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)

December 2021

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: April 2019
Date of review: December 2021

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria, rituximab can continue to be 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 is not licensed to treat this indication and is therefore 'off-label'. Each provider organisation must ensure all internal governance arrangements are completed before this medicine is prescribed.

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 guidance 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 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 following 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 2021.

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

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[1]. 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[2]. In 2017 NHS England reviewed and subsequently concluded not to commission rituximab for the treatment of connective tissue disease-associated interstitial lung disease[3]. This use of rituximab is currently off-label. Clinicians in Wales considered there to be an unmet need within the service and identified a cohort of patients who could benefit from rituximab treatment. Based on this unmet need, this medicine was considered suitable for assessment via the One Wales process.

Current One Wales Interim Commissioning Decision

Using the agreed starting and stopping criteria, rituximab can continue to 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. November 2020.

Licence status

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 remains an off-label indication.

Guidelines

No new guidelines for the treatment of fibrotic interstitial lung disease have been issued since the National Institute for Health and Care Excellence (NICE) published a rapid COVID-19 guideline (NG177) in May 2020[4]. The guideline stressed the importance of talking with patients about the risks and benefits of taking immunosuppressant therapy during the pandemic.

In February 2020 an expert panel published a set of European evidence-based consensus statements on the identification and management of interstitial lung disease in systemic sclerosis[5]. Their clinical management algorithm lists mycophenolate mofetil, cyclophosphamide and nintedanib for pharmacological therapy. If these medicines do not work well enough, then the dose or medicine could be changed, and experts agreed that rituximab could be considered as a treatment option[5].

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines

NICE TA747: Nintedanib has been recommended by NICE for treating progressive fibrosing interstitial lung diseases[6]. Nintedanib would be used as an add-on treatment to standard care when interstitial lung disease has progressed despite conventional treatments[6].

Efficacy/Effectiveness

A repeat literature search conducted by AWTTC identified four **systematic reviews**.

Goswami et al. (2021) conducted a systematic review and meta-analyses to investigate the effect of rituximab on lung function parameters in systemic sclerosis-related interstitial lung disease[7]. The review identified 20 studies (two randomised controlled studies; six prospective studies; five retrospective studies and seven conference abstracts) in a total of 575 patients. Results showed that rituximab improved forced vital capacity (FVC) from baseline by 4.49% (95% confidence interval [CI] 0.25 to 8.73) at six months and by 7.03% (95% CI 4.37 to 9.7) at 12 months. Similarly, rituximab improved the diffusing capacity of the lung for carbon monoxide (DLCO) by 3.47% (95% CI 0.99 to 5.96) at six months and by 4.08% (95% CI 1.51 to 6.65) at 12 months. FVC at 6 months improved more in patients treated with rituximab than in patients in the control groups. Patients treated with rituximab had a lower chance of developing infections than patients in the control groups (odds ratio 0.256 [95% CI 0.104 to 0.626]; I^2 = 0%; p = 0.47)[7].

Three other systematic reviews of rituximab treatment were identified:

- Caldas et al. (2021) included 10 studies in 218 people with systemic sclerosis[8];
- Borrirukwisitsak et al. (2021) included 8 studies in 908 people with pulmonary manifestations of systemic sclerosis[9]; and
- Xing et al. (2021) included 6 studies in 242 people diagnosed with connective tissue disease-associated interstitial lung disease[10].

These 3 systematic reviews included some of the studies that Goswami et al. reviewed; their results all broadly supported the conclusions of Goswami et al.

AWTTC's repeat literature search also identified seven relevant **clinical studies**.

One study, by **Kelly et al**. (2021), was conducted in the UK[11]. This retrospective multicentre study investigated the outcomes of 290 people, aged 42–83 years, with rheumatoid arthritis-related interstitial lung disease over a 25-year period. All-cause and respiratory mortality were compared between these patients and control patients with rheumatoid arthritis, including the effects of specific medicines on mortality. Mortality from rheumatoid arthritis-related interstitial lung disease fell progressively over 25 years, partly due to recent therapeutic developments. A total of 37 patients had received rituximab treatment. The relative risk of death from any cause was lower in patients who had received rituximab therapy than in those who received anti-TNF therapy (8% versus 31%; p = 0.03). Respiratory mortality was lower in patients treated with rituximab than in those treated with an anti-TNF (4% versus 15%; p = 0.04). Patients who received rituximab as their first biologic had longer survival at three years (92%), five years (82%) and seven years (80%) than those whose first biologic treatment was an anti-TNF medicine (82%, 76% and 64%, respectively) (p = 0.037)[11].

Benad et al. (2021) conducted a single-centre study in Germany to analyse the effects of immunomodulatory therapy with cyclophosphamide combined with or followed by rituximab to treat interstitial lung disease in patients with systemic sclerosis[12]. Three patients with anti-synthetase syndrome and two patients with Sjogren's syndrome were treated with rituximab without cyclophosphamide. A total of 21 patients received rituximab treatment (14 as rescue therapy), which lead to FVC improvements (of at least 5%) in eight patients and stabilisation in another six patients, compared with four

and eight patients, respectively who received cyclophosphamide. Eight patients who received rituximab and six that received cyclophosphamide experienced severe adverse events. Five patients treated with rituximab died: two patients treated with rituximab alone died of cancer, and three patients treated with rituximab with or after cyclophosphamide died (two had pulmonary embolisms and one had pneumonia)[12].

Vadillo et al. (2020) conducted a longitudinal, multicentre study in Spain to evaluate the efficacy of rituximab in treating rheumatoid arthritis-related interstitial lung disease[13]. Patients were included in a registry (NEREA) from the time of diagnosis of interstitial lung disease. A total of 68 patients were included; 42 developed functional respiratory impairment: in 50% of these the impairment developed within 1.75 years of diagnosis. Thirty-one patients were treated with rituximab: multivariate analysis showed that rituximab resulted in a lower risk of respiratory impairment compared with non-exposure (Hazard ratio 0.51 [95% CI 0.31 to 0.85]; p = 0.01). Two patients discontinued rituximab treatment due to adverse events (one of sepsis and one of pancytopenia) and three patients discontinued treatment due to lack of effect[13].

Four retrospective, observational studies showed that rituximab improved lung function in a total of 112 patients with interstitial lung disease associated with systemic sclerosis, antisynthetase syndrome, rheumatoid arthritis or other autoimmune diseases[14-17]. In patients with progressive rheumatoid arthritis-related interstitial lung disease; rituximab treatment reversed the decline of pulmonary function after 1 year of treatment: 8.06% increase in FVC compared with baseline (95% CI −10.9 to −5.2; p < 0.001) and 12.7% increase in DLCO (95% CI −16.3 to −9.1; p < 0.001)[16]. Patients with systemic sclerosis-related interstitial lung disease treated with rituximab had significant increases in DLCO% values from baseline after 15 months and 18 months of treatment (p = 0.008 and p = 0.01, respectively) compared with patients receiving cyclophosphamide[14]. One study in 26 patients with autoimmune disease-related interstitial lung disease showed a sustained improvement in pulmonary function tests from the start of rituximab treatment, with an mean increase of 4.2% in DLCO from baseline to one year (p = 0.024)[17]. One study showed better pulmonary progression-free survival at 2 years in patients treated with rituximab than patients treated with cyclophosphamide[15]. A total of nine patients discontinued rituximab treatment due to adverse events and three patients died[14-17].

A randomised UK study (RECITAL) comparing rituximab with cyclophosphamide (n=104) completed in January 2021[18]. A phase III study (EvER-ILD) of the efficacy and safety of rituximab given with mycophenolate mofetil to treat interstitial lung disease in 122 patients in France, has also completed[19]. Results are awaited for both studies.

Safety

Varley & Winthrop (2021) published a long-term safety study of rituximab treatment and the risks of infections over the past five years[20]. The study identified a higher risk of infection in patients with underlying diseases if they required a therapy switch, had a history of smoking, and if they were having re-treatment and had a serious infection during their first course of therapy. There were little data available regarding COVID-19 infection severity in rituximab treatment; however, rituximab, especially in

combination with corticosteroids, may lead to more severe disease and higher mortality[20].

Cost effectiveness
There were no cost-effectiveness analyses of rituximab in the treatment of interstitial lung disease.

Budget impact
Clinical experts in Wales reported that in the last 12 months, rituximab has been used to treat idiopathic fibrotic nonspecific interstitial pneumonia [confidential information removed]

Impact on health and social care services
The impact on the service remains minimal.

Patient outcome data
[confidential information removed]

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