Appendix 1

Reference	Study details	Main results
Systematic reviews		
Macrea et al. 2023	Systematic review and meta-analysis to determine if SSc-ILD should be treated with RTX. Found 3 relevant studies in 84 patients. RTX given at a dose of 375 mg/m^2 once weekly for 4 weeks in 2 studies (one repeated the dose at 24 weeks); or at a dose of 1000 mg at 0, 2 and 24 weeks. Two studies compared RTX with placebo.	Pooled data showed significant differences that exceeded MCID in the FVC% and mRSS at 24–28 weeks, favouring RTX. Otherwise, the pooled and individual study data analyses showed no significant differences in other critical or important outcomes between the RTX and placebo groups.
Wang and Li, 2023	Systematic review and meta-analysis of efficacy of RTX on lung function and prevalence of adverse events in CTD-ILD. Identified 29 studies in 827 patients (median age 53.05 years) with CTD-ILD. 16 studies analysed predicted change in FVC% and 13 analysed predicted change in DLCO%.	In observational studies, FVC% and DLCO% decreased significantly after RTX treatment; in RCTs FVC% decreased after RTX treatment but change in DLCO% was not significant. Data from 9 studies showed the prevalence of adverse events was 29.7% (95% CI [0.17, 0.42]); data from 18 studies showed the prevalence of all-cause mortality was 11.6% (95% CI [0.08, 0.16]); data from 8 studies showed the prevalence of infections was 20.9% (95% CI [0.15, 0.27]).
He et al. 2022	Systematic review of RTX to treat ILD in anti-MDA5 DM. Identified 17 studies in 35 patients (13 men; 22 women). 27 patients had previous treatments, including glucocorticoids and at least one additional immunotherapeutic agent.19 patients had been treated with two or more immunotherapy treatments.	71.4% (25/35) of patients responded to RTX treatment. Survival rates were 100% (4 of 4 patients) in chronic ILD and 64.5% (20 of 31 patients) in rapidly progressive ILD. Survival rate in patients who responded to RTX was 92% (23 of 25 patients); it was 10% (1 of 10 patients) in those who did not respond to RTX. The most common side effects were infections, reported by 37.1% (13/35) of the patients after RTX treatment.

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Xu et al. 2022	Systematic review of the efficacy and safety of RTX in the treatment of CTD-ILD. A meta-analysis included 13 studies in 312 patients. 157 patients were refractory to conventional treatments. Previous treatments before RTX included: cyclophosphamide, MMF, azathioprine and steroids. Follow-up duration ranged from 6 months to 36 months.	In the 13 studies the pooled improvement rate in lung function after treatment was 35% (95% CI 0.277 to 0.442); the pooled lung function stability rate (12 studies) was 59.2% (95% CI 0.534 to 0.656). In 12 studies a total of 106 adverse events associated with RTX or progressive ILD were reported; 55.7% were mild to moderate. 19 patients died: 17 due to ILD progression, 1 due to severe pulmonary arterial hypertension and 1 due to *Pneumocystis jirovecii* infection.
Zhao et al. 2022	Systematic review of effect of RTX on pulmonary function in CTD-related ILD. Identified 20 studies in 411 patients; 14 studies included in meta-analysis (n = 296) and 6 studies in the descriptive review. Most patients had progressive ILD that had not responded to initial immunosuppression; previous treatments included azathioprine, MMF, cyclophosphamide and methotrexate. In most studies RTX was given as two 1000 mg infusions two weeks apart, or 375 mg/m^2 weekly for 4 weeks.	Random effects meta-analysis of pre- and post-treatment pulmonary function showed increases in FVC of 4.57% (n = 296; 95% CI 2.63 to 6.51) and DLCO of 5.0% (n = 246; 95% CI 2.71 to 7.29) after RTX treatment. The adverse events reported most often were infusion-related reactions (including fever, chills and rigors) and non-serious infections. Of 411 patients, 56 (13.6%) reported some type of adverse event. There were no reported deaths as a direct result of RTX treatment.
Clinical studies		
Maher et al. 2023	RECITAL: a double-blind, double-dummy phase IIb RCT of RTX versus iv cyclophosphamide to treat CTD-ILD, conducted in patients in the UK. Patients (n = 97) received iv cyclophosphamide (n = 48; 600 mg/m^2 every 4 weeks for 6 doses) or iv RTX (n = 49; 1000 mg at weeks 0 and 2).	The primary endpoint was rate of change in FVC at 24 weeks compared with baseline. FVC improved from baseline in both groups: cyclophosphamide (unadjusted mean increase 99 ml [SD 329]) and RTX (97 ml [234]). In an adjusted mixed effects model, the difference at 24 weeks was −40 ml (95% CI −153 to 74; p = 0.49) between RTX and cyclophosphamide.

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		Quality of life scores improved by a mean 9.4 points in the cyclophosphamide group and 8.8 points in the RTX group. Both groups showed improvements in lung function and respiratory-related quality of life. The RTX group recorded lower corticosteroid exposure over 48 weeks. 5 patients died; all due to complications of CTD or ILD: 2 in the cyclophosphamide group and 3 in the RTX group. Overall survival, PFS and time to treatment failure did not differ significantly between the 2 groups. All participants reported at least one adverse event; gastrointestinal and respiratory disorders were the most commonly reported. 445 adverse events were reported in the RTX group (including 29 SAEs) and 646 events were reported in the cyclophosphamide group (including 33 SAEs).
Mankikian et al. 2023	EVER-ILD: a double-blind, randomised, placebo-controlled, parallel-group study of RTX given in combination with MMF to treat ILD in patients with connective tissue disease or idiopathic interstitial pneumonia. 122 patients received RTX (1000 mg; n = 63) or placebo (n = 59) on Day 1 and Day 15 plus MMF (2 g daily) for 6 months. The primary endpoint was change in percentage of FVC from baseline to 6 months.	The least-squares mean change from baseline to 6 months in FVC (% predicted) was +1.60 (SE 1.13) in the RTX+MMF group and −2.01 (SE 1.17) in the placebo+MMF group (between-group difference, 3.60 [95% CI 0.41 to 6.80]; p = 0.0273). PFS was better in the RTX+MMF group (crude HR 0.47 [95% CI 0.23 to 0.96]; p = 0.03). 54 patients in the RTX+MMF group (86%) had at least one adverse event, as did 57 patients (97%) in the placebo-MMF group. More patients had SAEs considered related to the study treatment in the RTX+MMF group (n = 15) than in the placebo+MMF group (n = 6).

Reference	Study details	Main results
		SAEs occurred in 26 patients in the RTX+MMF group (41%) and in 23 patients in the placebo group (39%). Nine infections were reported in the RTX+MMF group (5 bacterial, 3 viral and 1 other), and 4 bacterial infections in the placebo+MMF group.
Matson et al. 2023	A retrospective study of 212 patients with RA-ILD assessing the pulmonary function trajectory following treatment with MMF (n = 77), azathioprine (n = 92) or rituximab (n = 43). 67.9% of patients were receiving baseline prednisolone and 69.3% were on DMARD therapy; all patients received azathioprine, MMF or RTX in addition to their current treatment.	Combined analysis of all three agents showed an improvement in FVC % predicted after 12 months of treatment compared with the potential 12-month response without treatment (+3.90%; p ≤ 0.001; 95% CI 1.95 to 5.84). DLCO % also improved at 12 months. A random mixed-effect model showed no significant differences in FVC% predicted response between the 3 additional treatments. Adverse events were reported in 5 patients receiving RTX. The adverse events were: gastrointestinal upset (n = 1); cytopenia (n = 1); recurrent infections (n = 1); and nonspecific symptoms (n = 2). One patient (2.3%) receiving RTX discontinued treatment because of adverse events; 12 patients (13.0%) discontinued azathioprine due to adverse events and 3 patients (3.9%) discontinued MMF due to adverse events.
Mena-Vazquez et al. 2022	A multicentre, prospective, observational cohort study of 37 people (mean age 63 years; 27 women) with CTD-ILD (due to RA, SSc or IM) who were treated with RTX for a median of 38.2 months (IQR 17.7–69.0 months). At the start of RTX therapy, 15 patients (40.5%) were receiving a combination of RTX and a conventional synthetic DMARD, 20 (54.1%)	At the end of follow-up, disease had improved or stabilised in 23 patients (62.1%) and worsened in 7 patients (18.9%). 7 patients (18.9%) died, from progression of ILD and superinfection. There was no significant decline in median FVC (72.2 versus 70.8; p = 0.530) or DLCO (55.9 versus 52.2; p = 0.100).

Reference	Study details	Main results
	were receiving a combination of RTX and an immunosuppressant, and 2 (5.4%) were receiving RTX monotherapy. RTX was given in 2 iv infusions of 1000 mg on Days 1 and 15 every 6 months or more, depending on symptoms.	29 patients (78.4%) had an infection during follow-up; these were mostly respiratory (70.3%). 16 patients were hospitalised: 10 for progression of ILD and 14 for respiratory infection. No significant differences were seen between disease sub-groups for infection, hospitalisation or mortality. In addition to the patients who died, 2 patients (5.4%) stopped RTX treatment due to adverse events (1: superinfected ulcers refractory to antibiotics after 79 months of RTX treatment and 1: urinary tract infection and recurrent herpes simplex labialis after 24 months of RTX treatment).
Abbreviations: anti-MDA5 DM: anti-melanoma differentiation-associated protein 5 dermatomyositis; CI: confidence interval; CTD-ILD: connective tissue disease-associated interstitial lung disease; DLCO: diffusing capacity of the lungs for carbon monoxide; DMARD: disease-modifying anti-rheumatic drug; FVC: forced vital capacity; HR: hazard ratio; ILD: interstitial lung disease; IM: inflammatory myopathy; iv: intravenous; IQR: interquartile range; MCID: minimal clinically important difference; MMF: mycophenolate mofetil; mRSS: modified Rodnan Skin Score; PFS: progression-free survival; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; RCT: randomised controlled trial; RTX: rituximab; SAE: serious adverse event; SD: standard deviation; SE: standard error; SSc-ILD: systemic sclerosis-associated interstitial lung disease		