visit
Questionnaires
Anaerobic Threshold
MR spectroscopy
Activity monitoring
Bloods and B cell samples
Visit 2
Rituximab
Visit 2
Placebo
Adverse events
Concomitant medication
Infusion of Rituximab or placebo
Physical examination and bloods
Visit 3
Safety
Adverse events
Concomitant medication
Physical examination and bloods
Visit 4
Rituximab
Visit 4
Placebo
Adverse events
Concomitant medication
Infusion of Rituximab or placebo
Physical examination and bloods
Visit 5-15
Telephone calls
Adverse events
Concomitant medication
Visit 16
Follow up – 12 weeks
Questionnaires
Anaerobic Threshold
MR spectroscopy
Activity monitoring
Bloods and B cell samples
Visit 17-19
Follow-up – 6,9 and 12 months
Questionnaires
Adverse events
Concomitant medications
Physical examination and bloods

BMJ Open

RITPBC: B-Cell Depleting Therapy (Rituximab) as a Treatment for Fatigue in Primary Biliary Cirrhosis: study protocol for a randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-007985.R1
Article Type:	Protocol
Date Submitted by the Author:	22-May-2015
Complete List of Authors:	Jopson, Laura; Newcastle University, Institute of Cellular Medicine Newton, Julia; Newcastle University, Institute of Ageing and Health Palmer, Jeremy; Newcastle University, Institute of Cellular Medicine Floudas, Achilleas; Newcastle University, Institute of Cellular Medicine Isaacs, John; University of Newcastle, Qian, Jessica; Newcastle University, Institute of Health and Society Wilkinson, Jennifer; Newcastle University, Institute of Health and Society Trenell, Michael; Newcastle University, Blamire, Andrew; Newcastle University, Institute for Cellular Medicine and Newcastle Magnetic Resonance Centre Howel, Denise; Newcastle University, Jones, David; Newcastle University, Institute of Cellular Medicine
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Immunology (including allergy)
Keywords:	Hepatobiliary disease < GASTROENTEROLOGY, IMMUNOLOGY, Clinical trials < THERAPEUTICS

RITPBC: B-Cell Depleting Therapy (Rituximab) as a Treatment for Fatigue in Primary Biliary Cirrhosis: study protocol for a randomised controlled trial

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Abstract

Introduction

Primary Biliary Cirrhosis (PBC) is an autoimmune liver disease with approximately 50% of patients experiencing fatigue. This can be a particularly debilitating symptom, affecting quality of life and resulting in social isolation. Fatigue is highlighted by patients as a priority for research and patient support groups were involved in designing this trial. This is the first randomised controlled trial to investigate a treatment for fatigue in PBC. The trial protocol is innovative as it utilises novel Magnetic Resonance Spectroscopy (MRS) techniques as an outcome measure. The protocol will be valuable to research groups planning clinical trials targeting fatigue in PBC and also transferrable to other conditions associated with fatigue.

Methods and analysis

RITPBC is an MRC and NIHR Efficacy and Mechanism Evaluation Programme (EME) funded project. It is a phase II, single-centre, randomised controlled, double blinded trial comparing rituximab with placebo in fatigued PBC patients. 78 patients with PBC and moderate to severe fatigue will be randomised to receive two infusions of rituximab or placebo. The study aims to assess whether rituximab improves fatigue in patients with PBC, the safety and tolerability of rituximab in PBC and the sustainability of its beneficial actions. The primary outcome will be an improvement in fatigue domain score of the PBC-40, a disease-specific quality of life measure, evaluated at 12 week assessment. Secondary outcome measures include novel MRS techniques assessing muscle bio-energetic function, physical activity, anaerobic threshold and symptom and quality of life measures.

The trial started recruiting in October 2012 and recruitment is ongoing.

Ethics and dissemination

The trial has ethical approval from the NRES Committee North East, has Clinical Trial Authorisation from MHRA and local R&D approval. Trial results will be communicated to participants, presented at national and international meetings and published in peer-reviewed journals.

Trial registration: ISRCTN03978701

Strengths and Limitations of this study

Strengths

- RITPBC is the first randomised controlled trial of a treatment for fatigue in Primary Biliary Cirrhosis.
- The trial describes novel mechanistic outcome measures using magnetic resonance spectroscopy.
- Novel recruitment strategies utilising the UK-PBC trials platform are described.

Limitations

- The main limitation is the responsivity of the primary outcome measure to meaningful improvement in fatigue. Responsivity is one of the 6 psychometric properties of any measure and determines its ability to measure meaningful change in a symptom in response

to effective therapy. It is the untested one for the PBC-40 fatigue domain for the obvious reason that there is no therapy able to improve fatigue to allow us to test it. We have mitigated against this by having both an objective measure as well (activity) and biomarkers (MRS).

Keywords

Primary Biliary Cirrhosis

Fatigue

Rituximab

Anti-mitochondrial Antibody

Anti-PDH Antibody

Randomised Controlled Trial

Health related quality of life

Background

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with a prevalence of 30 per 100,000(1). It affects approximately 20,000 people in the UK, predominantly females (10:1)(2). PBC has an autoimmune aetiology with the majority of patients expressing autoantibodies directed against mitochondrial and nuclear antigens(3) and has strong associations with other autoimmune diseases(4). PBC is characterised by inflammation and subsequent loss of the small intrahepatic bile ducts. Despite its name only a small number of patients will progress to cirrhosis and end-stage liver disease and a number of these will require liver transplantation(5). There is only one licensed treatment, ursodeoxycholic acid (UDCA) which slows progression of liver disease(6).

PBC is associated with a number of symptoms including fatigue, cognitive impairment and pruritus. There are treatments available for PBC associated pruritus but at present there are no licensed treatments for fatigue or cognitive dysfunction. Fatigue, which patients describe as physical exhaustion or their "batteries running down" can be a very debilitating symptom. Fatigued patients are often unable to carry out normal day to day activities and frequently are unable to work resulting in a negative impact on quality of life(7). Recent data suggests that when patients have social isolation in combination with fatigue this has a negative impact on quality of life(8). One patient with PBC has very eloquently described the impact of fatigue in PBC and the loneliness, frustration and despair that can result(9). In addition to the impact on the patients and their friends and family, fatigue is associated with economic costs (loss of earning, paying for assistance). Interestingly, fatigue is not related to the severity of liver disease(10) and is unresponsive to UDCA therapy(11), suggesting that the processes responsible for fatigue in PBC are linked to the condition but not directly to liver injury.

There have been many advances in our understanding of fatigue over the years, starting initially with recognising it as a symptom associated with PBC, and then appreciating the scale of the problem(10) and the impact it has on patient's quality of life(8). Fatigue is a subjective symptom and not particular easy to study in clinical trials, and therefore the development and validation of the PBC-40, a disease-specific quality of life questionnaire, provides a key tool for studying fatigue in PBC(12). Studies have improved our understanding of the potential mechanisms driving fatigue in PBC and culminated in this clinical trial of rituximab. Magnetic Resonance studies point to an abnormality in muscle bio-energetic function as a potential cause of fatigue in PBC. Using the methods of phosphorous magnetic resonance spectroscopy (31P-MRS) they have demonstrated excessive intra-muscular acidosis during and in the recovery from exercise. The severity of fatigue that patients describe is associated with the length of time that the acidosis is present and the recovery time back to the baseline pH(13). As a result of these observations we hypothesise that the anti-mitochondrial antibodies which are seen in over 90% of people with PBC lead to over-utilisation of anaerobic pathways through their activity against pyruvate dehydrogenase (PDH). This is supported by MRS studies which have shown that mitochondrial dysfunction in directly related to AMA levels(14). Unpublished data from the Newcastle group have demonstrated significantly lower anaerobic threshold (AT) values compared with age and sex matched Primary Sclerosing Cholangitis (PSC) patients and sedentary controls, again supporting a muscle bio-energetic abnormality contributing to the fatigue seen in PBC. These findings support a trial to investigate rituximab, an anti-CD20, B cell depleting monoclonal antibody as a potential treatment for fatigue in PBC.

To date there have been two pilot studies of rituximab in PBC(15, 16). Neither had fatigue as a primary outcome measure, and instead focussed on UDCA-unresponsive disease and biochemical outcomes. Both studies found that rituximab resulted in an improvement in liver biochemistry and is safe and well tolerated in PBC. The pilot study in Canada reported a clinically significant reduction in fatigue but the trial was not optimised for the study of fatigue and didn't include fatigue in the inclusion criteria, therefore potentially underestimating the clinical effect of rituximab on fatigue(16).

The RITPBC trial aims to investigate rituximab as a treatment for fatigue in PBC. RITPBC will provide important data on the efficacy, safety and tolerability of rituximab in PBC, as the pilot studies have suggested there may be a role for rituximab in treating UDCA unresponsive disease. The second and important aspect of the trial will be the mechanistic data which aims to gain a better understanding of the mechanisms underpinning fatigue in PBC, and if a benefit is seen, to establish the mechanism of action. The novel MRS techniques used as a secondary outcome measure are unique to this trial. Given that fatigue is not specific to PBC, any advances in the understanding of the mechanisms of this symptom are likely to be transferrable to other conditions associated with fatigue.

Research has been moving forward over the past 20 years to improve our understanding of the impact of fatigue and identify potential mechanisms but clinical trials of therapeutic agents have been lacking. Patients highlight fatigue as a priority for research and close working with the patient support groups re-iterates that trials and subsequent treatments for fatigue are much needed. RITPBC is the first randomised controlled trial of a therapeutic agent to target fatigue in PBC. RITPBC also pilots novel recruitment techniques through utilisation of the UK-PBC stratified medicine trials platform. If this recruitment strategy proves successful it has the potential to revolutionise trials in PBC and provide an approach for trial recruitment transferrable to any rare disease. This article discusses the protocol design and methodology and will hopefully aid further trials to target fatigue in PBC as well as being transferrable to the many other conditions that have fatigue as a prominent symptom.

Methods/Design

Study Design

RITPBC is a phase II, single-centre, randomised controlled, double-blinded trial comparing rituximab with placebo in fatigued Primary Biliary Cirrhosis patients. A total of 78 patients (39 per arm) with definite or probable PBC and moderate-severe fatigue (PBC-40 fatigue domain score >33) will be recruited. The primary outcome is improvement in fatigue severity, assessed using the PBC-40, a disease-specific quality of life measure(12) which will be evaluated at baseline and 12 weeks.. The secondary objectives will be to explore the extent to which any such improvement in fatigue is related to a reduction in the level of anti-PDH antibody and any associated effect on biomarkers of bio-energetic function assessed using novel MRS protocols. Other secondary outcome measures are improvement in anaerobic threshold, physical activity levels, liver biochemistry, daytime somnolence, autonomic symptoms, functional status, cognitive dysfunction and anxiety and depressive symptoms. The safety of rituximab in PBC will be explored and the sustainability of any beneficial actions evaluated.

Screening, Recruitment and Consent

Recruitment will principally be from the large clinical cohort under follow-up at the Joint Autoimmune Liver Disease Clinic in the Newcastle upon Tyne Hospitals NHS Foundation Trust (>500, the largest clinical PBC service in the UK). Participant Identification Centres (PICs) in hospital trusts in the North of England will be opened to aid recruitment. Articles will be written for the patient support group LIVErNORTH and PBC Foundation and published in their newsletters and magazines. This trial is unique as it was the first trial to utilise the UK-PBC platform for recruitment to trials. UK-PBC is a £5 million MRC stratified medicine trials platform which holds genetic, symptom and biochemical data on over 3,000 PBC patients in the UK. Patients recruited to UK-PBC have consented to be contacted about trials and can therefore be easily accessed and recruited. The UK-PBC database can be searched for patients with a PBC-40 fatigue domain score >33. The clinicians looking after these patients can then be contacted and can approach the patients to see if they would be interested in taking part in the trial. This recruitment strategy targets patients with moderate to severe fatigue on a national level that would be impossible to do usually in a single centre trial.

Potentially eligible participants are given a study Participant Information Sheet (PIS) after which they will have a minimum of 48 hours to consider this information before written informed consent is obtained.

Participants will have a diagnosis of definite or probable PBC established using recognised epidemiological criteria (17, 18).

Eligibility Criteria

Inclusion Criteria

- Age ≥ 18 years
- Patient has capacity and provided written informed consent for participation in the study prior to any study specific procedures
- Moderate or severe fatigue as assessed using previously designated cut-offs of the PBC-40 fatigue domain score (i.e. fatigue domain score >33)
- Presence of AMA at a titre of >1:40
- Adequate haematological function Hb>9g/L, neutrophil count >1.5x10^9/L, platelet count >50x10^9/L
- Bilirubin <50µmol
- INR ≤ 1.5
- Child-Pugh score <7
- ECOG performance status <2
- Adequate renal function; Cockcroft and Gault estimation >40ml/min
- Women of child bearing potential should have a negative pregnancy test prior to study entry and be using an adequate contraceptive method which must be continued for 12 months after completion of treatment

Exclusion Criteria

- 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)
- Average alcohol ingestion >21 units/week (male) or >14 units/week (female)
- Chronic sepsis or intercurrent condition likely to predispose to chronic sepsis during the study
- Previous history of aberrant response or intolerance to immunological agents
- Presence of significant untreated intercurrent medical condition itself associated with fatigue
- Presence of significant risk of depressive illness (HADS score indicating caseness)
- Current statin therapy or statin therapy within 3 months of enrolment
- 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
- Major surgery within 4 weeks of study entry
- Vaccination within 4 weeks of study entry; patients requiring seasonal flu or travel vaccines will be required to wait a minimum of 4 weeks post vaccination to enrol in the study
- Pregnant or lactating women
- Psychiatric or other disorder likely to impact on informed consent
- Patient is unable and/or unwilling to comply with treatment and study instructions
- Any other medical condition that, in the opinion of the investigator would interfere with safe completion of the study
- Hypersensitivity to the active substance (Rituximab) or to any of the excipients (sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water (for injection)) or to murine proteins
- Active, severe infections (e.g. tuberculosis, sepsis or opportunistic infections)

Known HIV infection
Clinical history of latent TB infection unless patient has completed adequate antibiotic prophylaxis
AST/ALT 4x upper limit of normal
Severe immune-compromised state
Severe heart failure (NYHA Class IV) or severe uncontrolled cardiac disease
Malignancy (other than basal cell carcinoma) within the last 10 years
Demyelinating disease
Previous participation in this study
Any contraindication to Rituximab therapy not covered by other exclusions

Intervention

Patients in the study will be randomised on a 1:1 ratio to receive either:

- Rituximab 1g on days 1 and 15 - study drug
- 100mls 0.9% sodium chloride on days 1 and 15 - placebo

Experimental Intervention: Rituximab

The investigational medicinal product used in the clinical trial is rituximab, 1000 mg IV. This product has been approved with the European Commission decision (MA number: EU/1/98/067/002). Patients randomised to receive rituximab therapy will be given treatment at the infusion rates recommended for rheumatoid arthritis patients as per the Newcastle upon Tyne Hospitals NHS Foundation Trust protocol.

Control Intervention: Placebo

Patients randomised to receive placebo will receive a control infusion of normal saline. The control infusion will be delivered in a double blinded manner to participants using the same protocol.

Conditioning

In line with recommendations for the administration of rituximab in other conditions, all patients will receive a conditioning regimen prior to the infusions of study medication on days 1 and 15 to maintain double-blinding. The conditioning regimen compromises paracetamol 1g PO and chlorpheniramine 4mg PO to be administered 1 hour prior to infusion and methylprednisolone 100mg IV to be administered 30 minutes prior to infusion.

Concomitant Medications

For patients who are on ursodeoxycholic Acid (UDCA), the dose will not be changed during the period of study. No other disease modifying agents should be introduced during the duration of the trial. Therapy aimed at reducing pruritus can be introduced if unavoidable at the discretion of the investigators.

Live vaccines must not be given during the study.

Randomisation and blinding

Randomisation will be conducted by the Newcastle Clinical Trials Unit (NCTU) web based system on a 1:1 ratio and random-permuted blocks with random block length. The treatment allocation will be kept blind from the subjects, study assessors and investigators until study completion. The randomisation system will generate a treatment number for each participant that links to the corresponding allocated study drug (blinded). A code-break list will be kept in the pharmacy department.

Study procedures and outcome measures

The schedule of events which includes completion of study questionnaires and collection of mechanistic data is described in Figure 1.

Quality of Life and symptom questionnaires

The primary outcome measure if the fatigue domain of the PBC-40. Severity of other symptoms will be assessed in terms of numerical change for the relevant domain of the PBC-40 (itch, cognitive symptoms, social and emotional symptoms). The PROMIS HAQ(19) measures the functional and physical ability of the participants (washing, dressing, arising, eating, walking, hygiene, reach, grip and activity). The score is on a 0-100 scale with higher scores indicating worse functional ability. Anxiety and Depression will be assessed by the Hospital and Anxiety and Depression Scale (HADS)(20). Improvement in daytime somnolence will be assessed using the Epworth Sleepiness Scale (ESS) (21). Vasomotor autonomic symptoms will be assessed using the Orthostatic Grading Scale (OGS)(22).Cognitive function will be assessed with the COGFAIL questionnaire. (23)

Fatigue Diary

Participant held diaries will be used to gather qualitative information as to symptoms and functional ability. We will use diaries that include both structured (quantitative) and unstructured (qualitative) methods of data collection. The diaries measure fatigue using a scale of 1 to 6 (1 – no fatigue and 6 – extreme fatigue). Participants will be asked to complete the diaries six times during the study. They will complete the diaries for a period of a week at the beginning of each month at baseline, 1, 3, 6, 9 and 12 months. They will return the diaries at the final visit.

Muscle Acidosis

Magnetic resonance data will be acquired at baseline and at 12 weeks using a 3T Intera Achieva scanner (Philips, Best, NL) which is equipped with additional specialist hardware to perform phosphorous-31 MRS. The protocol used for acquisition and analysis has been described elsewhere but in summary, involves controlled plantar flexion using a purpose-built exercise apparatus developed for operation within the MRI scanner(14). Participants will perform 2 x 180s bouts of plantar flexion contractions at 25% and then 35% of maximal voluntary contraction, with each bout preceded by 60s of rest and followed by 390s of recovery. Phosphorous spectra will be collected at 10s intervals.

Anaerobic Threshold

Participants will cycle on a stationary ergometer (Corival, Lode, Nederland) at between 60-70rpm. The test will be terminated voluntarily by the participant or when they were unable to maintain a pedal frequency of 60rpm. Expired air will be collected at rest and during exercise using a breathing mask and analysed online using a gas analysis system (MetaLyzer II, CORTEX, Germany). Anaerobic threshold will be assessed using the computerised v-slope method and values compared at baseline and 12 week follow up.

Physical Activity Levels

Physical activity will be measured objectively using two activity monitors which will be worn for 7 days at baseline and week 12. The first is a validated multi-sensor array (SenseWear Pro$_3$, Bodymedia Inc, PA, USA) which measures 4 key metrics; skin temperature, galvanic skin response, heat flux and motion via a 3-axis accelerometer. The sensors combined with algorithms, calculate the average daily energy expenditure relative to baseline metabolism (metabolic equivalent: MET per day,

1MET=resting metabolic rate), total energy expenditure (calories per day), active energy expenditure (total calories expended over 3METS per day), physical activity duration (min over 3METS per day) and average daily number of steps walked. Patterns of sedentary behaviour will be assessed by power law analyses of the lengths of sedentary bouts fitted from raw sedentary data. Outcome measure for study evaluation will be mean number of steps/24 hours. The second, the GENEActiv (ActivInsights, Ltd) is a waterproof, lightweight (16 grams) triaxial accelerometer. Raw accelerations are collected at a range of +/- 8g with a recording frequency of 40Hz.

B cell biology

Quantification and phenotyping of total B-cell populations and B-cell subsets will be carried out using a FACS-based approach with a well-described protocol utilising markers other than CD20(24). Outcome measure will be change in individual parameters with therapy. Total and activated B-cells in peripheral blood will be evaluated using a direct immune-fluorescence reagent (Fast Immune CD19/CD69/CD45, BD Biosciences). B cell subsets will be analysed to assess naïve, memory (CD27) and plasma cell (CD38) populations. Finally, activation status of the B cell populations will be analysed using CD80, CD86 and CD268.

Anti-PDH antibody total and individual isotype levels and antibody functional inhibitory capacity will be studied on day 0 and at the primary end point (12 weeks after therapy). Antibody levels will also be correlated with long term fatigue status during the secondary follow-up period to 12 months. Anti-PDH levels and isotype patterns will be assessed using a well established ELISA developed within our research group(25). In the analysis phase impact of rituximab on fatigue in PBC will be correlated with changes in individual autoantibody isotype responses and with PDH-inhibitory capacity of serum.

Liver Biochemistry

We will collect data on a reduction in serum alkaline phosphatase level and attainment of the previously identified positive outcome measure of drop in baseline alkaline phosphatase of >40% or normalisation (Barcelona Criteria)(26).

Data Analysis

Sample size calculation

A total sample size of 78 participants (39 per arm) will be recruited and randomised; this includes an assumption of 10% attrition at 12-week follow-up (based on experience in clinical trials in PBC). The primary outcome is the PBC-40 fatigue domain score (range 11-55) after 12 weeks of intervention. The standard deviation of fatigue scores is 8 units (based on the PBC-40 derivation studies utilising >1000 patients(12)), with a correlation of 0.6 between baseline and follow-up time points based on previous studies. The study is powered to detect a mean change in PBC-40 fatigue domain score of 5 units (equating to an average of 0.5 point change per question; a difference in PBC-40 score demonstrated in our population-based studies to be associated with significantly higher levels of social function and which was therefore deemed to be clinically significant for the purposes of the study design) with a power of 90% and a 5% significance level. This equates to 35 participants in each group providing data on the primary outcome (PBC-40 fatigue score at 12 weeks): incorporating an assumption of a 10% attrition gives a total of 78. The number of participants lost to follow-up, or withdrawing consent prior to initial treatment is expected to be minimal.

Analysis of outcome measures

Analysis will be on the basis of intention to treat.

Primary Outcome

Differences between intervention and control groups at 12 weeks on PBC-40 fatigue domain scores will be analysed by analysis of covariance (ANCOVA) using baseline scores as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

Secondary Outcome

Secondary outcomes, covering comparison of other clinical symptom and functional capability scales at 12 weeks will also be analysed by ANCOVA using baseline values as covariates. The time course of the comparison between intervention and control groups over the 12 month follow-up period will be assessed using repeated measures analysis of variance.

The analysis of the mechanistic variables will be more descriptive in nature, and will involve comparison of means or proportions between intervention groups, as appropriate, and the use of correlation coefficients to explore the relationship between physiological/immunological measurements and fatigue. For the secondary outcome measures the variables will be compared at baseline and 12 week assessment. Physical activity levels will compare mean number of steps per 24 hours measured over a seven day period. Anaerobic threshold will be measure during cardio-pulmonary exercise testing. MRS will compare the minimum pH seen in the exercise and recovery period, the time required post-exercise for pH to return to within 0.01 units of baseline levels (calculated as the sum for each individual for the two bouts to form a total pH recovery time) and the mean “area under the curve” for pH for the 2 exercise episodes which reflects total acid exposure. A change in the number of B cells and B cell subsets will be reported and a change in anti-PDH titres. The safety and tolerability of rituximab in PBC will also be reported as a secondary outcome measure.

There are no planned interim analyses for efficacy, however if the data Monitoring and Ethics Committee (DMEC) requires interim analysis for safety it will be performed. Final analyses will be carried out when all participants have completed follow up.

Withdrawal of participants

Study drug must be discontinued if:

- the participant develops elevated serum Alanine Transaminase (ALT)/Aspartate Transaminase (AST) 4 times above the upper limit of normal
- the participant decides she/he no longer wishes to continue
- cessation of study drug is recommended by the investigator

Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from study medication will be asked to confirm whether they are still willing to provide the following:

- study specific data at follow-up visits 5 to 19
- end of study data as per visit 19, at the point of withdrawal
- questionnaire data collected as per routine clinical practice at annual follow up visits

If participants agree to any of the above, they will be asked to complete a confirmation of withdrawal form to document their decision

Data monitoring, quality control and quality assurance

Data Collection

To preserve confidentiality, all patients will be allocated a unique study identification number, which will be used on all data collection forms and questionnaires. Only a limited number of members of the research team will be able to link this identification number to identifiable details which will be held on a password-protected database. All study documentation will be held in secure offices and the research team will operate to a signed code of confidentiality. A clinical data management software package will be used for data entry and processing, allowing a full audit trail of any alterations made to the data post entry. Original questionnaires, case report forms and consent forms will be securely archived at the Newcastle upon Tyne Hospitals NHS Foundation Trust archive facility for fifteen years following publication of the last paper or report from the study. Data will be handled, computerised and stored in accordance with the Data Protection Act 1998. No participant identifiable data will leave the study site. The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy. All laboratory samples will be stored and identified using the patient's unique study identification code.

Discontinuation rules

The study may be prematurely discontinued on the basis of new safety information, or for other reasons given by the Data Monitoring and Ethics Committee and/or Trial Steering Committee, Sponsor, regulatory authority or Research Ethics Committee concerned.

Monitoring, quality control and quality assurance

The study will be managed through the Newcastle Clinical Trials Unit (NCTU). The Trial Management Group (TMG) will include the Chief Investigator, Senior Trial Manager, Trial Manager, Assistant Trial Manager, Data Manager and other members of the trial team when applicable. NCTU will provide day-to-day support for the site and provide training through Investigator meetings, site initiation visit and routine monitoring visits. Protocol amendments will be managed by the NCTU and communicated to the trial team.

Data Monitoring and Ethics Committee (DMEC)

An independent data monitoring and ethics committee (DMEC) has been appointed. It will consist of two physicians not connected to the study and one independent statistician and will be convened to undertake independent review. The purpose of this committee will be to monitor efficacy and safety endpoints. Only the DMEC will have access to un-blinded study data. The committee will meet a minimum of three times, at the start, middle and completion of the study.

Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be established to provide overall supervision of the study. The TSC will consist of an independent chair, two independent clinicians, independent consumer representative, the Chief Investigator, Co-investigator, Senior Trial Manager, Trial Manager and trial statistician. Representatives of the Trial Sponsor and Funder should be invited to all TSC meetings. The committee will meet every 3 months during recruitment, and annually thereafter for the duration of the study.

Study Monitoring

Monitoring of study conduct and data collected will be performed by a combination of central review and site monitoring visits to ensure the study is conducted in accordance with GCP. Study site monitoring will be undertaken by the Trial Manager. The main areas of focus will include consent, serious adverse events, essential documents in study site files and drug accountability and management. All monitoring findings will be reported and followed up with the appropriate persons in a timely manner. The study may be subject to inspection and audit by the Newcastle upon Tyne Hospitals NHS Foundation Trust under their remit as sponsor, and other regulatory bodies to ensure adherence to GCP.

Recording and reporting Serious Adverse Events or Reactions

All adverse events should be reported. Depending on the nature of the event, the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator or the named contact within the management team within the NCTU in the first instance.

Adverse Event (including Adverse Reaction)

All non-serious adverse events / reactions during drug treatment will be reported on the study CRF and sent to the NCTU management team within two weeks. Severity of AEs will be graded on a Five -point scale (Mild, Moderate, Severe, Life threatening, causing death). Relation of the AE to the treatment should be assessed by the investigator at site. The individual investigator at each site will be responsible for managing all adverse events / reactions according to local protocols.

Serious Adverse Event / Reaction (SAE/SAR, including SUSARs)

All SAEs, SARs and SUSARs during drug treatment shall be reported to the Chief Investigator within 24 hours of the site learning of its occurrence. The initial report can be made by secure fax which will also generate an email copy to the Chief Investigator, Senior Trial Manager and Trial Manager. In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as follow-up, on the appropriate SAE follow-up form. As indicated above, relationship of the SAE to the treatment (causality) should be assessed by the investigator at site, as should the expected or unexpected nature (by reference to the SmPC for Rituximab) of any serious adverse reactions. The MHRA and main REC will be notified by the Chief Investigator or trials management team (on behalf of the Sponsor) of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study on a case-by-case basis. The Chief Investigator will ensure the Newcastle upon Tyne Hospitals NHS Foundation Trust as Sponsor is notified of any SUSARs in accordance with local trust policy.

Insurance and finance

The Newcastle upon Tyne Hospitals NHS Foundation Trust has liability for clinical negligence that harms individuals toward whom they have a duty of care. NHS Indemnity covers NHS staff and medical academic staff with honorary contracts conducting the study for potential liability in respect of negligent harm arising from the conduct of the study. The Newcastle upon Tyne Hospitals NHS Foundation NHS Trust is Sponsor and through the Sponsor, NHS indemnity is provided in respect of potential liability and negligent harm arising from study management. Indemnity in respect of potential liability arising from negligent harm related to study design is provided by NHS schemes for those protocol authors who have their substantive contracts of employment with the NHS and by Newcastle University Insurance schemes for those protocol authors who have their substantive contract of employment with Newcastle University. This is a non-commercial study and there are no arrangements for non-negligent compensation.

Dissemination

The data will be the property of the Chief Investigator and Co-Investigator(s). Publication will be the responsibility of the Chief Investigator. It is planned to publish this study in peer review journals and to present data at national and international meetings. Results of the study will also be reported to the Sponsor and Funder, and will be available on their web site. All manuscripts, abstracts or other modes of presentation will be reviewed by the Trial Steering Committee and Funder prior to submission. Individuals will not be identified from any study report. Participants will be informed about their treatment and their contribution to the study at the end of the study, including a lay summary of the results.

Discussion

Over recent years there have been many advances in gaining a better understanding of fatigue in PBC. We now appreciate what a significant problem it is, both in terms of the prevalence of fatigue as a symptom as well as the impact that it can have on patient's lives. Although the pathophysiology of fatigue is not entirely understood research has enabled us to have a much better understanding of the potential causes of fatigue in PBC and possible targets for treatment. Given the recent increases in our understanding of fatigue the next step was to design and deliver a trial of a therapeutic agent aimed to improve fatigue in PBC which would also improve our understanding of the mechanisms of fatigue.

The trial is designed to provide useful information about the physiological effects of fatigue, the pathophysiology of fatigue as well as assessing the role of rituximab in treating fatigue.

Fatigue is a subjective symptom and is not always an easy symptom to study in a trial which is why the protocol of this trial has been published with the hope of aiding others who may wish to design and deliver trial on fatigue in PBC as well as the many other conditions that have fatigue as a key symptom. The trial also incorporates novel techniques that can provide objective data on fatigue

(MRS, anaerobic threshold and physical activity monitoring) as well as describing new recruitment techniques using national disease-specific databases. 40 patients have now received either rituximab or placebo infusions as part of the trial which make it the largest biological trial in PBC. We believe the high number of patients recruited to this trial is because we are addressing fatigue which is the issue that matters most to patients.

Trial Status

Recruitment to RITPBC opened in October 2012 and will close in April 2015.

At the time of manuscript submission the trial is open to recruitment.

Lists of abbreviations used

AE	Adverse Event
ALT	Alanine Transaminase
AMA	Anti-mitochondrial Antibody
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
COGFAIL	Cognitive Failure Questionnaire
DMEC	Data Monitoring and Ethics Committee
DOH	Department of Health
ECOG	Eastern Cooperative Oncology Group
ESS	Epworth Sleepiness Scale
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
INR	International Normalised ratio
IV	Intravenous
MRS	Magnetic Resonance Spectroscopy
MRC	Medical Research Council
NCTU	Newcastle Clinical Trials Unit
NIHR	National Institute for Health Research
NYHA	New York Heart Association
OGS	Orthostatic Grading Scale
PBC	Primary Biliary Cirrhosis

PDH	Pyruvate Dehydrogenase
PIC	Participant Identification Centre
PO	Per oral
PROMIS	Patient-Reported Outcomes Measurement Information System Health Assessment Questionnaire
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
TSC	Trial Steering Committee
UDCA	Ursodeoxycholic Acid

Competing Interests

DJ is PI on the UK-PBC consortium which receives research funding from Lumena, Intercept and GSK.

Authors Contributions

DJ and JN designed and developed the trial protocol. JI advised on the study design. JW and JQ developed the trial protocol and manage the trial. DH, as the trial statistician did the sample size calculation and analysis plan. JP and AF designed the B cell experiments. AB developed the MRS protocol. MT developed the cardio-pulmonary exercise testing protocol to measure anaerobic threshold. LJ is involved in the coordination of the trial and drafted the manuscript for this publication.

Acknowledgements

The authors would like to thank LIVErNORTH for their ongoing support of trials in PBC and for their input in the trial design and assistance in raising awareness of the trial and recruiting patients.

This Research was supported by the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals NHS Foundation Trust and Newcastle University. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Funding and Ethical Approval

This is an MRC and NIHR Efficacy and Mechanism Evaluation Programme (EME) funded project. The trial has received Ethical Approval from the NRES Committee North East – Newcastle & North Tyneside, has Clinical Trial Authorisation from the MHRA and Newcastle upon Tyne Hospitals Foundation Trust Research and development (R&D) approval. The study has been included in the National Institute for Health Research Clinical Research Network (NIHR CRN) portfolio with co-adoption to the Hepatology Specialty Group. (NIHR CLRN study ID: 12953). The study has also been registered with ISRCTN as part of the portfolio adoption. (ISRCTN03978701). Newcastle upon Tyne Hospitals NHS Foundation Trust are the sponsor for the study.

Figure 1

Schedule of events for the RITPBC trial.

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Figure 1

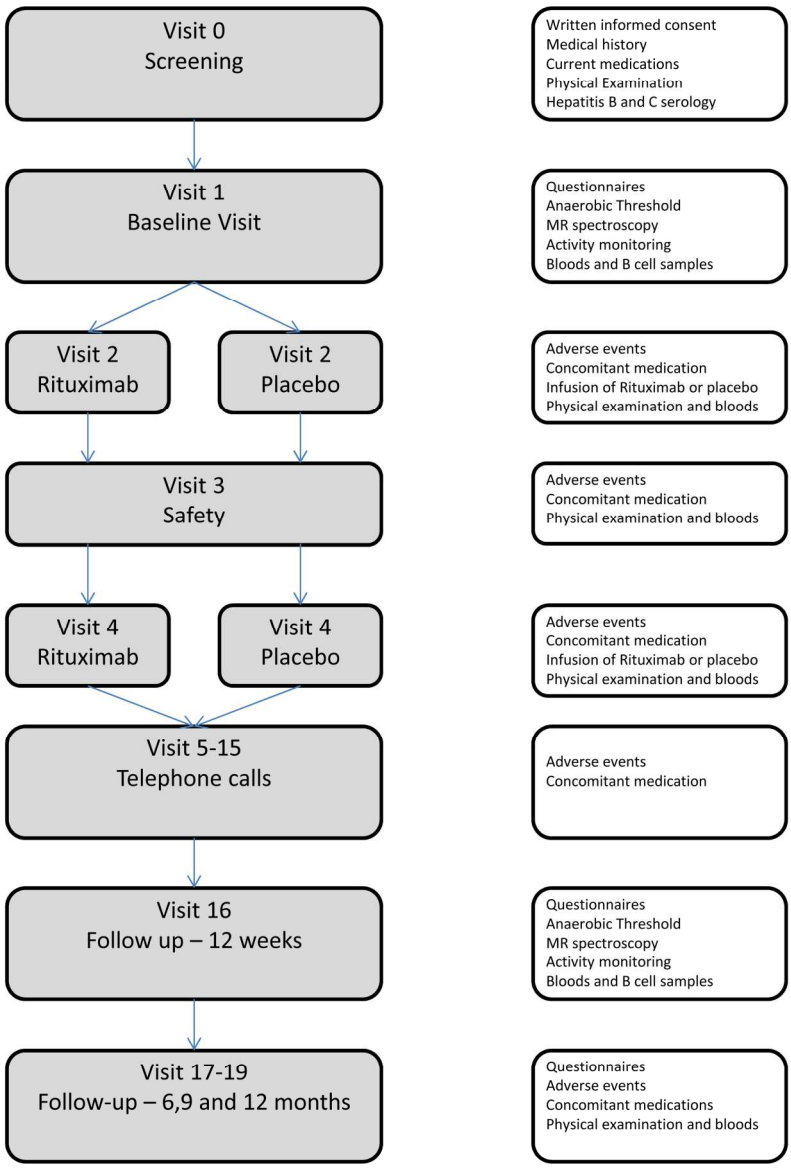

Figure 1
Schedule of events
225x292mm (300 x 300 DPI)

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