AWTTC
All Wales Therapeutics & Toxicology Centre
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Evidence Status Report: 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

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KEY FINDINGS

Report 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 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 subsequently concluded not to commission rituximab for the treatment of connective tissue disease-associated interstitial lung disease. This use of rituximab is currently off-label. A phase III clinical study of rituximab as first-line therapy to treat interstitial lung disease associated with connective tissue disease is under way. Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from rituximab treatment. This medicine was therefore considered suitable for assessment via the One Wales process.

Efficacy/Effectiveness
The evidence of clinical effectiveness of rituximab to treat interstitial lung disease associated with connective tissue disease comes from open-label controlled studies, a phase II study and retrospective case studies. Three comparative studies of rituximab to treat interstitial lung disease associated with scleroderma showed a significant increase in lung function compared with cyclophosphamide and conventional treatments. Results from a phase II study and case studies showed an improvement or stabilisation of lung function with rituximab treatment in the majority of patients. No studies of rituximab in the treatment of idiopathic fibrotic non-specific interstitial pneumonia were found. Clinical expert opinion is that the treatments are likely to be similar to that for connective-tissue associated disease.

Safety
No new safety signals have been observed for rituximab to treat interstitial lung disease associated with connective tissue disease of idiopathic fibrotic non-specific interstitial pneumonia.

Patient factors
Rituximab is administered by intravenous infusion. Different doses and regimens have been used to treat interstitial lung disease associated with connective tissue disease.

Cost effectiveness
There are no studies on the cost-effectiveness of rituximab as a second- or third-line treatment of fibrotic interstitial lung disease associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia.

Budget impact
The addition of rituximab to the treatment pathway is assumed to be life extending and to subsequently delay cyclophosphamide treatment and palliative care. The budget impact is estimated to be [confidential data removed]. This is based on 20 people in Wales per year eligible to receive rituximab and a discontinuation rate of five people per year. It is assumed that rituximab would displace cyclophosphamide treatment and palliative care.

Welsh commercial access agreements
This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Impact on health and social care services
The impact is expected to be minimal considering the small numbers of patients needing treatment.

Innovation and/or advantages
Rituximab represents an alternative treatment option for those patients who have failed on standard oral immunosuppressants.

BACKGROUND

Target group

The indication being considered is 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. The treatment algorithm is the same for both disease aetiologies and clinical expert opinion is that pathological disease progression is virtually indistinguishable. Rituximab is recommended as a treatment option for rheumatoid arthritis[1]; therefore, interstitial lung disease-associated with rheumatoid arthritis is not being considered in this report.

Technology

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20 on pre-B and mature B lymphocytes[2]. This binding mediates B-cell lysis by complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and also induces cell death by apoptosis[2].

Marketing authorisation date

Rituximab is not licensed to treat fibrotic interstitial lung disease; its use in this indication is off-label.

Dosing

There is no agreed optimal dose regimen for rituximab to treat interstitial lung disease and several different doses have been used in clinical and case studies. The dose used in the ongoing clinical study is 1 g rituximab given by intravenous infusion and repeated at two weeks[3].

Clinical background

Interstitial lung diseases are a heterogeneous group of disorders that cause scarring of the lungs[4]. The scarring causes stiffness in the lungs which makes it difficult to breathe. As well as shortness of breath, other symptoms may include dry cough and weight loss[4]. Initially, interstitial lung disease may be subclinical and people may have no respiratory symptoms. In such cases, interstitial lung disease would have been identified through both radiological appearances and lung function abnormalities[5]. Within three years, 5–80% of people go on to develop clinically significant lung disease, with variation depending on specific connective tissue disease[5].

Often, interstitial lung disease has no identifiable underlying cause and is regarded as idiopathic[6]. Frequently, interstitial lung disease is associated with a specific environmental exposure or underlying connective tissue disease. Connective tissue diseases include various systemic autoimmune diseases: rheumatoid arthritis; systemic lupus erythematosus; systemic sclerosis (scleroderma); primary Sjogren's syndrome; polymyositis, dermatomyositis, and antisynthetase syndrome; mixed connective tissue disease; and undifferentiated connective tissue disease. These disorders manifest with autoimmune-mediated organ damage, frequently targeting the lungs. There are multiple pulmonary manifestations; essentially every component of the respiratory tract is at risk of injury[6].

Non-specific interstitial pneumonia is a rare disease that causes inflammation and scarring of the lungs[7]. Non-specific interstitial pneumonia can be idiopathic or can be seen in association with connective tissue disease, HIV infection, a variety of drugs, and hypersensitivity pneumonitis[8]. Approximately two-thirds of people with idiopathic non-specific interstitial pneumonia who receive treatment are stable or improved in long-term follow-up; mortality at five years is 15–26%[8]. There are two primary forms of non-specific interstitial pneumonia: cellular and fibrotic[7]. The prognosis for patients with the cellular form is excellent, with a low mortality rate. In the case of fibrotic non-specific interstitial pneumonia, the prognosis is less favourable, with a median survival period of 6–13.5 years after diagnosis[7].

Incidence/prevalence

The precise number of people with connective tissue disease-associated interstitial lung disease is not well defined. The majority of cases would be controlled with conventional oral immunosuppressants.

In the NHS England Commissioning Policy on the use of rituximab for connective tissue disease associated with interstitial lung disease, between 30–50 people in England per year with connective tissue disease-associated interstitial lung disease are estimated to be eligible for treatment with rituximab[9]. This equates to 2–3 patients in Wales. This estimate does not include people with interstitial lung disease associated with idiopathic fibrotic non-specific interstitial pneumonia. Given that idiopathic non-specific interstitial pneumonia has only recently been identified as a distinct clinical entity from other idiopathic interstitial pneumonias, incidence and prevalence are unknown[10]. Based on retrospective data from mixed cohorts of idiopathic pulmonary fibrosis and idiopathic non-specific interstitial pneumonia, the prevalence of idiopathic non-specific interstitial pneumonia is estimated to be 1–9/100,000[10]. Using the lower range of this estimate, and assuming that 10% of people are eligible for rituximab, this equates to around three patients in Wales per year.

A specialist clinician consulted by AWTTC considers that the figures derived from the NHS England Commissioning Policy are lower than would be anticipated in Wales. The estimates for non-specific interstitial pneumonia are considered to be reasonable. The clinician estimates that 20 people in Wales per year would be likely to be eligible to have rituximab as second- or third-line treatment for fibrotic interstitial lung disease associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia.

Current treatment options

Treatments for interstitial lung disease aim to control the disease, prevent further lung damage and improve breathing. Given the wide variation in manifestations of interstitial lung disease in autoimmune disease, no one management strategy is appropriate for every possible clinical scenario. The British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society (2008) recommend:

- for the majority of connective tissue disease, with the exception of systemic sclerosis, oral prednisone at an initial dose of 0.5–1 mg/kg with the aim of tapering to a

maintenance dose of 10 mg per day or less, often in association with an immunosuppressive agent (usually oral or intravenous cyclophosphamide or oral azathioprine)
- early treatment with oral prednisone (0.75–1 mg/kg) for interstitial lung disease associated with polymyositis/dermatomyositis, and cyclophosphamide or other immunosuppressive therapy to prevent disease progression
- low-dose oral steroids (10 mg/day) and/or cyclophosphamide (oral or intravenous) for systemic sclerosis-associated interstitial lung disease if treatment is required; high-dose corticosteroid treatment (daily prednisone dose > 10 mg) should be avoided if possible because of the risk of renal crisis[11].

For the majority of patients with non-specific interstitial pneumonia, systemic glucocorticoids should be considered for first-line treatment[8]. For those patients with more severe initial disease or an inadequate response to or intolerance of glucocorticoids, an additional immunosuppressant, such as azathioprine or mycophenolate, may be given. Due to their substantial adverse effects, cyclophosphamide, calcineurin inhibitors and rituximab are usually reserved for refractory disease that has not responded to prednisone in combination with azathioprine or mycophenolate[8].

Cyclophosphamide is also recommended by the European League against Rheumatism (EULAR) for the treatment of systemic sclerosis-associated interstitial lung disease[12]. Clinical expert opinion indicate that cyclophosphamide is poorly tolerated and few patients are treated with it. Clinical expert opinion indicates that at this stage of disease the most appropriate comparator is cyclophosphamide.

With the exception of the glucocorticoids, none of these medicines are specifically licensed to treat interstitial lung disease.

In 2017, NHS England reviewed and subsequently concluded that there was not enough evidence to commission rituximab for the treatment of connective tissue disease-associated interstitial lung disease[9]

Guidance and related advice

- Kowal-Bielecka et al. (2017) Update of EULAR recommendations for the treatment of systemic sclerosis[12]
- NHS England clinical commissioning policy (2017): rituximab for connective tissue disease associated with interstitial lung disease[9]
- British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society (2008) Interstitial lung disease guideline[11].

SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

A comprehensive literature search conducted by AWTTC identified two open-label, controlled studies[13-16] three case series and a literature review[17-22] of rituximab to treat interstitial lung disease associated with connective tissue disease published since the NHS England Commissioning Policy. These studies together with the relevant studies included in the NHS England Commissioning Policy are briefly described below; a summary of the studies designs and key endpoints are tabled in the appendix. The evidence has been divided according to the type of connective tissue disease the patients had in the studies: scleroderma; antisynthetase syndrome or mixed connective tissue disease. Case reports and case series which included fewer than ten patients were excluded. A UK, multicentre, randomised, double-blind, controlled study is recruiting patients with interstitial lung disease associated with systemic sclerosis, idiopathic inflammatory myositis or mixed connective

tissue disease to compare the efficacy of rituximab with cyclophosphamide as first-line treatment. The estimated study completion date is November 2020. .

Efficacy

The Outcome Measures in Rheumatology (OMERACT) Connective Tissue Disease associated Interstitial Lung Disease Working Group endorsed outcome measures to be considered in clinical trials for interstitial lung disease in systemic sclerosis[23]. The Group recommends that percent predicted forced vital capacity (FVC) should be the primary outcome in clinical trials and the following secondary outcomes should be considered: diffusing capacity of carbon monoxide (DLCO) percent predicted and thoracic high-resolution computed tomography (HRCT) extent of global interstitial lung disease or the extent of fibrosis or ground-glass appearance separately[23]. The Group defined a clinically meaningful progression in interstitial lung disease associated with connective tissue disease as either ≥ 10% relative decline in FVC or ≥ 5% to < 10% relative decline in FVC and ≥ 15% relative decline in DLCO[24]. According to the international consensus statement of the American Thoracic Society on idiopathic pulmonary fibrosis, a clinically significant improvement in response to therapy is defined as ≥ 10% increase in FVC and ≥ 15% increase in DLCO[25].

Rituximab to treat interstitial lung disease associated with sclerodoma: comparative studies and a retrospective case series

Rituximab was shown to be non-inferior to cyclophosphamide for the treatment of interstitial lung disease in patients with early diffuse sclerodoma at a single centre in India[13]. All patients (n = 60) were immunosuppressant-naive and received prednisone (10 mg/day) throughout the course. Results showed a clinically and statistically significant increase in the primary endpoint of percent FVC at 24 weeks compared to baseline in the rituximab group; there was no difference in the cyclophosphamide group. The mean difference in percent predicted FVC at 24 weeks between both groups was in favour of rituximab (9.46; 95% confidence interval [CI] 3.01 to 15.90; p = 0.003)[13].

Daoussis et al. (2017) compared rituximab with conventional therapy for the treatment of interstitial lung disease associated with systemic sclerosis at centres in Greece (n = 51)[14]. Thirteen patients in the rituximab group received concurrent immune based therapies and similar numbers in each group received low dose oral corticosteroids (< 10 mg prednisone or equivalent). Seven patients in the rituximab group and three patients in the control group had received cyclophosphamide in the past; in all these patients, cyclophosphamide was stopped at least one year before enrolment. Median follow-up for all patients was four years (range 1–7)[14].

Results showed a non-significant increase in FVC during the first year of treatment in the rituximab group, which reached statistical but not clinical significance (mean increase approximately 8%), at two years[14]. Patients in the control group had no change in FVC during the first two years of follow-up. Direct comparison between the two groups at the 2-year time point did not show a statistically significant difference. At the 7-year time point, patients in the rituximab group (n = 5) had a numerically higher and clinically significant (not statistically significant) FVC compared to baseline, in contrast to patients in the control group (n = 9), where FVC showed a statistically and clinically significant deterioration. Direct comparison between the two groups showed a significant benefit for the rituximab group (p = 0.013). DLCO remained stable in both groups compared with baseline at the 2-year time point; there was no difference between the two groups. At the 7-year time point, DLCO remained stable in the rituximab group and statistically significantly declined in the control group compared with baseline; direct comparisons between the two groups did not reveal any differences[14].

Daoussis et al. (2010) conducted an open-label study in Greece[15]. A total of 14 patients were randomised to receive rituximab (n = 8) or standard therapy (n = 6) for the treatment of

interstitial lung disease associated with systemic sclerosis. At the 1-year time point, there was a statistically and clinically significant increase in FVC compared with baseline in the rituximab group; no change was seen in the control group. Direct comparisons between the two groups showed a statistically significant improvement with rituximab compared with control. At the 1-year time point, there was a clinically and statistically significant increase in DLCO (mean > 15%) in the rituximab group compared with baseline; there were no changes in the control group. At 24-weeks, HRCT of the chest showed no statistically significant difference in the two groups compared with baseline[15]. The 20-item Health Assessment Questionnaire Disability Index (HAQ-DI) was scored at baseline and one year. There was a significant improvement (defined as a 0.2 decrease in HAQ-DI score) in scores at Year 1 compared with baseline in the rituximab group ($p = 0.03$), no change was noticed in the control group[15]. All patients in the rituximab group received two additional cycles of rituximab at 12 and 18 months and completed a 2-year follow-up[16]. Results showed a statistically and clinically significant increase in FVC, and a clinically and statistically significant increase in DLCO at two years compared to baseline. On HRCT at 18 months, five patients showed a modest decrease (5–10%) in ground glass lesions compared to baseline, reticular lesions remained unchanged[16].

Sari et al. (2017) reviewed the charts of 14 patients in Turkey who received rituximab for the treatment of systemic sclerosis associated with interstitial lung disease[17]. Thirteen patients had unsatisfactory clinical response to cyclophosphamide and/or mycophenolate mofetil or disease progression. At the end of median follow-up (15 months) there was no significant change in FVC compared to baseline [17].

Rituximab to treat interstitial lung disease associated with antisynthetase syndrome: open-label phase II study, literature review and retrospective case review

Allenbach et al. (2015) conducted a prospective study in centres in France evaluating the efficacy of rituximab for the treatment of interstitial lung disease associated with antisynthetase syndrome[26]. A total of ten patients, with disease refractory to conventional treatments, received rituximab. Twelve months after the first rituximab infusion, FVC was improved (increased ≥ 10%) in five patients, stabilised in four patients and worsened (decreased ≥ 10%) in one patient. One patient with increased FVC also had an improvement of DLCO corrected for haemoglobin, and another patient had an improvement of DLCO corrected for haemoglobin without a significant change in FVC. Health-related quality of life was scored using the Study 36-Item Short-Form Health Survey (SF-36). Twelve months after the first rituximab infusion, SF-36 scores for physical functioning, role physical and bodily pain significantly increased (more than 10 points) compared with baseline[26].

Dasa et al. (2016) performed a literature review and identified 14 reports that included a total of 45 patients with interstitial lung disease associated with antisynthetase syndrome[18]. The studies included were open label, case reports and retrospective case series; controlled studies were not identified. An improvement in interstitial lung disease was reported in the majority of reported patients who received rituximab[18].

Doyle et al. (2018) retrospectively reviewed 25 patients in two centres in the USA who received rituximab for the treatment of interstitial lung disease associated with antisynthetase syndrome[19]. The main indication for rituximab use in the majority of patients (84%) was recurrent or progressive disease, owing to failure of other agents. At 12 months, FVC was stable (< 10% increase and < 10% decline) or improved (> 10%) in 79% of patients compared with baseline[19].

Rituximab to treat interstitial lung disease associated with mixed connective tissue disease: retrospective case series

Two studies analysed 74 patients who received rituximab for the treatment of interstitial lung disease associated with a connective tissue disease[5,21]. The majority of patients (73/74) had previously received conventional treatments and had had an inadequate response. All patients received one cycle of rituximab. Results showed a statistically significant improvement in FVC (median FVC increase of 6.7% in one study and 4.1% in the other study) following rituximab treatment compared with baseline. DLCO remained stable in both studies compared with baseline[5,21].

Safety

Adverse events associated with rituximab, reported in ≥ 1 in 10 patients, include bacterial and viral infections, neutropenia, leucopenia and thrombocytopenia, infusion related reactions, nausea, headache and decreased immunoglobulin G levels[2]. Interstitial lung disease is a rare (≥ 1/10,000 to < 1/1,000) adverse event associated with rituximab. Cases of hepatitis B reactivation have been reported in patients receiving rituximab, screening should be performed in all patients prior to treatment[2]. A drug safety alert was issued in 2014 following cases of progressive multifocal leukoencephalopathy (PML)[27], this is listed as a very rare adverse event in the Summary of Product Characteristics[2]. In the studies evaluated in this report, the main adverse event reported with the use of rituximab was respiratory infection[13-17]. The majority (6 out of 8 patients) required hospitalisation and intravenous antibiotics[14,15,17]. When compared with conventional treatment, adverse events were comparable, apart from a case of hepatitis B reactivation in the rituximab group[14]. A similar percentage of deaths were reported in each group; of the five deaths in the rituximab group none were attributed to treatment[14]. When compared with cyclophosphamide treatment, the number of patients who had an adverse event was statistically significant lower in the rituximab group (70% in the cyclophosphamide group versus 30% in the rituximab group; $p = 0.002$)[13]. Serious adverse events were only reported in the cyclophosphamide group[13].

Among Doyle and colleagues' case review of 21 patients with interstitial lung disease associated with antisynthetase syndrome, 3 patients had an adverse event after the initial rituximab dose: 1 anaphylaxis and 2 serious gastrointestinal complications requiring surgery; they all later resumed rituximab treatment[19]. Infectious complications while taking rituximab were: pneumonia (n = 1); influenza (n = 1); bronchitis (n = 1); *Clostridium difficile* colitis or urinary tract infection (n = 1); diverticulitis (n = 1); varicella zoster (n = 2); cellulitis (n = 1) and sinus infection (n = 1)[19].

Of the 45 patients with interstitial lung disease associated with antisynthetase syndrome reviewed by Dasa et al., one patient died of pneumonia infection three months after receiving rituximab[18]. Adverse events were not reported for the other patients in this review[18].

Clinical effectiveness issues

- There are no results available yet from large, prospective studies of rituximab as second- or third-line treatment of interstitial lung disease associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia. The evidence reviewed here is from open-label studies, retrospective case series and a case report. A clinical study in the UK of rituximab as first-line treatment is under way.
- There are no studies of rituximab in the treatment of idiopathic fibrotic non-specific interstitial pneumonia. In terms of treatment pathway, clinical expert opinion is that the treatments are likely to be similar to that for connective-tissue associated disease as pathologically the processes are virtually indistinguishable.

- There are limited long term data related to the use of rituximab to treat interstitial lung disease. Results from a 7-year follow-up showed a favourable response to rituximab, suggesting that continuous treatment is warranted; long term treatment with cyclophosphamide cannot be given due to its toxicity[14].
- The studies included show heterogeneity in study design, methodology and patient cohorts including disease duration and severity, as well as different previous medicines received and concurrent medicines with rituximab. Some of the studies included patients from India, Greece and Turkey and therefore practice might not reflect that of the UK.
- There is currently no recommended dose of rituximab to treat interstitial lung disease associated with connective tissue disease or idiopathic fibrotic non-specific interstitial pneumonia. The evidence from open label studies, case series and a case report includes different doses of rituximab given in different treatment protocols. The UK multicentre study under way is assessing rituximab at a dose of 1 g given intravenously, twice at an interval of two weeks and this tends to have been the favoured dose submitted through Individual Patient Funding Requests.
- The studies did not raise any new safety concerns associated with use of rituximab in this patient group.

SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

There are no studies on the cost-effectiveness of 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.

BUDGET IMPACT

Rituximab is administered by intravenous infusion on two days of a cycle. In the published studies the regimens followed varied, some studies followed the rheumatoid arthritis regimen and other studies followed the oncology monotherapy regimen. Based on clinical expert advice, the rituximab regimen most likely to be used is 1 g on days 0 and 15 followed by a further 1 g within 12 months, followed by an annual dose of 1 g (Table 1). It is estimated that 20 patients will be eligible for treatment with rituximab annually. A clinical expert has suggested that around five patients per year will discontinue rituximab due to predominantly recurrent infections. After discontinuing rituximab, patients would go on to receive intravenous cyclophosphamide (500 mg/m^2 body surface area given monthly, assuming an average body surface area of 1.79 m^2) for six months, then palliative care for six months in the following year. Palliative care consists of daily oxygen therapy and a weekly home visit from a specialist nurse. It is estimated that these patients would require admission to hospital twice a year. A clinical expert has suggested that the comparator, and therefore the displaced medicine, would be intravenous cyclophosphamide and palliative care (as above). Table 1 details the estimated annual budget impact in Wales.

Table 1. Projected budget impact in Wales

	Year 1	Year 2	Year 3
Number of patients receiving treatment in a market with rituximab*	20	40	60
Number of patients receiving treatment in a market without rituximab allowing for mortality†	20	40	40
Medicine acquisition costs and administration costs in a market with rituximab§	¶¶	¶¶	¶¶
Medicine acquisition costs and administration costs in a market without rituximab¶	£37,813	£186,413	£186,413
Net financial cost	¶¶	¶¶	¶¶

* Assumes 20 new patients per year eligible for treatment with rituximab
† This assumes that patients receive intravenous cyclophosphamide for six months in the first year, followed by palliative care for six months in the second year before death
§ Rituximab (MabThera®) or rituximab biosimilar (Truxima®): 1 g on days 0 and 15, followed by 1 g within 12 months, followed by an annual dose of 1 g. Assumes five patients per year discontinue rituximab treatment and go on to receive intravenous cyclophosphamide (500 mg/m^2 body surface area given monthly, assuming an average body surface area of 1.79 m^2) for six months in the next year, followed by palliative care for six months in the following year
¶ Intravenous cyclophosphamide (500 mg/m^2 body surface area given monthly, assuming an average body surface area of 1.79 m^2) for six months in the first year, followed by palliative care for six months in the following year
¶¶ Confidential figure removed
Administration costs taken from National Schedule of Reference Costs[28]
Hospital admission and specialist nurse home visit costs taken from Personal Social Service Research Unit costs of health and social care[29]
Palliative care consists of daily oxygen therapy (this cost has not been included) with a weekly home visit (assumes an hour visit) from a specialist nurse (assumes band 7) and two hospital admissions (four to eight days)

Budget impact issues

- In the absence of published data, patient numbers, discontinuation rates and treatment options have been provided by a clinical expert in Wales.
- The analysis does not include costs of adverse events.
- It is assumed that a home nurse visit during palliative care would be for an hour. The cost of daily oxygen therapy has not been included.
- It is assumed that rituximab would be life extending, as patients in the cyclophosphamide arm move on to palliative care and then die in Year 3. This assumption is highly uncertain as there are no published data to support this. If this group of patients remained alive and on palliative therapy this would be associated with higher costs and the net financial cost could be lower/cost saving in Year 3.
- It is assumed that patients would remain on any concurrent treatments irrespective of the treatment option chosen therefore the analysis does not include concomitant treatments.

Welsh commercial access agreement

This medicine is currently not licensed for the indication under consideration (i.e. off-label) and therefore as the Pharmaceutical Industry's code of practice prevents a company from promoting an off-label use of a medicine, a commercial agreement cannot be offered by the company.

Prescribing unlicensed medicines

Rituximab is not licensed to treat this indication and is therefore 'off label'. Providers should consult the General Medical Council Guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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Appendix
Summary of study designs and key outcomes

Authors and study type	Associated CTD/patient population	Duration /follow-up	Prior treatment	Intervention(s)	Concurrent treatments	FVC	DLCO	Other outcomes
Sircar et al. 2018[13] Open-label, randomised controlled, single centre in India (n = 60)	Early diffuse sclerodoma	6 months	No previous immunosuppression therapy	**RTX (n = 30):** • 2 x 1 g at day 0 and 15 • after 6 months,1 g **CYC (n = 30):** • 500 mg/m^2 four weekly for 24 weeks • azathioprine or MMF maintenance treatment after 24 weeks	Prednisone (10 mg/day), calcium and vitamin D	**Percent predicted FVC Mean (SD)** **RTX group:** Baseline: 61.30 (11.28) 6 months: 67.52 (13.59); p = 0.002 **CYC group:** Baseline: 59.25 (12.96) 6 months: 58.06 (11.23); p = 0.496 Mean difference in RTX group vs CYC group: 9.46 (95% CI 3.01 to 15.90; p = 0.003) The lower limit of the 95% CI was 3.01 which was greater than the non-inferiority margin (−2%).		**6-minute walking test (meters) Mean (SD)** **RTX group:** Baseline: 359.63 (65.95) 6 months: 409.60 (69.29); p < 0.001 **CYC group:** Baseline: 335.90 (89.30) 6 months: 349.14 (99.75); p = 0.428

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Daoussis et al. 2017[14] Open-label, controlled study at centres in Greece (n = 51)	Systemic sclerosis Mean disease duration: RTX group 5.73 years; control 2.56 years	Median follow-up for all patients 4 years Patients in the RTX group were evaluated during a median follow-up of 2 years (range 1 to 7 years).	**RTX group:** • CYC (n = 7) **Control group:** • CYC (n = 3) CYC treatment was stopped ≥ 1 year before enrolment	**RTX (n = 33):** • ≥ 2 cycles of 4 x 375 mg/m^2 once weekly; cycles repeated every 6 months **Control (n = 18):** • Azathioprine (n = 2); MTX (n = 6); mycophenolate (n = 10)	**RTX group:** • MTX (n = 2) • hydroxychloroquine (n = 1) • MMF (n = 10, 2 g/day) • oral corticosteroids (< 10 mg prednisone or equivalent; n = 18) **Control group:** • oral corticosteroids (< 10 mg prednisone or equivalent; n = 17)	**Mean ± (SD)** **RTX group:** Baseline: 80.60 ± 21.21 1 year (n = 33): 83.02 ± 19.05; p = 0.136 compared to baseline 2 year (n = 19): 86.90 ± 20.56; p = 0.041 compared to baseline 7-year (n = 5): 91.60 ± 14.81; p = 0.158 compared to baseline **Control group:** Baseline: 77.72 ± 18.29 1 year (n = 18): 77.18 ± 19.25; p = NS compared to baseline 2 year (n = 17): 77.59 ± 19.45; p = NS compared to baseline 7-year (n = 9): 61.11 ± 15.73; p = 0.001 compared to baseline RTX group vs control group at 2 year: p = 0.063 RTX group vs control group at 7 year: p = 0.013 (significant benefit for RTX group)	**Mean ± (SD)** **RTX group:** Baseline: 59.22 ± 18.17 2 year (n = 19): 61.51 ± 17.58; p = 0.053 compared to baseline 7-year (n = 5): 60.66 ± 24.71; p = ns compared to baseline **Control group:** Baseline: 64.24 ± 25.56 2 year (n = 17): 63.12 ± 23.98; p = 0.384 compared to baseline 7-year (n = 9): 51.08 ± 15.69; p = 0.004 compared to baseline RTX vs control at 1-year and 2-year: p = 0.398 and p = 0.966, respectively RTX group vs control group at 7 year: p = 0.495	

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Sari et al. 2017[17] Retrospective case series (n = 14)	Long standing (median disease duration 9.1 years) systemic sclerosis with an inadequate response to conventional treatments ILD: Mild (n = 2) Moderate (n = 7) Severe (n = 5)	End of follow-up was 6 months after last dose of RTX. Median follow-up 15 months (range 6 to 30 months)	CYC and/or MMF (n = 13)	RTX treatment regimens differed among patients	Oral corticosteroids (n = 14)	Median (IQR) at baseline: 52.5 (41.5–64.0) Median (IQR) at end of follow up: 58.0 (44.7–58.7); p = 0.06 FVC was improved (≥ 10%) in four patients and stabilised in ten patients. No patients experienced a decrease in FVC by ≥ 10%.		HRCT imaging was available for 10 patients. Compared with baseline, findings were stable in 7 patients and ILD progressed in 3 patients.
Daoussis et al. 2010[15] Open-label, randomised controlled study (n = 14) and long term follow up (Daoussis et al. 2012[16])	Systemic sclerosis Mean disease duration: RTX group 6.87 years; control 8.33 years	**Daoussis et al. 2010**: 1-year follow up **Daoussis et al. 2012**: 2 year follow up	**RTX group:** • CYC (n = 3) **Control** • CYC (n = 1) CYC treatment was stopped ≥ 3 year before enrolment	**RTX (n = 8):** • 2 cycles of 4 x 375 mg/m^2 once weekly at baseline and 24 weeks **Control (n = 6):** • Prednisone, bosentan, MMF or CYC **Daoussis et al. 2012:** All patients in the RTX group received two additional cycles of RTX at 12 and 18 months	**RTX group:** • MMF (n = 4) **Control** • MMF (n = 2)	**Daoussis et al. 2010** **Mean ± (SD)** **RTX group:** Baseline: 68.13 ± 19.69 1 year: 75.63 ± 19.73; p = 0.0018 **Control group:** Baseline: 86 ± 19.57 1 year: 81.67 ± 20.69; p = 0.23 **Daoussis et al. 2012** **Mean ± SEM** **RTX group:** Baseline: 68.13 ± 6.96 2 year: 77.13 ± 7.13; p = 0.0001	**Daoussis et al. 2010** **Mean ± (SD)** **RTX group:** Baseline: 52.25 ± 20.71 1 year: 62.00 ± 23.21; p = 0.017 **Control group:** Baseline: 65.33 ± 21.43 1 year: 60.17 ± 23.69; p = 0.25 **Daoussis et al. 2012** **Mean ± SEM** **RTX group:** Baseline: 52.25 ± 7.32 2 year: 63.13 ± 7.65; p < 0.001	**Daoussis et al. 2010** HRCT scores were identical at baseline and at 6 months in all patients in the RTX group. In the control group, there was a modest increase that was not statistically significant. **Daoussis et al. 2012** Five patients had a modest decrease (5–10%) in ground glass lesions at 18 months compared to baseline, while reticular lesions remained unchanged

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Allenbach et al. 2015[26] Prospective, multicentre (France), open-label, phase II study (n = 12)	Anti-synthetase syndrome refractory to conventional treatments (glucocorticoids and ≥ 2 other immunosuppressive/ immunomodulatory agents All patients had ILD confirmed by CT scan showing a nonspecific interstitial pneumonia (n = 9) and /or organised pneumonia (n=1)	1-year	Median of 3 immunosuppressive or immunomodulatory treatments plus corticosteroids	RTX: 1 g on days 0, 15 and month 6	All patients had corticosteroids and some had MTX, AZA, and/or IVIg	At 1-year, median variation of FVC was 5% (range −16% to 59%; p = 0.23); improvement (≥ 10%) in 5 patients, stabilisation in 4, and worsening (≤ 10%) in 1.	1 patients with increased FVC had improved DLCOcor. 1 patient had an improved DLCOcor without change in FVC.	Reduction of interstitial infiltrates at 1-year vs baseline in 1 patient, aggravation in 1 other patient, and no significant change in the remaining patients Overall, 5 patients had improved ILD measured by pulmonary function tests

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Keir et al. 2013[21] Retrospective case series (n = 50)	CTD-ILD (n = 33): • Idiopathic inflammatory myopathy (n = 10) • Systemic sclerosis (n = 8) • Undifferentiated CTD (n = 9) • Mixed CTD (n = 2) • RA (n = 2) • SLE (n = 1) • Sjogren's (n = 1) Hypersensitivity pneumonitis (n = 6) Other ILDs (n =11)	Median follow-up after RTX treatment was 11.6 (range 1.2–28) months	• CYC (n = 44) • Methylprednisone (n = 1) • Oral immunosuppression (prednisone, AZA or MMF) (n = 4)	RTX: 1 g on day 0 and day 14. Following RTX, oral immunosuppression continued unchanged in the majority of patients.		Median improvement in FVC (6.7%; range −25.0 to 45.5%; p < 0.01) and stabilisation of DLCO (median 0% change; range −34.4 to 76.2%; p < 0.01) at 6–12 months following RTX compared with just prior to RTX treatment.		
Sharp et al. 2016[5] Retrospective case series (Bristol; n = 24)	• Antisynthetase syndrome (n = 10) • Dermatomyositis (n = 3) • Scleroderma (n = 3) • Sjogren's syndrome (n = 2) • SLE (n = 2) • Unclassifiable (n = 4)	Mean duration of follow-up after treatment was 29.6 months (SD 16.7).	• CYC with methylprednisone (n = 16) • MMF (n = 10)	RTX: 1 g on days 0 and 14. Following treatment, all patients continued oral immunosuppression	NR	Mean change versus baseline: 4.1% (95% CI 0.9 to 7.2; p = 0.01)	DLCO remained stable, with a mean change of 2.1% (95% CI −1.0 to 5.2; P = 0.18) versus baseline.	HRCT imaging was available for 22 patients. The mean change in disease extent was −3.75% (95% CI −11.6 to 4.1; p = 0.33). By radiological criteria, the imaging had deteriorated for 9/22 patients, with 13/22 showing disease stability or improvement following treatment.

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Doyle et al. 2018[19] Retrospective case series in two centres in the United States	Antisynthetase syndrome In 21 cases (84%), the principal indication for RTX was recurrent or progressive interstitial lung disease, owing to failure of other agents.	• 1-year follow up • 3-year follow up (n = 7)	• AZA (n = 16) • MMF (n = 16) • CYC (n = 11) • Tacrolimus (n = 9) • MTX (n = 11) • IVIg (n = 6) • LEF (n = 3) • ETN (n = 1)	In one centre, RTX was given every six months, in the second centre, RTX was given in variable intervals.	• AZA (n = 1) • MMF (n = 8) • CYC (n = 1) • Tacrolimus (n = 1) • MTX (n = 1) • IVIg (n = 1) • Prednisone (n = 23)	• 1-year: FVC (n = 19) was stable or improved compared with baseline in 79% of patients • 3-year: increase in FVC of 21% (p = 0.016)	Baseline: 42 ± 17 1-year: 36 ± 16 2-year (n = 9): 53 ± 26 3-year (n = 4): 70 ±20	1-year: average CT score improved or was stable compared with baseline in 80% of patients. Average glucocorticoid dose decreased from 18 ± 9 at baseline (n = 20) to 6 ± 6 (n = 4) at 3 years.
Dasa et al. 2016[18] Literature review (open label case reports and retrospective case series; n = 45)	Antisynthetase syndrome		AZA, Cs, IVIg, MTX, ETN, CSA, CYC LEF, P, TAC, MMF, SSZ, HCQ, ADA, anakinra	RTX treatment regimens differed among patients	NR	An improvement in pulmonary function tests in the majority of patients		Improvement in lung imaging in the majority of patients

ADA: adalimumab; AZA: azathioprine; CI: confidence interval; CTD: connective tissue disease; CYC: cyclophosphamide; CSA: cyclosporine A;DLCO: diffusing capacity of lungs for carbon monoxide; DLCOcor: DLCO corrected for haemoglobin; ETN: etanercept; FVC: forced vital capacity; HCQ: hydroxychloroquine; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IQR: Interquartile range; IVIg: Intravenous immunoglobulin; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; NR: not reported; NS: not significant; PFT: pulmonary function test; RA: rheumatoid arthritis; RTX: rituximab; SD: standard deviation; SEM: standard error of the mean; SLE: systemic lupus erythematosus; SSZ: sulfasalazine; TAC: tacrolimus