Rituximab compared to intravenous cyclophosphamide in adults with connective tissue disease-associated interstitial lung disease: the RECITAL RCT

Toby M Maher,[1,2*] Veronica A Tudor,[2] Peter Saunders,[3] Fernando Zanghelini,[4] Carlota Grossi Sampedro,[4] Georgios Xydopoulos,[4] Michael Gibbons,[5] Sophie V Fletcher,[6] Christopher P Denton,[7] Maria Kokosi, Rachel K Hoyles,[3] Helen Parfrey,[8] Elisabetta A Renzoni,[2,9] Athol U Wells,[2,9] Deborah Ashby,[10,11] Richard J Fordham,[4] Matyas Szigeti[12,13] and Philip L Molyneaux[2,9]; on behalf of the RECITAL Investigators

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine, University of Southern California, Los Angeles, USA
[2]Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, UK
[3]Oxford Centre for Respiratory Medicine, Churchill Hospital, Oxford, UK
[4]Norwich School of Medicine, University of East Anglia, Health Economics Consultancy, Norwich Research Park, Norwich, UK
[5]Academic Department of Respiratory Medicine, Royal Devon and Exeter Foundation Trust, Exeter, UK
[6]NIHR Southampton Biomedical Research Centre, University Hospital Southampton, Southampton, UK
[7]Centre for Rheumatology, Division of Medicine, Royal Free Campus, University College London, London, UK
[8]Interstitial Lung Disease Unit, Royal Papworth, Hospital NHFT Cambridge Biomedical Campus, Cambridge, UK
[9]National Heart and Lung Institute, Imperial College London, London, UK
[10]School of Public Health, Imperial College London, London, UK
[11]Imperial NIHR Biomedical Research Centre, London, UK
[12]Imperial Clinical Trial Unit, Imperial College London, London, UK
[13]Physiological Controls Research Centre, Obuda University, Budapest, Hungary

[*]Corresponding author toby.maher@med.usc.edu

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/LYWQ8541.

Primary conflicts of interest: Toby M Maher declares institutional grants from Astra Zeneca and GlaxoSmithKline R&D, and personal fees from Astra Zeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Fibrogen, Galapagos, Galecto, GlaxoSmithKline R&D, IQVIA, Pliant, Roche Trevi Therapeutics and Veracyte. Peter Saunders declares personal fees from Trevi Therapeutics and Boehringer Ingelheim.

Sophie V Fletcher declares personal fees from Chiesi and Boehringer Ingelheim.

Helen Parfrey declares personal fees from Boehringer Ingelheim, Trevi Therapeutics and Pliant Therapeutics. Athol U Wells declares personal fees from Boehringer Ingelheim, Roche and Veracyte. Philip L Molyneaux declares an institutional grant from Astra Zeneca and personal fees from Astra Zeneca, Boehringer Ingelheim and Roche.

Published February 2024
DOI: 10.3310/LYWQ8541

Scientific summary

Rituximab compared to intravenous cyclophosphamide in adults with connective tissue disease-associated interstitial lung disease: the RECITAL RCT

Efficacy and Mechanism Evaluation 2024; Vol. 11: No. 4
DOI: 10.3310/LYWQ8541

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

Scientific summary

Background

Interstitial lung disease (ILD) is characterised by inflammation and/or fibrosis within the parenchymal compartment bounded by the alveolar epithelium and capillary endothelium and frequently results in breathlessness progressing over time to respiratory failure. Autoimmune injury to the lung is a frequent cause of ILD. As such, the connective tissue diseases (CTDs), including systemic sclerosis (SSc), the inflammatory myopathies and mixed connective tissue disease (MCTD), are important causes of ILD. For individuals with CTD the development of ILD is an important cause of morbidity and mortality; for people with scleroderma, ILD is now the leading cause of death. Despite this there are few evidence-based treatments for CTD-associated ILD.

At the time of planning this research there were no approved therapies available for CTD-ILD and all of the trial data which existed had been generated in the context of scleroderma-associated ILD. The Scleroderma Lung Study I assessed the efficacy of 52 weeks of treatment with oral cyclophosphamide (CP) compared to placebo in individuals with systemic sclerosis-associated ILD and evidence of an active inflammatory cell infiltrate on bronchoalveolar lavage. The trial demonstrated a positive effect of CP at 52 weeks but the drug was poorly tolerated and the benefit compared with placebo had disappeared by 2 years. A smaller 52-week study, also conducted in individuals with scleroderma-associated ILD, compared placebo to once-monthly intravenous CP given for 6 months followed by azathioprine and low dose prednisolone for the subsequent 6 months and showed a trend towards benefit in the active treatment arm. In the absence of treatment guidelines or evidence generated in other forms of CTD-ILD, most centres in the UK were routinely using intravenous CP as first-line therapy for individuals with clinically advanced or rapidly progressive ILD arising in the context of CTD.

Rituximab, a chimeric (human/mouse) monoclonal antibody with a high affinity for the CD20 surface antigen expressed on B-lymphocytes, results in rapid depletion of B cells from the peripheral circulation for 6–9 months. Evidence for the efficacy of B cell depletion exists in a number of immune-mediated conditions, including rheumatoid arthritis, antineutrophil cytoplasmic antibody-associated vasculitis and immune thrombocytopenic purpura. Several case series suggest rituximab may also be effective in ILD occurring in the context of immunological over-activity, with favourable responses reported in antisynthetase-associated ILD and SSc-ILD. Our own clinical experience suggested that rituximab is an effective, potentially life-saving therapeutic intervention in the treatment of very severe, progressive CTD-ILD unresponsive to conventional immunosuppression. In head-to-head studies in the context of other autoimmune diseases rituximab has been shown to have a favourable safety and tolerability profile compared to CP.

The absence of high-quality evidence to guide treatment of CTD-ILD provided an opportunity to assess the efficacy of rituximab compared to the accepted standard of care, CP.

Objectives

The primary objective of the study was to demonstrate that intravenous rituximab has superior efficacy compared to current best treatment (intravenous CP) for CTD-ILD as measured by assessment of change in forced vital capacity (FVC) at 24 weeks.

Secondary objectives were:

- to compare the safety profile of rituximab to intravenous CP in individuals with CTD-ILD
- to assess the health economic benefits of rituximab compared to current standard of care for CTD-ILD – including measurements of healthcare utilisation, quality of life (QoL) and carer burden
- to evaluate a range of exploratory biomarkers for disease severity, prognosis and treatment response in CTD-ILD.

Methods

The study was a Phase IIb, UK multicentre, prospective, randomised, double-blind, double-dummy trial of intravenous rituximab compared with intravenous CP in patients with severe, progressive CTD-ILD. Patients were randomised 1 : 1 to two groups, both groups received placebo to match the different regimens. Patients were followed for 48 weeks after first treatment; after 24 weeks subjects were permitted additional immunotherapy as determined by their treating physician.

Study settings

The study was conducted in rheumatology or ILD units at 11 UK centres.

Participant inclusion criteria

- A diagnosis of CTD, based on internationally accepted criteria, in one of the following categories:
    - systemic sclerosis
    - idiopathic interstitial myopathy (including polymyositis/dermatomyositis)
    - MCTD.
- Severe and/or progressive ILD associated with the underlying CTD.
- Chest high-resolution computer tomography performed within 12 months of randomisation.
- Intention of the caring physician to treat the ILD with intravenous CP.
- Able to provide written informed consent.

Participant exclusion criteria

- Previous treatment with rituximab and/or intravenous CP.
- Age <18 or >80 years.
- Known hypersensitivity to rituximab or CP or their components.
- Significant (in the opinion of the investigator) other organ comorbidity including cardiac, hepatic or renal impairment.
- Coexistent obstructive pulmonary disease (e.g. asthma, chronic obstructive pulmonary disease, emphysema) with pre-bronchodilator forced expiratory volume in 1 second (FEV_1) and FVC ratio < 70%.
- Patients at significant risk for infectious complications following immunosuppression including those with human immunodeficiency virus positive or other immunodeficiency syndromes (including hypogammaglobulinemia).
- Suspected or proven untreated tuberculosis.
- Viral hepatitis.
- Infection requiring antibiotic treatment in the preceding 4 weeks.
- Unexplained neurological symptoms (which may be suggestive of progressive multifocal leucoencephalopathy). Neurological symptoms arising because of the underlying CTD do not necessitate exclusion.

- Other investigational therapy (participation in research trial) received within 8 weeks of randomisation.
- Immunosuppressive or CTD modifying therapy (other than corticosteroids) received within 2 weeks of the first intravenous treatment.
- Pregnant or breastfeeding women, or women of child-bearing potential, not using a reliable contraceptive method for up to 12 months following IMP.
- Unexplained haematuria, or previous bladder carcinoma.
- Computerised tomography scan > 12 months from randomisation.
- Unable to provide informed written consent.

Interventions

Patients were randomised to receive either:

- Rituximab 1000 mg for two doses at day 0 and day 14. Placebo was administered monthly from week 4 to week 20.
- CP given at a dose of 600 mg/m^2 body surface area rounded to the nearest 100 mg every 4 weeks from day 0 to week 20. Placebo was given at day 14.

Patients were pre-medicated on day 0 with hydrocortisone, paracetamol, chlorpheniramine and mesna, at day 14 with hydrocortisone, paracetamol and chlorpheniramine and at visits from week 4 to 20 with mesna.

Measurements

Wherever possible, even if treatment could not be given, spirometry was undertaken at the time of each planned visit and performed according to standards outlined in the American Thoracic Society/European Respiratory Society guidelines. Lung function tests (plethysmography and gas transfer) were measured at screening, baseline, week 12, week 24 and week 48.

Assessment for adverse events (AEs) and clinical end points began from randomisation and continued for the individual patient until they completed their follow-up at 48 weeks. At each study visit the investigator or designee made an assessment of safety and reviewed the clinical history and investigation findings with regard to the occurrence of adverse or serious adverse events (SAEs).

Peripheral blood was taken at the time of each planned visit. Collection of blood for laboratory analyses included full blood count, erythrocyte sedimentation rate, urea and electrolytes, glucose, hepatitis A, B and C serology (screening only) and liver function tests. Blood for lymphocyte subsets and biomarker analysis was taken at day 0, week 12, 24 and 48 only.

Quality of life was assessed by self-administered validated questionnaires undertaken at baseline and repeated at the primary end point visit at 24 weeks and at the final follow-up visit at 48 weeks. The instruments used were:

- the Short Form 36 (SF36) questionnaire
- EuroQol-5 Dimensions (EQ-5D)
- St George's Respiratory Questionnaire (SGRQ)
- King's Brief Interstitial Lung Disease (K-BILD)
- Scleroderma Health Assessment (SHA) Questionnaire which was disease-specific.

For individuals with scleroderma, assessment of skin thickening was undertaken using the modified Rodnan skin score at baseline, 24 and 48 weeks.

Sample size

The primary outcome was changed in FVC at 24 weeks. The trial was designed to have 90% power to detect a 5% difference in 24-week FVC between treatment groups with a significance level (alpha) of 0.05 (two-tailed). The target sample size was 116 with the anticipation that 52 patients would reach the end-of-study in each arm with an expected 10% drop out. Because of the COVID-19 pandemic and an anticipated prolonged interruption to recruitment, trial enrolment was halted in March 2020 after randomisation of 101 subjects.

Statistical analysis

No formal interim analysis was planned. A statistical analysis plan was produced and agreed prior to analysis. Analysis of the primary outcome was by modified intention to treat. In other words, data were included in respect of all subjects who met all the entry criteria for the trial and had been randomised and received at least one dose of study drug.

Results

The study recruitment period was from December 2014 until March 2020 from 11 sites. In total 145 subjects were assessed for eligibility and of these 104 participants were enrolled. Three of these failed screening and were excluded. One hundred and one subjects were therefore randomised and 97 subjects received at least one dose of study drug and were included in the modified intention-to-treat population for the primary and secondary efficacy analyses (49 in the rituximab group and 48 in the CP group).

Overall, baseline characteristics between the rituximab and CP arms were well balanced albeit with slightly more male participants in the rituximab arm. For the total cohort the mean ± S.D. age was 56 ± 11.4 years. Seventy subjects (69.3%) were female, 70 (69.3%) were white, 16 (15.8%) Asian and 12 (11.9%) black. The most frequently encountered CTD was idiopathic inflammatory myopathy (44.6%), followed by scleroderma (38.6%) and then MCTD (16.8%).

Primary outcome

At week 24 the unadjusted mean [± standard deviation (SD)] change in FVC in the CP treatment arm was a gain of 99 ± 329 ml. In the rituximab arm the change was 97 ± 234 ml. The relative change from baseline for each arm was 4.35 ± 15.67% for CP and for rituximab 4.31 ± 11.80%. Using a mixed-effects model adjusted for baseline FVC and diagnosis the difference (and 95% confidence interval) at 24 weeks between rituximab and CP was −40 ml [95% confidence interval (CI) −153 to 74 ml], $p = 0.49$.

Secondary outcomes

The unadjusted change in FVC at 48 weeks was 138 ± 440 ml in the CP arm and 112 ± 249 ml in the rituximab group. In relative terms, over 48 weeks, the improvement in the CP group was 5.08 ± 19.96% and in the rituximab group 4.22 ± 10.31%. An adjusted mixed-effects model demonstrated a −58 (95% CI −178 to 62) ml difference at 48 weeks between the rituximab and CP arms ($p = 0.251$).

At week 24 the mean relative change in diffusing capacity of the lung for carbon monoxide (DLco) in the CP arm was 1.43 ± 23.05% compared to 6.98 ± 17.19% in the rituximab arm. At 48 weeks the changes in DLco were 3.00 ± 31.35% and 7.43 ± 16.08% in the CP and rituximab arms, respectively.

For 6-minute walk distance the 24-week change in the CP and rituximab arms was 10.4 ± 78.6 and 10.9 ± 74.2 m, respectively. At week 48 the changes were 15.1 ± 82.8 and −6.8 ± 69.8 m. Using an adjusted mixed-effects model the differences between the rituximab and CP arms were −0.72 (−24.76 to 23.32) m, p = 0.953 at 24 weeks and −22.46 (−48.43 to 3.51) m, p = 0.090 at 48 weeks.

Quality of life was assessed using the K-BILD questionnaire. Change at 24 weeks was 9.4 ± 20.8 in the CP arm and 8.8 ± 17.0 in the rituximab arm. At 48 weeks the difference compared to baseline was 5.6 ± 25.6 and 6.4 ± 16.2 in the CP and rituximab arms, respectively. Analysis in an adjusted mixed-effects model showed the difference between rituximab and CP was 0.4 (−5.73 to 6.52) and 1.15 (−5.34 to 7.64) at weeks 24 and 48, respectively.

Survival

Over the 48-week course of the study there were five deaths. All were deemed to be due to complications of either CTD or ILD. Three occurred in subjects receiving rituximab and two in subjects receiving CP. There was no difference between groups in time to death as assessed by an adjusted Cox proportional hazards model [hazard ratio (HR) 1.72 (95% CI 0.311 to 9.56, p = 0.534)]. The rates of progression-free survival [HR 1.11 (95% CI 0.625 to 1.99, p = 0.715)], and time to treatment failure [HR 1.25 (95% CI 0.34 to 4.65, p = 0.742)] did not differ between treatment arms.

Corticosteroids

The mean per-subject total steroid exposure during the study (measured in hydrocortisone equivalents) was 13,291 (±14,657) mg in the CP and 11,469 (±10,041) mg in the rituximab group; a 12% reduction in corticosteroid exposure in the rituximab arm. The daily mean dose per patient was 42.89 mg hydrocortisone/day in the CP and 37.61 mg hydrocortisone/day in the rituximab group.

Safety

All subjects in both arms experienced at least one AE. There were more AEs reported in the CP arm (646) than in the rituximab arm (445). The imbalance was less marked for SAEs with 33 and 29 in the CP and rituximab arms, respectively. Gastrointestinal disorders (170 vs. 71), general disorders and administration site reactions (91 vs. 52) and nervous system disorders (72 vs. 35) were more common in the CP arm. The frequency of other AEs was balanced between groups including infections and infestations (50 vs. 46). One patient in each arm withdrew because of side effects. There were no reported cases of COVID-19 during the trial.

Cost-effectiveness

Over the 48-week trial period treatment with CP was associated with a cost of £94,338 compared with a cost of £93,227 for rituximab; a difference of £1110 in favour of rituximab. Rituximab was associated with a 0.022 gain in quality-adjusted life-years over that seen with CP. The incremental net monetary benefit was significantly higher in the rituximab group under a wide range of monetary values and quality-adjusted life-years.

Conclusion

This study demonstrated that both rituximab and CP improve FVC and QoL in patients with CTD-ILD. There were numerically fewer AEs and a trend towards reduction in corticosteroid exposure in the

rituximab-treated subjects. Rituximab should therefore be considered as a treatment option in patients with severe or rapidly progressive CTD-associated ILD.

Implications for health care

Although this study failed to show superiority of rituximab over CP in improving FVC when used as first-line treatment for CTD-ILD, the consistent positive effects of rituximab on physiological end points, QoL, and corticosteroid requirements support the clinical use of this drug in what is a population of patients with high unmet need (especially in situations where CP is contraindicated or likely to cause deleterious effects such as gonad failure or bladder malignancy).

Implications for research

Further trials will be necessary to confirm whether repeated dosing with rituximab confers additional benefit as compared to a single baseline dose. Similarly, additional studies are necessary to confirm findings in individual CTDs and to assess the optimal longer-term therapeutic regimen following initial intravenous therapy.

Trial registration

This trial is registered as ISRCTN16474148.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation Programme (NIHR award ref: 11/116/03) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 11, No. 4. See the NIHR Funding and Awards website for further award information.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

A list of Journals Library editors can be found on the NIHR Journals Library website

Efficacy and Mechanism Evaluation (EME) was launched in 2014 and is indexed by Europe PMC, DOAJ, Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and NCBI Bookshelf.

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.

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal
Manuscripts 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 funds ambitious studies evaluating interventions that have the potential to make a step-change in the promotion of health, treatment of disease and improvement of rehabilitation or long-term care. Within these studies, EME supports research to improve the understanding of the mechanisms of both diseases and treatments.

The programme supports translational research into a wide range of new or repurposed interventions. These may include diagnostic or prognostic tests and decision-making tools, therapeutics or psychological treatments, medical devices, and public health initiatives delivered in the NHS.

The EME programme supports clinical trials and studies with other robust designs, which test the efficacy of interventions, and which may use clinical or well-validated surrogate outcomes. It only supports studies in humans and where there is adequate proof of concept. The programme encourages hypothesis-driven mechanistic studies, integrated within the efficacy study, that explore the mechanisms of action of the intervention or the disease, the cause of differing responses, or improve the understanding of adverse effects. It funds similar mechanistic studies linked to studies funded by any NIHR programme.

The EME programme is funded by the Medical Research Council (MRC) and the National Institute for Health and Care Research (NIHR), with contributions from the Chief Scientist Office (CSO) in Scotland and National Institute for Social Care and Health Research (NISCHR) in Wales and the Health and Social Care Research and Development (HSC R&D), Public Health Agency in Northern Ireland.

This manuscript

The research reported in this issue of the journal was funded by the EME programme as project number 11/116/03. The contractual start date was in September 2013. The final report began editorial review in April 2022 and was accepted for publication in February 2023. 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' manuscript and would like to thank the reviewers for their constructive comments on the final manuscript document. However, they do not accept liability for damages or losses arising from material published in this manuscript.

This manuscript 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, 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, the EME programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).