AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Rituximab as second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia (OW13)

February 2024

One Wales Interim Decision

Rituximab as second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia

Date of original advice: August 2019
Date of review: February 2024

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.

Using the agreed starting and stopping criteria, rituximab can be made available within NHS Wales for the second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia in patients where other health technology appraisal-approved regimens are unsuitable.

Rituximab should be prescribed on the basis of lowest acquisition cost.

The risks and benefits of the off-label use of rituximab for this indication should be clearly stated and discussed with the patient to allow informed consent. Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after two years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for rituximab as second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia

Start criteria:
Rituximab may be commenced after evidence of progression on azathioprine and/or mycophenolate mofetil and nintedanib, in line with current National Institute for Health and Care Excellence (NICE) recommendations.[1] For some patients nintedanib may be used as adjunctive treatment with rituximab. A request for rituximab should be made following regional interstitial lung disease multi-disciplinary team diagnosis review and treatment recommendation. Rituximab is recommended only in circumstances where other health technology appraisal-approved regimens are unsuitable or treatment has failed.

Progression is defined as:
- 10% decline percent predicted forced vital capacity (FVC) on first- or second-line therapy within 12 months; or
- 15% decline percent predicted transfer factor for carbon monoxide (TLCO) on first- or second-line therapy within 12 months; or
- significant radiological evidence of progression whilst on first- or second-line therapy within 12 months.

Patients who satisfy the start criteria will be prescribed rituximab after consultation with the patient and/or carer considering potential adverse effects, cautions and contraindications. This consultation should be recorded in the patient's notes.

The recommended rituximab treatment dose regimen is 1,000 mg rituximab followed by a second 1,000 mg dose two weeks later administered by intravenous infusion. A further 1 g may be offered within the first 12 months and then annually, according to response.

Monitoring:
- Pulmonary function tests every 4–6 months.
- Repeat high resolution CT scan in event of physiological decline

Stop criteria:
Treatment with rituximab should be discontinued according to one or more of the following definitions of disease progression:
- 10% decline percent predicted FVC on rituximab therapy within 12 months; or
- 15% decline percent predicted TLCO on rituximab therapy within 12 months; or
- significant radiological evidence of progression whilst on rituximab therapy within 12 months.

1. National Institute for Health and Care Excellence. Nintedanib for treating progressive fibrosing interstitial lung diseases (TA747). Nov 2021. Available at: https://www.nice.org.uk/guidance/ta747. Accessed Dec 2023.

This is a summary of new evidence available and patient outcome data collected to inform the review.

Third Review of One Wales Decision – December 2023

Rituximab as second- or third-line treatment of fibrotic interstitial lung disease (not idiopathic pulmonary fibrosis) associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia (OW13)

This report was prepared by the All Wales Therapeutics and Toxicology Centre in December 2023. It summarises any new evidence available since the last review in November 2021 and patient outcome data collected in the last 12 months.

Background: Interstitial lung diseases are a heterogeneous group of disorders that cause scarring of the lungs. The scarring causes stiffness in the lungs which makes it difficult to breathe. A small number of people in Wales have interstitial lung disease associated with a connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia that does not respond to treatment with conventional oral immunosuppressants.

In 2017 NHS England reviewed and concluded not to routinely commission rituximab to treat connective tissue disease-associated interstitial lung disease. Clinicians in Wales considered there to be an unmet need in NHS Wales and identified a cohort of patients who could benefit from rituximab treatment. Based on this unmet need, rituximab was considered suitable for assessment through the One Wales process**.** In November 2021, the National Institute for Health and Care Excellence (NICE) recommended nintedanib (Ofev®; TA 747) to treat progressive fibrosing interstitial lung diseases. A clinical expert has indicated that although nintedanib is now an option for this patient group, rituximab remains an option for those patients with a predominately inflammatory phenotype where other immunosuppressants are unsuitable. This place in pathway is reflected in the current start/stop criteria.

Current One Wales Decision: recommended as a second or third-line option.

Licence status: Off-label use for this licensed medicine.

Guidelines: The European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of systemic sclerosis have been updated in 2023 to include new recommendations, including the use of rituximab to treat interstitial lung disease in systemic sclerosis (Del Galdo et al., 2023). This is currently available as a conference abstract, the 2023 recommendations have not yet been published in full.

In 2023 the American Thoracic Society published an evidence-based clinical practice guideline for the treatment of systemic sclerosis-associated interstitial lung disease (SSc-ILD). It includes a conditional recommendation for giving rituximab to patients with SSc-ILD, balancing a significant reduction in disease progression with no difference in adverse events against the very low-quality evidence (Raghu et al., 2023).

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: No new treatments have been approved for this indication.

Effectiveness: A literature search by AWTTC identified 5 systematic reviews and 4 studies, which include results from the RECITAL and EVER-ILD studies, mentioned in our previous review in 2021 (see Appendix 1).

Three systematic reviews and meta-analyses studied the use of rituximab to treat connective tissue disease-associated interstitial lung disease. Two meta-analyses reported some improvements in lung function after rituximab treatment; one meta-analysis found that lung function decreased after rituximab treatment.

One meta-analysis by Macrea et al., 2023 in treatment of SSc-ILD showed clinically significant differences in forced vital capacity in favour of rituximab; although no significant differences between rituximab and placebo were seen in other critical or important outcomes. He et al., 2022 conducted a meta-analysis in the treatment of anti-melanoma differentiation-associated protein 5 dermatomyositis (anti-MDA5 DM) which showed that 71% of patients responded to rituximab.

Studies included in the systematic reviews were generally of low quality, with heterogeneity between studies. There was also some overlap between the studies included in each review.

The RECITAL study results showed rituximab was not superior to cyclophosphamide to treat connective tissue disorder-associated ILD in 101 patients in the UK. Patients in both treatment groups had increased FVC at 24 weeks, and clinically important improvements in patient-reported quality of life. Rituximab was associated with fewer adverse events, and the authors concluded that it should be considered as a therapeutic alternative to cyclophosphamide in people with CTD-ILD who need intravenous therapy (Maher et al., 2023).

The EVER-ILD study results showed that treatment with rituximab and mycophenolate mofetil (MMF) was superior to MMF alone in patients with ILD associated with connective tissue disease or idiopathic interstitial pneumonia (Mankikian et al., 2023).

Safety: Adverse events reported in the studies were consistent with those previously reported: most commonly bacterial and viral infections. No new safety concerns with rituximab were identified.

Cost-effectiveness: No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact: Clinical experts report that 16 patients have started treatment with rituximab in the last year. Only partial data are available for three health boards;, therefore, usage may be slightly higher. In the original assessment it was estimated that 20 patients per year would be started on rituximab for interstitial lung disease, which is comparable to actual usage.

Impact on health and social care services: Minimal.

Patient outcome data: [confidential information removed]

Evaluation of evidence
No significant new clinical evidence has been published that challenges the original recommendation. Since the One Wales recommendation was last reviewed, European and US guidelines for the treatment of systemic sclerosis-associated interstitial lung disease have been updated to include the use of rituximab. Data provided indicate patient numbers are within the original budget impact estimates and where outcomes are available, have resulted in disease stability or clinical improvement.

Next review date: February 2026

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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References: a full reference list is available on request.

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.

Reference	Study details	Main results
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.

Reference	Study details	Main results
		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		