Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

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Summary

Background Rituximab is often used as rescue therapy in interstitial lung disease (ILD) associated with connective tissue disease (CTD), but has not been studied in clinical trials. This study aimed to assess whether rituximab is superior to cyclophosphamide as a treatment for severe or progressive CTD associated ILD.

Methods We conducted a randomised, double-blind, double-dummy, phase 2b trial to assess the superiority of rituximab compared with cyclophosphamide. Patients aged 18–80 years with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD, recruited across 11 specialist ILD or rheumatology centres in the UK, were randomly assigned (1:1) to receive rituximab (1000 mg at weeks 0 and 2 intravenously) or cyclophosphamide (600 mg/m² body surface area every 4 weeks intravenously for six doses). The primary endpoint was rate of change in forced vital capacity (FVC) at 24 weeks compared with baseline, analysed using a mixed-effects model with random intercepts, adjusted for baseline FVC and CTD type. Prespecified secondary endpoints reported in this Article were change in FVC at 48 weeks versus baseline; changes from baseline in 6 min walk distance, diffusing capacity of the lung for carbon monoxide (DL_{CO}), physician-assessed global disease activity (GDA) score, and quality-of-life scores on the St George's Respiratory Questionnaire (SGRQ), King's Brief Interstitial Lung Disease (KBILD) questionnaire, and European Quality of Life Five-Dimension (EQ-5D) questionnaire at 24 and 48 weeks; overall survival, progression-free survival, and time to treatment failure; and corticosteroid use. All endpoints were analysed in the modified intention-to-treat population, which comprised all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov (NCT01862926).

Findings Between Dec 1, 2014, and March 31, 2020, we screened 145 participants, of whom 101 participants were randomly allocated: 50 (50%) to receive cyclophosphamide and 51 (50%) to receive rituximab. 48 (96%) participants in the cyclophosphamide group and 49 (96%) in the rituximab group received at least one dose of treatment and were included in analyses; 43 (86%) participants in the cyclophosphamide group and 42 (82%) participants in the rituximab group completed 24 weeks of treatment and follow-up. At 24 weeks, FVC was improved from baseline in both the cyclophosphamide group (unadjusted mean increase 99 mL [SD 329]) and the rituximab group (97 mL [234]); in the adjusted mixed-effects model, the difference in the primary endpoint at 24 weeks was –40 mL (95% CI –153 to 74; p=0·49) between the rituximab group and the cyclophosphamide group. KBILD quality-of-life scores were improved at 24 weeks by a mean 9·4 points (SD 20·8) in the cyclophosphamide group and 8·8 points (17·0) in the rituximab group. No significant differences in secondary endpoints were identified between the treatment groups, with the exception of change in GDA score at week 48, which favoured cyclophosphamide (difference 0·90 [95% CI 0·11 to 1·68]). Improvements in lung function and respiratory-related quality-of-life measures were observed in both treatment groups. Lower corticosteroid exposure over 48 weeks of follow-up was recorded in the rituximab group. Two (4%) of 48 participants who received cyclophosphamide and three (6%) of 49 who received rituximab died during the study, all due to complications of CTD or ILD. Overall survival, progression-free survival, and time to treatment failure did not significantly differ between the two groups. All participants reported at least one adverse event during the study. Numerically fewer adverse events were reported by participants receiving rituximab (445 events) than those receiving cyclophosphamide (646 events). Gastrointestinal and respiratory disorders were the most commonly reported adverse events in both groups. There were 62 serious adverse events of which 33 occurred in the cyclophosphamide group and 29 in the rituximab group.

Interpretation Rituximab was not superior to cyclophosphamide to treat patients with CTD-ILD, although participants in both treatment groups had increased FVC at 24 weeks, in addition to clinically important improvements in patient-reported quality of life. Rituximab was associated with fewer adverse events. Rituximab should be considered as a therapeutic alternative to cyclophosphamide in individuals with CTD-ILD requiring intravenous therapy.

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See Online for appendix

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Introduction

Interstitial lung disease (ILD) is a frequent, often fatal, complication of systemic autoimmune diseases including systemic sclerosis, idiopathic inflammatory myositis, and mixed connective tissue disease (CTD).

Based on trials in patients with systemic sclerosis-associated ILD, immunosuppressive therapy with cyclophosphamide is frequently used as an effective treatment for individuals with severe or rapidly progressive CTD-associated ILD (CTD-ILD); however, cyclophosphamide use is limited by toxicity. Cyclophosphamide frequently causes nausea, gastrointestinal upset, and haematuria, can cause gonad-failure in both males and females, and increases risk of bladder malignancy. This latter effect is dose related and therefore limits individual cumulative lifetime use of cyclophosphamide to less than 20 g.[1–3] Rituximab, a chimeric anti-CD20 monoclonal antibody, has been reported in retrospective cohorts and small open-label studies to be a potentially effective treatment for CTD-ILD. To date there have been no randomised controlled trials of rituximab in this patient group. Rituximab is typically given intravenously as two separate doses given at an interval of 2 weeks. In some conditions, rituximab is administered long term with repeat dosing every 6–9 months. Potential adverse effects of rituximab include infusion reactions, reactivation of hepatitis B virus infection, and, very rarely, progressive multifocal leukoencephalopathy. There have been no head-to-head studies of cyclophosphamide and rituximab in CTD associated ILD.[4–7]

The RECITAL study tested the hypothesis that intravenous rituximab would be superior to intravenous cyclophosphamide for CTD-ILD, using a randomised controlled trial with a basket design combining patients with a range of CTD-ILD diagnoses.[8]

Research in context

Evidence before this study

Rituximab is a monoclonal antibody that depletes B lymphocytes. It is approved for the treatment of a range of autoimmune disorders, including rheumatoid arthritis, and is often used off-label as rescue therapy in treatment-refractory connective tissue disease-associated interstitial lung disease (CTD-ILD). We searched PubMed from database inception to March 31, 2022, for reports published in any language using the search terms ("scleroderma" OR "systemic sclerosis" AND "interstitial lung disease" AND "rituximab" AND "clinical trial") OR ("myositis" OR "idiopathic inflammatory myopathy" AND "interstitial lung disease" AND "rituximab" AND "clinical trial") OR ("mixed connective tissue disease" OR "MCTD" AND "interstitial lung disease" AND "rituximab" AND "clinical trial"). This yielded seven articles, of which four were review articles and one was a case series of three patients. Of the two remaining studies, one was a secondary manuscript of a randomised controlled trial comparing rituximab with cyclophosphamide, conducted in patients with systemic sclerosis, a proportion of whom had ILD—the primary manuscript was in an unlisted journal and was thus incorporated into our evidence review. The remaining manuscript was an open-label study of rituximab in ten patients with idiopathic inflammatory myositis and associated ILD. Thus, our search identified no randomised controlled trials investigating rituximab specifically as a treatment for ILD in any of the CTDs studied in RECITAL.

Added value of this study

To our knowledge this is the first randomised controlled trial to assess the efficacy and safety of rituximab in patients with a range of CTD-ILDs (including ILD related to systemic sclerosis, idiopathic inflammatory myositis, and mixed CTD). We included patients with severe or rapidly progressive CTD-ILD and compared rituximab with the existing standard of care, intravenous cyclophosphamide, over 24 weeks. The study showed no benefit of rituximab over cyclophosphamide for the primary outcome, as measured by 24-week rate of change in forced vital capacity (FVC) from baseline. However, both treatment groups had clinically meaningful improvements in measures of lung physiology and quality of life. These benefits persisted to 48 weeks. Rituximab was associated with fewer adverse events than cyclophosphamide and with reduced corticosteroid exposure over 48 weeks.

Implications of all the available evidence

At present, there is no direct evidence to guide the treatment of CTD-ILD except in patients with scleroderma-associated ILD, for whom two approved therapies exist. Although rituximab is used in clinical practice for the treatment of CTD-ILD, no evidence base exists to guide this therapy. The results of this trial are, therefore, important for patients with CTD-ILD and clinicians involved in their treatment. The improvements in FVC and quality of life at 24 weeks following administration of rituximab suggest that the drug offers an effective treatment option for this group of patients. Furthermore, rituximab appeared to be better tolerated and associated with lower corticosteroid use than cyclophosphamide, the existing first-line treatment option for CTD-ILD.

Methods

Study design and participants

We conducted a phase 2b, randomised, double-blind, double-dummy trial of intravenous rituximab compared with intravenous cyclophosphamide in patients with severe or progressive ILD occurring in the context of a confirmed diagnosis of systemic sclerosis, idiopathic inflammatory myositis, or mixed CTD, at 11 centres in the UK.

Key eligibility criteria were an age of 18–80 years and a diagnosis, based on internationally accepted criteria,[9–12] of systemic sclerosis, idiopathic inflammatory myositis (including polymyositis or dermatomyositis), or mixed CTD with associated severe or progressive ILD. Determination of ILD progression or severity was left to individual investigators, with the guidance that patients should be those who would be considered for treatment with intravenous cyclophosphamide in routine clinical practice. Participants were required to have had a high-resolution CT scan of the chest in the 12 months preceding randomisation to document evidence of ILD. Participants were excluded if they had previously received cyclophosphamide or rituximab therapy, or if they were receiving immunosuppressants, other than oral corticosteroids, within 2 weeks of the first intravenous therapy—because of concerns regarding over-immunosuppression, it is standard practice to discontinue other immunomodulatory drugs before initiating cyclophosphamide.[13] Participants were also excluded if they had a history of coexistent obstructive lung disease (eg, asthma, emphysema, or chronic obstructive pulmonary disease) with a pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio of less than 0·7. Full eligibility criteria are provided in the published protocol.[8]

All patients provided written informed consent. The trial was conducted in accordance with the International Council for Harmonisation guidelines for good clinical practice and the Declaration of Helsinki, as well as local regulations, and was approved by the National Research Ethics Service London—Westminster (13/LO/0968). An independent data safety and monitoring committee was used (appendix p 8).

Randomisation and masking

Patients were randomly allocated (1:1) to receive either rituximab or cyclophosphamide. Randomisation was by interactive web-based randomisation system (Oracle, Reading, UK). To ensure equal representation of CTD subtypes in each treatment group, randomisation was stratified on the basis of the three possible underlying CTD diagnoses (systemic sclerosis, idiopathic interstitial myopathy, or mixed connective tissue disease). Access to the randomisation system at each participating centre was restricted to authorised study staff. All study staff were masked to treatment allocation. Unmasking, by the local principle investigator, was permitted if judged to be in the best medical interests of the study participant; three subjects were unmasked before week 24 of the study.

Procedures

Patients in the rituximab group received 1000 mg of intravenous rituximab on day 0 and day 14 and placebo every 4 weeks from week 4 to week 20. Patients in the cyclophosphamide group received 600 mg/m² body surface area, rounded to the nearest 100 mg, of intravenous cyclophosphamide every 4 weeks from day 0 to week 20, with placebo given on day 14. Both active therapies (and matching placebo, consisting of normal saline alone) were supplied by a single centralised pharmacy (Bath ASU, Corsham, UK) in matching 250 mL bags of normal saline. For the day 0 dose when both groups received active therapy, an ascending rate of infusion was used in line with usual protocols for administering rituximab.

All patients were pre-medicated on day 0 with hydrocortisone, paracetamol, chlorphenamine, and mesna; on day 14 with hydrocortisone, paracetamol, and chlorphenamine; and at visits from week 4 to 20 with mesna. The decision to use other therapies (eg, co-trimoxazole for pneumocystis prophylaxis) was left to the discretion of the treating physician. Background corticosteroids were permitted and dosage was managed at the discretion of the local treating physician. Additional immunosuppressant therapy was prohibited until week 24; after week 24, additional immunosuppression could be prescribed at the discretion of the treating physician.

Spirometry to measure FVC was done at the time of each planned visit (baseline and weeks 2, 4, 8, 12, 16, 20, 24, 36, and 48) and according to the standards outlined in the guidelines of the American Thoracic Society and European Respiratory Society.[14]

Assessment for adverse events and clinical endpoints began from randomisation and continued for each individual patient until they completed follow-up at 48 weeks. Pharmacovigilance definitions were adapted from European Commission guidance (2011/C 172/01) and were categorised using the Medical Definitions for Regulatory Activity (MedDRA) dictionary. Collection of blood for laboratory analyses—including full blood count, urea and electrolytes, liver function tests, and inflammatory markers—was completed at each visit. 6 min walk distance,[15] diffusing capacity of the lung for carbon monoxide (DL_{CO}), and quality-of-life scores were assessed at baseline and weeks 24 and 48. Quality of life scores were measured using the St George's Respiratory Questionnaire (SGRQ; 0–100 scale with higher scores representing poorer quality of life),[16] King's Brief Interstitial Lung Disease (KBILD) questionnaire (0–100 scale with higher scores representing better quality of life),[17] and European Quality of Life Five-Dimension (EQ-5D) questionnaire (0–100 scale

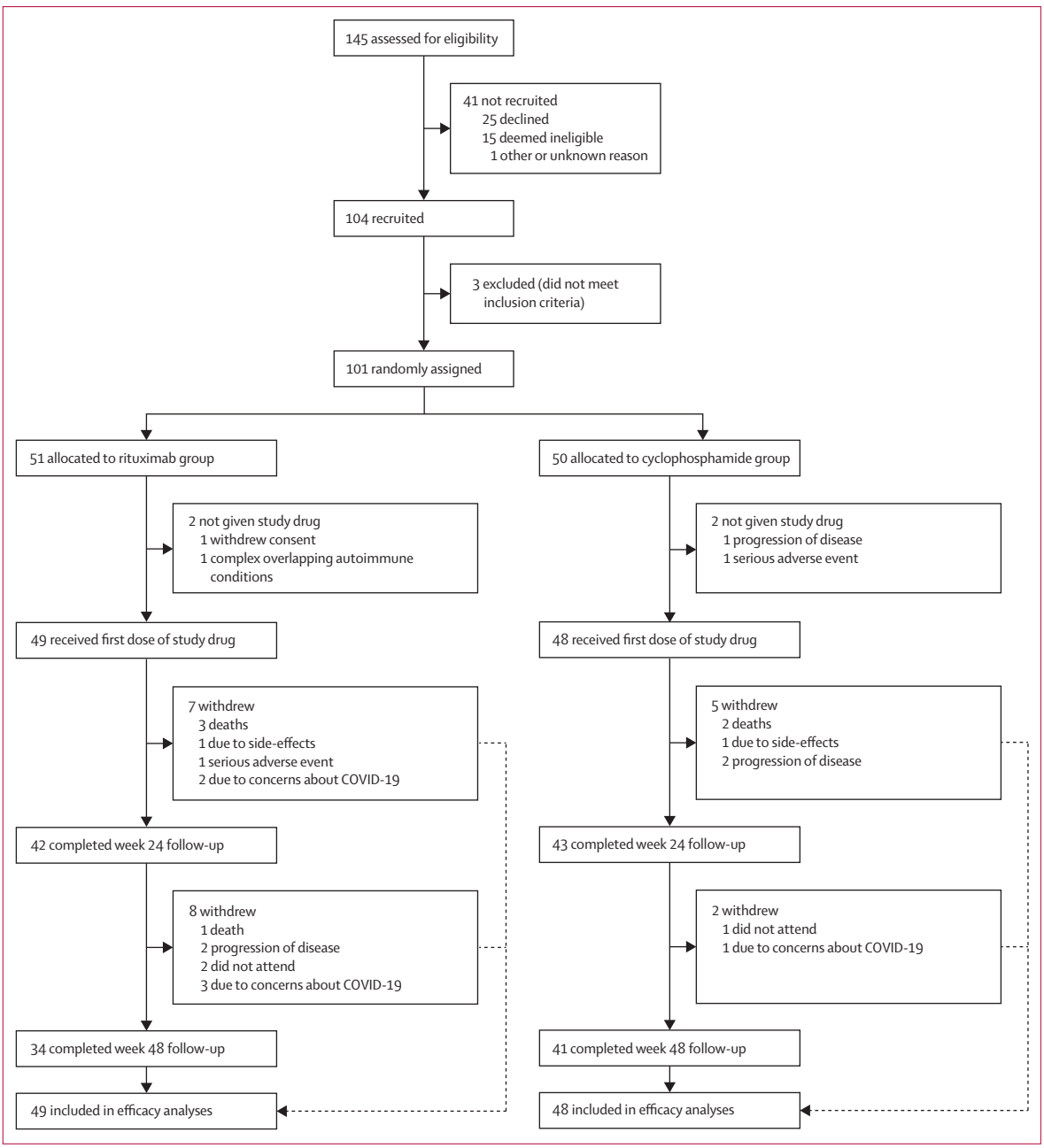

Figure 1: **Trial profile**

across five domains, with 100 representing best imaginable health).[18] A global physician assessment of disease activity was also measured using a 10 cm visual analogue scale.

Outcomes

The primary study endpoint was the 24-week rate of change in FVC from baseline, measured in mL. Secondary efficacy endpoints were the 48-week rate of change in FVC; change from baseline in 6 min walk distance, DL_{CO}, and quality-of-life scores on the SGRQ, KBILD, and EQ-5D, measured at 24 and 48 weeks; overall survival and progression-free survival times and time to treatment failure; and total corticosteroid use (calculated, before unmasking, by converting all recorded corticosteroid use into equivalent units of hydrocortisone). Mean corticosteroid dose per patient (mg hydrocortisone per day) was added as a post hoc analysis. Financial constraints prevented assessment of scores on the SF-36 survey, which was initially specified in the protocol.

	Cyclophosphamide group (n=48)	Rituximab group (n=49)
Age, years	56·7 (11·6)	56·6 (11·4)
Sex		
Female	35 (73%)	31 (63%)
Male	13 (27%)	18 (37%)
Race and ethnicity*		
Asian	7 (15%)	9 (18%)
Black	5 (10%)	7 (14%)
White	34 (71%)	32 (65%)
Any other ethnic group	2 (4%)	1 (2%)
Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)
Years since onset of connective tissue disease	4·8 (6·2)	4·5 (7·6)
FVC, L	2·23 (0·85)	2·25 (0·77)
FVC, % of predicted	71% (20)	68% (17)
DL_{CO}, mL/min per kPa	3·35 (1·42), n=46	3·46 (1·33), n=45
DL_{CO}, % of predicted	40% (14), n=46	40% (14), n=45
SpO_2 on room air, %	96% (2)	97% (2)
6 min walk distance, m	363 (111)	356 (126)
EQ-5D score	55 (20)	58 (22)
GDA score	5·03 (1·76), n=40	4·58 (1·97), n=38
KBILD score	46·1 (20·3)	51 (21·2)
SGRQ score	55·8 (20·0), n=47	52·1 (17·6), n=45

Data are mean (SD) or n (%). FVC=forced vital capacity. DL_{CO}=diffusing capacity of the lung for carbon monoxide. SpO_2=arterial oxygen saturation. EQ-5D=European Quality of Life Five-Dimension. GDA=global disease activity (physician-assessed). KBILD=King's Brief Interstitial Lung Disease. SGRQ=St George's Respiratory Questionnaire. *Self-reported.

Table 1: **Baseline characteristics in the modified intention-to-treat population**

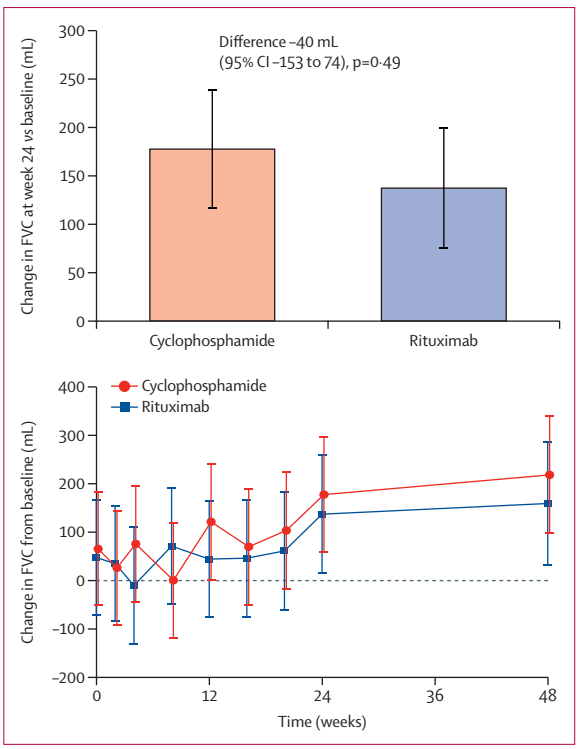

Figure 2: **Adjusted rate of change in FVC in the cyclophosphamide and rituximab groups at week 24 (A) and adjusted change in FVC from baseline to week 48 (B)**

Error bars in both panels are standard errors for the adjusted rate of change in FVC.

Disease progression was defined as death, transplant, decline in FVC greater than 10% from baseline, or treatment failure, whichever occurred first. Treatment failure was defined as the need for transplant or rescue therapy with either open-label cyclophosphamide or rituximab. All efficacy analyses were performed in the modified intention-to-treat population. Safety analyses are reported for all randomised participants.

Statistical analysis

A sample size of 104 participants was planned to give 90% power to detect a 5% difference in 24-week rate of change in FVC between treatment groups at a two-tailed significance level of 5%. We originally planned to aim for 10% over-recruitment to account for patient dropouts before week 24; however, because of the COVID-19 pandemic and an anticipated prolonged interruption to recruitment, study enrolment was halted in March, 2020, after randomisation of 101 participants.

A statistical analysis plan was produced and agreed with the trial steering committee and data safety and monitoring committee before analysis (appendix pp 11–41).

For the primary analysis to compare the 24-week rate of change in FVC (in mL) between groups, we used a mixed-effects model with random intercepts. The hypothesis tested was that rituximab would be superior to cyclophosphamide. A three-level hierarchical (mixed multilevel) model was used, with an unstructured correlation matrix, adjustment for baseline FVC and CTD type (stratification factor), and treatment of the primary outcome as an interaction term between treatment and visits, including at week 24. The primary analysis was done in the modified intention-to-treat population, defined as all subjects who met all the entry criteria for the trial, were randomised, and received at least one dose of study drug; four subjects (two per group) were randomised but did not receive treatment and were subsequently lost to the trial (figure 1), resulting in modification of the criteria for inclusion in the intention-to-treat analysis.

Analysis of secondary efficacy outcomes was also done in the modified intention-to-treat population. Change in continuous physiological variables between baseline and weeks 24 and 48 were assessed by similar multilevel model as described for the primary outcome. Categorical change in physiological variables was tested using χ^2 tests

under the null hypothesis of no difference between the treatment groups. Overall survival, time to treatment failure, and progression-free survival were measured using Kaplan-Meier estimates. A log-rank test was used to compare treatment groups and a Cox proportional hazards model was used to determine hazard ratios (HRs) for survival analyses. Missing data on daily corticosteroid doses were imputed to the worst measurement of previous or subsequent visits for each patient. Patients who received rescue therapy before week 24 were considered as having treatment failure, and data collected following administration of rescue therapy was excluded from analyses. Stata 15.1 software was used for all analyses.

This study was registered on ClinicalTrials.gov (NCT01862926).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Cyclophosphamide group		Rituximab group		Adjusted difference (95% CI)	p value
	n	Change from baseline	n	Change from baseline		
FVC, mL						
24 weeks	45	99 (329)	43	97 (234)	−40 (−153 to 74)	0·493
48 weeks	42	138 (440)	35	112 (249)	−58 (−178 to 62)	0·345
DL_{CO}, mL/min per kPa						
24 weeks	44	0·058 (0·706)	38	0·264 (0·573)	0·186 (−0·054 to 0·425)	0·425
48 weeks	38	0·131 (1·080)	32	0·288 (0·612)	0·117 (−0·137 to 0·372)	0·372
6 min walk distance, m						
24 weeks	46	10·4 (78·6)	40	10·9 (74·2)	−0·72 (−24·76 to 23·32)	0·953
48 weeks	39	15·1 (82·8)	32	−6·8 (69·8)	−22·46 (−48·43 to 3·51)	0·090
EQ-5D score						
24 weeks	43	3·5 (20·5)	41	6·2 (17·7)	3·06 (−3·05 to 9·18)	0·326
48 weeks	40	−1·2 (23·5)	35	3·9 (15·8)	4·77 (−1·73 to 11·27)	0·150
GDA score						
24 weeks	37	−2·9 (2·1)	35	−2·8 (1·8)	−0·14 (−0·85 to 0·57)	0·700
48 weeks	33	−2·9 (2·5)	26	−1·7 (2·3)	0·90 (0·11 to 1·68)	0·025
KBILD score						
24 weeks	45	9·4 (20·8)	42	8·8 (17·0)	0·40 (−5·73 to 6·52)	0·899
48 weeks	43	5·6 (25·6)	35	6·4 (16·2)	1·15 (−5·34 to 7·64)	0·728
SGRQ score						
24 weeks	42	−4·8 (19·6)	39	−3·4 (15·4)	0·63 (−5·64 to 6·91)	0·843
48 weeks	40	−6·4 (24·3)	35	−3·2 (16·6)	2·82 (−3·69 to 9·34)	0·396

Changes from baseline are unadjusted mean (SD). Difference between groups for each endpoint was analysed with a mixed-effects model with random intercepts; we used a three-level hierarchical (mixed multilevel) model with an unstructured correlation matrix, and adjusted for the baseline variable being assessed and connective tissue disease type (stratification factor), treating the measured outcome as an interaction term between treatment and visits (including at week 24 or 48). A negative difference favours cyclophosphamide for all endpoints except SGRQ and GDA scores (for which a positive difference favours cyclophosphamide). FVC=forced vital capacity. DL_{CO}=diffusing capacity of the lung for carbon monoxide. EQ-5D=European Quality of Life Five-Dimension. GDA=Global Disease Activity (physician-assessed). KBILD=King's Brief Interstitial Lung Disease. SGRQ=St George's Respiratory Questionnaire.

Table 2: **Differences in primary and secondary endpoints in the rituximab group versus the cyclophosphamide group**

Results

Between Dec 1, 2014, and March 31, 2020, 145 patients with CTD-ILD were screened for eligibility, of whom 101 were randomly allocated: 50 (50%) to receive cyclophosphamide and 51 (50%) to receive rituximab. 48 (96%) participants in the cyclophosphamide group and 49 (96%) in the rituximab group received at least one dose of treatment and were included in the modified intention-to-treat population for the primary and secondary efficacy analyses. 43 (86%) participants in the cyclophosphamide group and 42 (82%) in the rituximab group completed 24 weeks of treatment and follow-up (figure 1).

Of the 97 participants who received at east one dose of treatment, the mean age was 56·6 years (SD 11·5) and 66 (68%) participants were female. Baseline demographic and clinical characteristics were similar between groups (table 1). Idiopathic inflammatory myositis was the underlying CTD in 44 (45%) participants, systemic sclerosis in 37 (38%) participants, and mixed CTD in 16 (16%) participants. Of the four participants who did not receive any doses of study drug, mean age was 63·8 years (SD 9·1), all were White and female, one participant had idiopathic inflammatory myositis, two had systemic sclerosis, one had mixed connective tissue disease, and mean time since onset of CTD was 2·5 years (SD 3·3).

At week 24, the unadjusted mean change from baseline in FVC was a gain of 99 mL (SD 329; relative change 4·35% [SD 15·67]) in the cyclophosphamide group and 97 mL (234; 4·31% [11·80]) in the rituximab group. Using a mixed-effects model adjusted for age, sex, baseline FVC, and diagnosis, the difference in 24-week rate of change in FVC from baseline in the rituximab group versus the cyclophosphamide group was −40 mL (95% CI −153 to 74; p=0·49; figure 2, table 2). Sensitivity analysis using an unadjusted model showed results consistent with both the primary analysis and the results of a fixed-effects model using observed values alone. The effects of treatment were consistent across the three different CTD subgroups (data to be presented in a separate report).

Secondary outcome analyses are summarised in table 2. The unadjusted 48-week mean rate of change in FVC was 138 mL (SD 440) in the cyclophosphamide group and 112 mL (249) in the rituximab group (adjusted difference from mixed-effects model −58 mL [95% CI −178 to 62], p=0·345). The mean rate of change in DL_{CO} from baseline was 0·058 mL/min per kPa (SD 0·706; 1·43% [SD 23·05]) in the cyclophosphamide group and 0·264 mL/min per kPa (0·573; 6·98% [17·19]) in the rituximab group at week 24, and 0·131 mL/min per kPa (1·080; 3·00% [31·35]) in the cyclophosphamide group and 0·288 mL/min per kPa (0·612; 7·43% [16·08]) in the rituximab group at week 48. For 6 min walk distance, the change from baseline at week 24 was 10·4 m (78·6) in the cyclophosphamide group and 10·9 m (74·2) in the rituximab group (adjusted difference −0·72 [−24·76 to 23·32]), and the change from

baseline at week 48 was 15·1 m (82·8) in the cyclophosphamide group and –6·8 m (69·8) in the rituximab group (–22·46 m [–48·43 to 3·51]).

Quality of life assessed using the KBILD questionnaire showed a mean improvement from baseline of 9·4 points (SD 20·8) in the cyclophosphamide group and 8·8 points (17·0) in the rituximab group at week 24, and 5·6 points (25·6) in the cyclophosphamide group and 6·4 points (16·2) in the rituximab group at week 48. Similarly, SGRQ scores showed an improvement in quality of life in the cyclophosphamide group (–4·8 points [19·6] at week 24; –6·4 points [24·3] at week 48) and in the rituximab group (–3·4 points [15·4] at week 24; –3·2 points [16·6] at week 48). Compared with baseline, global quality of life measured using the EQ-5D was improved at week 24 in the cyclophosphamide group (3·5 points [20·5]) and in the rituximab group (6·2 points [17·0]); at week 48, the change was –1·2 points (23·5) in the cyclophosphamide group and 3·9 points (15·8) in the rituximab group.

Physician-assessed global disease activity scores showed improvement for both groups at week 24 (cyclophosphamide group –2·9 points [2·1] and rituximab group –2·8 points [1·8]) and week 48 (–2·9 points [2·5] and –1·7 points [2·3]).

Over the 48-week course of the study, five participants died: two (4%) of 48 participants who received cyclophosphamide and three (6%) of 49 who received rituximab. All deaths were adjudged to be due to complications of either CTD or ILD. Adjusted Cox proportional hazards analyses showed no evidence of a difference in the rituximab group relative to the cyclophosphamide group in overall survival (HR 1·72 [95% CI 0·31–9·56], p=0·534; appendix p 4), progression-free survival (1·11 [0·63–1·99], p=0·715; appendix p 5), or time to treatment failure (1·25 [0·34–4·65], p=0·742; appendix p 6).

The mean per-participant 48-week total steroid exposure during the study (measured in hydrocortisone equivalents) was 13 291 mg (SD 14 657) in the cyclophosphamide group and 11 469 mg (10 041) in the rituximab group. The mean dose per patient was 42·9 mg hydrocortisone per day in the cyclophosphamide cohort and 37·6 mg hydrocortisone per day in the rituximab group, equivalent to a 12·3% reduction (95% CI –25·9 to 50·5) in corticosteroid exposure in the rituximab group. A summary of the immunosuppressants used by treatment group are shown in the appendix (p 7).

All participants reported at least one adverse event during the study. More adverse events were reported in the cyclophosphamide group (646 events) than in the rituximab group (445 events; table 3). The imbalance was less marked for serious adverse events (appendix pp 8–9), with 33 in the cyclophosphamide group and 29 in the rituximab group. Gastrointestinal disorders (170 *vs* 71 events), general disorders and administration site reactions (91 *vs* 52 events) and nervous system disorders (72 *vs* 35 events) were more common in the cyclophosphamide group than in the rituximab group. The frequencies of other adverse events were balanced between groups, including infections and infestations (50 in the cyclophosphamide group *vs* 46 in the rituximab group). One patient in each group withdrew because of side-effects. No cases of COVID-19 were reported during the trial.

	Cyclophosphamide group (n=50)	Rituximab group (n=51)
All events	646	445
Blood and lymphatic system disorders	3 (<1%)	0
Cardiac disorders	10 (2%)	6 (1%)
Ear and labyrinth disorders	2 (<1%)	1 (<1%)
Eye disorders	16 (2%)	9 (2%)
Gastrointestinal disorders	170 (26%)	71 (16%)
General disorders and administration site conditions	91 (14%)	52 (12%)
Hepatobiliary disorders	1 (<1%)	1 (<1%)
Immune system disorders	0	2 (<1%)
Infections and infestations	50 (8%)	46 (10%)
Injury, poisoning, and procedural complications	8 (1%)	5 (1%)
Investigations	11 (2%)	8 (2%)
Metabolism and nutrition disorders	5 (1%)	3 (1%)
Musculoskeletal and connective tissue disorders	44 (7%)	40 (9%)
Nervous system disorders	72 (11%)	35 (8%)
Psychiatric disorders	9 (1%)	10 (2%)
Renal and urinary disorders	8 (1%)	1 (<1%)
Reproductive system and breast disorders	5 (1%)	4 (1%)
Respiratory, thoracic, and mediastinal disorders	94 (15%)	101 (23%)
Skin and subcutaneous tissue disorders	38 (6%)	32 (7%)
Surgical and medical procedures	1 (<1%)	0
Vascular disorders	7 (1%)	16 (4%)

Data are number of events (% of total events reported per cohort).

Table 3: **Adverse events by system, organ, and class, reported to week 48 for all randomised participants**

Discussion

RECITAL compared rituximab to intravenous cyclophosphamide in a basket design comprising ILD associated with any of three different CTDs. Although the study did not find superiority of rituximab over cyclophosphamide for the primary efficacy endpoint (change from baseline in FVC at week 24), improvements in lung function and respiratory-related and global quality of life measures were observed in both treatment groups. Rituximab was associated with fewer adverse events and lower corticosteroid exposure throughout 48 weeks of follow-up.

Despite causing significant toxic effects, including gonad failure and increased risk of uroepithelial malignancy, cyclophosphamide is recommended in international guidelines as the treatment of choice for severe or progressive scleroderma-associated ILD.[19,20] It is also widely used as first-line therapy for myositis-associated ILD.[21] Rituximab is most commonly used as

rescue therapy for treatment-refractory CTD-ILD.[20,22] An open-label study of 60 patients with systemic sclerosis-associated ILD reported an improvement in FVC in rituximab-treated participants, but a deterioration in those managed with cyclophosphamide.[7] In a Japanese randomised, placebo-controlled trial of 56 patients with systemic sclerosis and a baseline modified Rodnan skin score greater than 10, the subset of patients with ILD who were treated with rituximab showed preservation of FVC at 24 and 48 weeks when compared with placebo.[23,24] The data from RECITAL suggest that rituximab might be an effective alternative to cyclophosphamide in individuals with severe or progressive CTD-ILD.

Cyclophosphamide has been used in clinical practice for more than 60 years and rituximab for more than 25 years, and both have well established safety and tolerability profiles. To date, no data comparing rituximab and cyclophosphamide in CTD-ILDs have been published. However, head-to-head non-inferiority trials of the two drugs have been done in two other autoimmune conditions, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis[25] and ANCA-associated renal vasculitis.[26] In both disease groups, rituximab and cyclophosphamide had similar safety and efficacy profiles, with a suggestion (based on post hoc analysis) that rituximab might be more effective at preventing relapses of ANCA-associated vasculitis.[25] International guidelines consequently recommend both drugs as induction therapy for systemic and renal ANCA-associated vasculitis.[27,28]

FVC is the established endpoint of choice in clinical trials for ILD.[29,30] Worsening of FVC over 6 and 12 months in patients with CTD-ILD is associated with poorer survival.[31] The improvement in FVC observed in both treatment groups in our study, therefore, almost certainly reflects a meaningful change in disease status. The improvement in FVC with cyclophosphamide treatment in this trial is, if anything, greater than that reported in previous studies and potentially reflects the enrolment of a broader range of patients, including those with CTD-ILDs other than just systemic sclerosis-associated ILD.[1–3] The effect of rituximab on FVC was similar to that reported in retrospective cohorts and small open-label studies across a range of ILDs.[4–6] The absence of superiority of rituximab with regard to the primary endpoint in this study, therefore, probably reflects a better-than-expected outcome in the comparator cyclophosphamide group rather than an absence of treatment response in the rituximab group. Importantly, the improvements seen in respiratory and overall health-related quality of life in both treatment groups exceeded the minimal clinically important difference of the various tools used, further suggesting that both treatments were effective.[32–34]

In clinical practice, rituximab is frequently coadministered with either mycophenolate mofetil or methotrexate. Such an approach is avoided with cyclophosphamide because of concerns regarding susceptibility to infection. Although mycophenolate mofetil has not been compared with placebo in a randomised controlled trial in CTD-ILD, the available evidence suggests that the drug has a beneficial effect on disease progression.[2,35] Thus, it is possible that upfront combination therapy with rituximab and mycophenolate mofetil could be more effective than treatment with rituximab alone, and these regimens should be compared in future trials. Previous trials have shown a positive effect in slowing FVC decline over 52 weeks of the anti-fibrotic drug nintedanib in individuals with systemic sclerosis-associated ILD and progressive pulmonary fibrosis of any cause,[30,35,36] suggesting that combination therapy consisting of an immunosuppressant and an anti-fibrotic drug could have an additive therapeutic effect in the population studied in RECITAL.

Previous CTD-ILD studies have tended to be confined to patients with systemic sclerosis; consequently, there is an absence of evidence-based therapies for rarer CTD-ILDs not associated with systemic sclerosis. We used a basket design to permit enrolment of participants with a variety of CTDs. The range of CTD-ILDs chosen reflected those for which, at the time of study design, evidence existed for an effect of rituximab, and for which cyclophosphamide was frequently used as the standard of care. Inclusion and exclusion criteria were minimised with the goal of enrolling individuals for whom clinicians would realistically consider rituximab (or, by corollary, cyclophosphamide) therapy in a real-world setting. These criteria did not differ in any substantial way to those used in trials of cyclophosphamide, mycophenolate, or nintedanib in systemic sclerosis-associated ILD.[1,2,30] However, given the cytotoxicity of cyclophosphamide and its known side-effect profile, we anticipated that patients enrolled in RECITAL would have either severe or progressive disease. We specifically did not provide a protocolised definition of progressive or severe ILD for inclusion in the trial. We did, however, provide general guidance within the protocol on identifying appropriate study participants. Since we designed RECITAL, several trials have sought to define disease progression in ILD before enrolment, with the goal of enriching the study sample for individuals at highest risk of further deterioration.[36–38] These trials have used a variety of criteria that have also differed from those proposed in recent international guidelines.[39] Despite a lack of protocolised criteria, the 5% death rate observed in RECITAL confirms that this cohort of patients had clinically important disease. It was not a prerequisite that participants enrolled in this study had previously received treatment, and, in some cases, enrolment in RECITAL represented first-line therapy for the underlying CTD-ILD; these patients would have been excluded from the study had previous disease progression been a prerequisite. It is possible that design compromises that were taken to make the study open to the maximum number of patients resulted in treatment benefits being

overlooked in specific subgroups. For instance, the effects of treatment with either cyclophosphamide or rituximab could vary on the basis of the underlying histopathological lesion or autoantibody profile that characterises an individual's CTD-ILD. Nonetheless, we believe that this study provides a model for conducting future trials in CTD-ILD.

Other limitations of this trial include the lack of a placebo group, which, although ethically unavoidable, renders it impossible to ascertain whether rituximab has a true treatment effect in CTD-ILD. Nonetheless, given the natural history of CTD-ILD and the high associated mortality,[40,41] it is unlikely that the observed improvements in lung physiology and quality of life observed in both treatment groups would have occurred without active therapy. Additionally, trial enrolment was terminated early because of the COVID-19 pandemic, resulting in 97 patients being included in the modified intention-to-treat analysis rather than the planned 104. At study outset, we had planned to over-recruit by 10% to compensate for any dropouts that occurred because of disease progression. The use of a mixed-effects model for assessment of the primary and secondary endpoints made such over-recruitment unnecessary, because all participants who received at least one dose of therapy provided evaluable data and contributed to the efficacy assessments. Based on the actual trial outcomes, the slightly premature termination of trial recruitment did not have an appreciable effect on the final power of the study to show superiority of rituximab to cyclophosphamide. The actual variance seen in change in FVC at week 24 exceeded the assumed variance (which was established from the existing literature at the time) used in the power calculation that was done to inform the design of RECITAL. Consequently, the power of the study to show a difference between groups was closer to 70% than the 90% initially assumed.

Rituximab is a monoclonal antibody that depletes B lymphocytes, a cell type important in the host immune response to viral infection. Furthermore, B effector cells are crucial in mounting an appropriate immune response to vaccines.[42] The use of rituximab has been associated with an increased risk of developing serious COVID-19 in individuals with an underlying autoimmune disease.[43] Although we did not observe any cases of COVID-19 in participants during the trial, the data from RECITAL should help to inform patients and clinicians when deciding on the risks and benefits of treatment for CTD-ILD.

In summary, both rituximab and cyclophosphamide improved FVC and quality of life in individuals with CTD-ILD in this trial. Treatment with rituximab was associated with fewer adverse events and a reduction in corticosteroid exposure compared with cyclophosphamide. Rituximab should therefore be considered as a treatment option in individuals with severe or rapidly progressive CTD-ILD.

Contributors

TMM, CPD, RKH, HP, EAR, AUW, DA, and PLM designed the study and were involved in applying for funding. TMM, VAT, PS, MAG, SVF, CPD, RKH, MK, and PLM were involved in the running of the trial and in identifying and recruiting study participants. TMM, MS, and DA developed the statistical analysis plan. TMM, MS, VAT, DA, and PLM verified the data. All authors had access to the raw data. MS undertook statistical analyses. TMM drafted the manuscript which was read, revised, and approved by all authors. All authors were responsible for the final decision to submit the manuscript and vouch for the accuracy and completeness of the data, for adherence of the trial to the protocol, and for the complete reporting of adverse events.

Declaration of interests

TMM has (via his institution) received industry-academic funding from AstraZeneca and GlaxoSmithKline research and development, and has received consultancy or speaker's fees from AstraZeneca, Bayer, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Fibrogen, Galapagos, Galecto, GlaxoSmithKline, IQVIA, Pliant, Roche, Trevi, and Veracyte. CPD reports grants from GlaxoSmithKline; personal fees from Boehringer Ingelheim, Roche, Acceleron, Janssen, and Corbus; grants and personal fees from CSL Behring; and grants from Servier. PS reports consultancy fees from Trevi Therapeutics and Boehringer Ingelheim and fees for giving presentations sponsored by Boehringer Ingelheim. PLM (via his institution) has received industry-academic funding from AstraZeneca and has received speaker and consultancy fees from Boehringer Ingelheim, Trevi, and F Hoffman-La Roche. HP reports consultancy fees from Boehringer Ingelheim, Trevi Therapeutics, and Pliant Therapeutics, and is a trustee for Action for Pulmonary Fibrosis. EAR reports grants and lecture fees (paid to her institution) from Boeringher Ingelheim and lecture fees (paid to the institution) from Roche and Chiesi. SVF reports consultancy fees from Lilley, Boehringer Ingelheim, and Trevi Therapeutics. AUW reports personal fees from Boehringer Ingelheim, Roche, and Veracyte. No authors' disclosures are directly related to the current work. All other authors declare no competing interests.

Data sharing

Data sharing requests will be considered from research groups that submit a research proposal and an appropriate statistical analysis and dissemination plan. Data will be shared via a secure data access system.

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