Rituximab for the treatment of fatigue in primary biliary cholangitis (formerly primary biliary cirrhosis): a randomised controlled trial

Amardeep Khanna,[1,2†] Laura Jopson,[1,2†] Denise Howel,[3] Andrew Bryant,[3] Andrew Blamire,[2] Julia L Newton,[2] Jennifer Wilkinson,[4] Alison J Steel,[4] Jennifer Bainbridge,[2] Renae Stefanetti,[5] Sophie Cassidy,[5] David Houghton[5] and David E Jones[1,2*]

[1]Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[2]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK
[3]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK
[4]Clinical Trials Unit, Newcastle University, Newcastle upon Tyne, UK
[5]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

*Corresponding author d.e.j.jones@ncl.ac.uk
†Joint authorship

Declared competing interests of authors: Denise Howel was a member of Health Services and Delivery Research Commissioning Board until 30 November 2015.

Published April 2018
DOI: 10.3310/eme05020

Scientific summary

The RITPBC trial

Efficacy and Mechanism Evaluation 2018; Vol. 5: No. 2
DOI: 10.3310/eme05020

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

B-cell-depleting therapy (RITuximab) as a treatment for fatigue in Primary Biliary Cirrhosis (RITPBC) was a Phase II randomised placebo-controlled trial targeting moderate to severe fatigue in primary biliary cholangitis [formerly primary biliary cirrhosis (PBC)].

Primary biliary cirrhosis is an autoimmune liver disease characterised by loss of the intrahepatic bile ducts, accompanied by progressive cholestasis. Fifty per cent of patients experience significant fatigue, a particularly debilitating symptom affecting quality of life and resulting in social isolation. Fatigue can occur at any point in the disease course, and its severity is unrelated to liver disease activity or degree of liver damage. Unsurprisingly, in light of this, fatigue severity is not reduced by current first- and second-line therapy. Given its impact and lack of response to therapy, increasing understanding of, and treatment for, fatigue has been highlighted by patients as a priority for research. Patient support groups were actively involved in developing the concept underpinning this trial, contributing to the protocol and supporting recruitment for the trial. This was the first randomised controlled trial to investigate a treatment for fatigue in PBC.

Primary biliary cirrhosis is characterised immunologically by the presence of high-titre autoantibodies directed at pyruvate dehydrogenase complex (PDC), an enzyme complex that plays a critical role in cellular bioenergetics function-linking glycolysis and the Krebs cycle. Anti-PDC antibodies from PBC patients are highly effective, in vitro at least, at blocking PDC function. Clinically, PBC patients exhibit both central and peripheral elements to their fatigue. The peripheral component, likened by patients to feeling that their 'batteries are running down', is significant and associated with the inability to sustain repeat muscle contraction. Investigation of this phenomenon, using novel magnetic resonance (MR) spectroscopy approaches, revealed marked muscle acidosis with exercise, related to mitochondrial dysfunction, and a prolongation in the time taken for recovery of muscle acidosis following discontinuation of exercise, which was related to fatigue severity. The degree of mitochondrial dysfunction was also related to serum anti-PDC antibody level. In separate approaches, PBC patients have been shown to have lower anaerobic threshold levels than matched control subjects with normal or reduced bile flow (cholestasis). Taken together, these observations point to dysregulation of aerobic metabolism in muscle in PBC, with excessive or inappropriate utilisation of the anaerobic lactate dehydrogenase pathway. The link between anti-PDC antibody levels and mitochondrial dysfunction, and the capacity of anti-PDC antibodies to block PDC function (a key checkpoint in the progression from glycolysis to the Krebs cycle in aerobic metabolism), led us to postulate that anti-PDC antibodies are in fact the driver for the metabolic insult in PBC and that this insult underpinned fatigue. The potential for this approach was supported by a pilot study completed in Canada that demonstrated a beneficial action of rituximab (MabThera®, Roche Products Ltd) on fatigue in PBC.

If anti-PDC were a driver for fatigue in PBC, then the B-cell-targeting biological agent rituximab might be regarded as a plausible therapy option. This is a hypothesis that is supported by open-label pilot data, suggesting improvement in fatigue with this agent.

Objectives

- To assess if rituximab improved moderate or severe fatigue in patients with PBC and the sustainability of any improvement over time.
- To assess the safety and tolerability of rituximab in patients with PBC.
- To assess the effect of rituximab on anti-PDC antibodies in PBC and on bioenergetics abnormality potentially linked to fatigue.

Methods

Design

This was a Phase II, double-blind, randomised controlled trial comparing rituximab with placebo in fatigued PBC patients. Randomisation was conducted using a web-based system. Treatment allocation was kept blinded from the patients, study assessors and investigators until study completion. Participants received two infusions on days 1 and 15 and were then followed up at 3, 6, 9 and 12 months. The setting was a single centre in the UK.

Participants

Seventy-one patients aged ≥ 18 years with PBC and moderate or severe fatigue (as measured by a PBC-40 fatigue domain score of > 33) were screened and 57 participants were randomised to the trial.

The main inclusion criteria were that participants were aged ≥ 18 years with an established diagnosis of PBC and with stable or compensated liver disease. The major exclusion criteria were inability to give consent, alternative diagnosis of liver disease, advanced or decompensated disease, pregnancy or lactation, immune-compromised state, malignancy, active or severe infections, demyelinating disorder and psychiatric disorder.

Intervention

Participants in the study were randomised in a 1 : 1 ratio to receive either rituximab intravenous (i.v.) infusion (1000 mg) on days 1 and 15 ($n = 28$) or saline i.v. infusion (placebo) on days 1 and 15 ($n = 29$). The infusions were delivered in a double-blind manner to participants using the same protocol.

Outcome measures

The primary outcome measure was the PBC-40 fatigue domain score at 3 months, a disease-specific quality-of-life measure. The time course of the comparison between intervention and control groups over the 12-month follow-up period was also assessed. Secondary outcome measures included an extended panel of patient-reported outcome measures (PROMs) [including the other domains of the PBC-40 (cognitive, itch, social, emotional and other symptoms), and tools for depressions, anxiety, sleep disturbance and autonomic dysfunction], assessment of bioenergetics function [including anaerobic threshold assessed using conventional cardiopulmonary exercise testing (CPET) and post-exercise muscle pH assessed using MR] and physical activity monitoring.

Efficacy in terms of B-cell depletion was assessed using fluorescence-activated cell analysis and anti-PDC antibodies through enzyme-linked immunosorbent assay assessment of serum anti-PDC antibody levels.

The impact on biochemical markers of liver disease severity was assessed as an experimental analysis.

Results

Rituximab therapy was safe, with no serious adverse events linked to the drug and no difference in the adverse event profile between the rituximab and placebo groups.

Primary end point

There was no statistically significant difference in fatigue score at 3 months between the rituximab and placebo arms [adjusted mean difference –0.9, 95% confidence interval (CI) –4.6 to 3.1]. However, improvement was observed in both arms {with mean score decreasing from 41.2 [standard deviation (SD) 5.5] to 36.2 (SD 8.4) and from 43.0 (SD 5.9) to 38.1 (SD 8.7) in the rituximab and placebo arms, respectively}. There was no significant difference between the two trial arms over the repeated assessments at 3, 6, 9 and 12 months ($F = 1.81$; $p = 0.18$).

Secondary end points

Immunological analyses suggested that rituximab was effective in mediating depletion of B-cells: its primary proposed mode of action. No depletion was seen in the placebo arm. Complete depletion was maintained at 6 months with gradual repopulation to 50% of the baseline level by 12 months. The kinetics of fatigue reduction in the rituximab group mirrored the kinetics of B-cell depletion and recovery. Reduction in the levels of anti-PDC antibody (the characteristic autoantibody of PBC) was also seen in the rituximab (but not placebo) group. Peak reduction was seen at 6 months and this was sustained at 9 months. Reduction in total immunoglobulin, and in particular the immunoglobulin M fraction, was seen. Again, reduction was incomplete in the rituximab-treated group and absent from the placebo group.

Additional PROMs were used to assess other aspects of the patient experience [the five non-fatigue domains of the PBC-40 (addressing itch, cognitive, emotional, social and other symptoms), Epworth Sleepiness Scale (daytime somnolence), Orthostatic Grading Scale (autonomic dysfunction), Cognitive Failure Questionnaire (cognitive symptoms) and Hospital Anxiety and Depression Scale (depression and anxiety)]. The unadjusted and adjusted differences in mean scores between trial arms showed little difference at 3 months. The 95% CIs were generally wide, but there was no real suggestion that the results were consistent with any clinically important differences. In contrast to fatigue, which showed improvement in both the active drug and the placebo arms, no notable improvement in the other measures was seen in either group. Any placebo effect was therefore restricted to fatigue, and was absent even from the closely linked cognitive symptom domain. Physical activity levels [Euclidean Norm Minus One (ENMO)] differed little between arms at 3 months: the adjusted mean ENMO levels were slightly lower in the rituximab arm, but there was little indication of a large and meaningful difference.

We used a combination of MR spectroscopy of muscle and anaerobic threshold assessment using CPET to calculate changes in pH and recovery time post exercise. In keeping with previous reports, anaerobic threshold at baseline was low in this PBC patient group. The mean values rose in the rituximab arm from baseline to 3-month follow-up, with no change in the placebo arm. The anaerobic threshold score at 3 months was higher in the rituximab arm than in the placebo arm (adjusted difference 1.41, 95% CI 0.03 to 2.80).

There was no apparent correlation between degree of change in anaerobic threshold and change in fatigue over 3 months from baseline.

In keeping with our previous reported findings, the minimum pH following the specific exercise task was highly variable among the PBC patients, with substantial acidosis seen in some patients. Minimum pH in muscle seen following exercise was higher and the fall in pH with exercise was lower following rituximab therapy compared with placebo. No reduction in the time taken to recover to baseline pH after exercise and no reduction in the 'area under the curve' for pH (a factor combining the degree of acidosis and the length of time taken to recover to the baseline level and an estimate therefore of degree of muscle intracellular acid exposure) was seen in either arm. Comparison of bioenergetics outcomes between trial arms shows that the adjusted differences in means at 3 months were all small, with relatively narrow 95% CIs for the pH parameters.

No significant association was seen between changes in any MR parameter and change in fatigue severity.

Experimental analysis

The RITPBC trial was not designed or powered to explore the impact of the drug on liver injury; however, the trial provided some insight into the impact of rituximab therapy in early disease, which could inform future trials of disease-modifying therapy. Ninety-three per cent of patients in the rituximab arm had normal alkaline phosphatase (ALP) levels at 3 months, whereas 65% had ALP levels in the normal range in the placebo arm at 3 months. All parameters progressively returned to the baseline level by 12 months of follow-up.

Conclusions

The following conclusions can be drawn from this study:

- There is no evidence to support the use of rituximab for the treatment of fatigue in otherwise unselected populations of PBC patients with moderate to severe fatigue. On average, the trial end point of a 5-point reduction in fatigue severity was met; however, this did not significantly exceed the effect seen with placebo.
- Trials of fatigue-modulating therapy are deliverable in PBC and are acceptable to patients (retention was 100%). However, there is a significant issue with placebo effects that are similar in scale to those seen in recent PBC trials of anti-itch therapy.
- Rituximab when used in PBC was safe with no disease-attributable serious adverse events.
- The bioenergetics abnormality reported previously in fatigued PBC patients and that underpinned the trial concept was also seen in this trial.
- Anaerobic threshold was significantly improved by rituximab. Muscle bioenergetics abnormality on MR spectroscopy was not, however, significantly improved. The capacity of muscle to handle protons and lactate may therefore play a more important role in fatigue expression than PBC autoantibody. Future trials of therapy for fatigue might address these aspects (exercise therapy and targeting autonomic dysfunction).
- Although the trial was not designed or powered to explore impact on liver biochemistry, our findings point to a positive impact of rituximab on liver function when used in patients not defined by ursodeoxycholic acid failure.

Trial registration

This trial is registered as ISRCTN03978701, ClinicalTrials.gov identifier NCT02376335 and EudraCT number 2012-000145-12.

Funding

Funding for this study was provided by the Efficacy and Mechanism Evaluation programme of the National Institute for Health Research. Additional funding was received from the Medical Research Council and a Department of Health and Social Care subvention.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal
Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report

The research reported in this issue of the journal was funded by the EME programme as project number 10/90/03. The contractual start date was in October 2012. The final report began editorial review in March 2017 and was accepted for publication in August 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).