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)

November 2020

ONE WALES INTERIM COMMISSIONING 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: November 2020

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 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 guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months 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 Interim Commissioning decision.

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

One Wales advice assists consistency of access across NHS Wales.

Start and stop 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 mycophenlate mofetil following regional interstitial lung disease multi-disciplinary team diagnosis review and treatment recommendation.

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 taking into account 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.

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 combination 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 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. August 2019.

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 off-label.

Guidelines
COVID-19: Interim NICE guidance has been issued to maximise the safety of adults with interstitial lung disease, with and without COVID-19, during the COVID-19 pandemic (NG177)[4]. The guidance stresses the importance of discussing with the patient the risk/benefit of using immunosuppressants during the pandemic.

Licensed alternative medicines/Health Technology Appraisal advice for alternative medicines
NICE ID1599: Nintedanib for treating progressive fibrosing interstitial lung disease. Expected publication date: TBC. The appraisal was suspended due to COVID-19 in April 2020 as it was not considered to be therapeutically critical and was not prioritised. In May 2020, the marketing authorisation holder requested that NICE delay appraisal by a further six months[5].

NICE ID1420: Nintedanib for treating interstitial lung disease caused by systemic sclerosis. Expected publication date: TBC[6].

Efficacy/Effectiveness
A repeat literature search conducted by AWTTC identified one systematic review, one retrospective study and one conference abstract.

Bellan (2020) performed a systematic review on the use of rituximab for connective tissue disease related interstitial lung disease[7]. The review contained 24 studies investigating interstitial lung disease related to: systemic sclerosis (14 studies); idiopathic inflammatory myopathies and anti-synthetase syndrome (5 studies); Sjörgen's syndrome (2 studies); and mixed connective tissue disease (3 studies). Some of the studies were included in the original evidence status report. The review was descriptive; direct comparisons were not carried out due to the heterogeneity of outcomes, follow-up duration, severity of lung involvement and clinical features of the populations. Based on the included studies the authors conclude that rituximab can stabilise and possibly improve interstitial lung disease complicating systemic sclerosis and anti-synthetase syndrome but further investigations are needed. They state that it is not possible to draw conclusions about the

use of rituximab in Sjörgen's syndrome, mixed connective tissue disease or systemic lupus erythematosus due to paucity of data[7].

A peer-reviewed retrospective study evaluated the effect of rituximab in patients with progressive connective tissue disease-related interstitial lung disease who met criteria for inclusion on a lung transplant waiting list (n = 18)[8]. Mean age of patients was 52.9 years and 77.8% of patients were female with a mixed range of connective tissue related diseases. Nine patients had non-specific interstitial pneumonia. Rituximab (1 g) was administered intravenously on days 0 and 14 every six months. All patients had at least two cycles of rituximab, 50% had three or more cycles and two patients had six cycles. Seven patients discontinued rituximab treatment, four due to leucopenia, two due to severe infection and one patient switched to a different treatment. Statistically significant improvements were recorded for both forced vital capacity (FVC) (+6.3%; 95% confidence interval [CI]: 1-11.7; p = 0.033) and diffusion lung transfer of carbon monoxide (DLCO) (+12.4%; 95% CI: 6.6-18.3; p < 0.001) after one-year of rituximab treatment (n = 18). This improvement remained statistically significant for DLCO (+15.3%; 95% CI: 8.1-22.6; p = 0.001) but not for FVC (+7.2%; 95% CI: 0.4-13.9; p = 0.052) after two years of treatment (n = 10). FVC and DLCO increased sufficiently to surpass the limit for a lung transplant in eleven patients after one-year of rituximab treatment and in eight patients who remained stable after two years of treatment[8].

A published conference abstract described a case of refractory non-specific interstitial pneumonia in mixed connective tissue disorder successfully treated with rituximab[9]. A 50 year old female patient, diagnosed eight years previously, had received chronic steroids, mycophenolate mofetil, azathioprine and cyclophosphamide but her respiratory symptoms and pulmonary function results continued to worsen. The patient was referred for lung transplant evaluation and rituximab (1 g) was administered intravenously, followed by a second dose two weeks later; this was repeated every six months. After four cycles of rituximab, there was significant improvement in the patient's symptoms and pulmonary function tests and the lung transplant plan was postponed[9].

Safety
No new safety issues were identified.

Cost effectiveness
A repeat literature search found no new cost-effectiveness evidence.

Budget impact
No information on patient numbers has been received although the number of patients receiving rituximab for this indication may be lower over the last year as, in accordance with guidelines, healthcare professionals should have considered the risk/benefit of the use of immunosuppressants during COVID-19 and discussed this with the patient[4].

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

Patient outcome data
No patient outcome data have been provided.

References

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