

Clinical Commissioning Policy: Rituximab for connective tissue disease associated with interstitial lung disease

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Clinical Commissioning Policy: Rituximab for connective tissue disease associated with interstitial lung disease

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**Prepared by NHS England Specialised Services Clinical Reference Group for
Specialised Respiratory Medicine and Specialised Rheumatology**

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Policy Statement

NHS England will not routinely commission rituximab for the treatment of connective tissue disease (CTD) associated interstitial lung disease (ILD) in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain Language Summary

About connective tissue disease associated interstitial lung disease

Interstitial lung disease (ILD) (scarring or inflammation around the alveoli, which are the air sacs in the lung) is a potentially fatal complication that develops in 10–35% of

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patients with specific connective tissue diseases (CTD) (a group of conditions caused by over activity of the immune system).

About current treatments

The usual treatment of CTD-ILD is with medicines that dampen down the immune system. In patients with severe or progressive disease this treatment is followed by steroids.

About the new treatment

Rituximab is a type of drug called a monoclonal antibody which also works by damping down the body's immune system. It is approved as a treatment for certain specific immune-mediated disorders and some malignant diseases.

What we have decided

NHS England has carefully reviewed the evidence to treat connective tissue disease associated with interstitial lung disease with rituximab. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

Interstitial lung diseases (ILD) comprise a broad spectrum of conditions, all of which are characterised by inflammation of the alveolar wall with impairment of gas exchange. ILD is a potentially fatal complication that develops in 10-35% of patients with specific connective tissue diseases (CTD), a group of conditions caused by over activity of the immune system.

The usual treatment for CTD-ILD is with medicines that dampen down the immune system. In patients with severe or progressive disease this treatment is followed by steroids.

Rituximab is a type of drug called a monoclonal antibody which also works by damping down the body's immune system. It is approved as a treatment for certain specific immune-mediated disorders and some malignant diseases.

This document describes the evidence that has been considered by NHS England in formulating clinical policy to not routinely commission rituximab for the treatment of connective tissue disease associated with interstitial lung disease.

2 Definitions

The key terms used in this policy and their definitions are:

Rituximab: a monoclonal antibody that targets CD-20, which is a cell surface marker that is widely expressed on B-cells, leading to B cell depletion.

Connective tissue disease associated interstitial lung disease (CTD-ILD): interstitial lung disease is a potentially fatal complication that develops in 10–35% of patients with specific connective tissue diseases.

3 Aims and Objectives

This policy aims to define NHS England's commissioning position on the use of rituximab for patients with CTD-ILD.

The objective is to ensure evidence based commissioning in the use of rituximab for the treatment of patients with CTD-ILD.

4 Epidemiology and Needs Assessment

The precise numbers of individuals with CTD-ILD is not well defined. Of the conditions covered by this policy the best researched is scleroderma. Scleroderma has an estimated annual incidence of 19 per 1,000,000 population. Only 25–30% of patients with scleroderma develop clinically significant ILD. It can be estimated that in England there will be 250 new cases of ILD related to Scleroderma per year. The majority of these cases will be controlled with conventional oral immunosuppressant therapy. Less than 10% (approximately 25 patients per year) will have ILD resistant to conventional treatment thus may be considered for treatment with rituximab therapy. The remaining patients with CTD-ILD have a combined incidence that is similar to that of ILD associated with Scleroderma (the estimated incidence of idiopathic inflammatory myositis is 2–8 per million population with up to 33% having ILD; the incidence of MCTD (mixed connective tissue disease) is 2–5 per million with between 10%–35% having ILD. Based on available epidemiological evidence, existing specialist centre experience and previous individual funding requests it can be estimated that rituximab could be requested to treat between 30–50 patients in England per year.

5 Evidence Base

The majority of the existing evidence suggests that rituximab is associated with an improvement in lung function, CT appearance and skin condition in patients with ILD associated with scleroderma, myositis and mixed connective tissue disease, which has proved refractory to other treatments (including cyclophosphamide).

Limited data is available on the impact on quality of life, muscle strength and walking distance which shows some benefit. There is no data available on cost effectiveness. There is no data available that provides a direct comparison between rituximab and other treatments.

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The most common side effects associated with rituximab are infusion reactions, episodes of pyrexia and increased frequency of infections. Although relatively rare the latter can be fatal and must be closely monitored.

The quality of the studies available is low grade (case series and case reports). Rituximab has been used as 'rescue therapy' but in this patient cohort a randomised controlled trial (RCT) trial would be difficult to undertake due to ethical considerations.

Studies included in the evidence review

Seven case series (Sem et al., 2009, Keir, 2012, Keir, 2013, Fitzgerald, 2015, Allenbach et al., 2015, Paola et al., 2016, Sharp et al., 2016) were included. These studies reported on patients with a range of underlying diagnoses – the majority of which were CTD-ILD. Where possible only the specific data on relevant patients has been included.

Six case reports (Haroon et al., 2011, Yoo, 2012, Daoussis et al., 2010, McGonagle et al., 2008, Sumida et al., 2014, Koichi et al., 2015), with six patients in total were considered.

Due to the nature of case reports and case series there are serious limitations to the studies detailed. They are all retrospective, subject to significant bias in publishing, reporting and selection and the study design does make it challenging to infer causality. However, for this patient group there is little opportunity to design experimental studies as the only option for use as a control or comparison is stopping treatment.

Results

Lung function

The case series reported by Paola et al. (2016) included only one relevant patient. This study reported improvements in both percentage predicted FVC (Forced Vital Capacity) (from 64% to 115%) and percentage predicted DLCO (Diffusing capacity of the lungs for carbon monoxide) (from 20% to 74%).

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Keir et al. (2013) showed improvements in the median predicted DLCO ($p < 0.01$) and FVC ($p < 0.01$) 6-12 months post-rituximab for the CTD-ILD group (32/33 patients were relevant). At the point of rituximab administration the median FVC was 44% (24.0-99.0%) and DLCO of 24.5% (11.4-67.0%). Kier et al. (2013) showed improvement in percentage predicted median FVC of 8.9% ($p < 0.01$) and stabilisation of previously declining DLCO (median change 0% $p < 0.01$) in all patients. This compares with a median decline in FVC of 14.3% and DLCO of 18.8% in the preceding 6-12 months. Fitzgerald et al. (2015) showed improvement in DLCO and FEV (Forced Expiratory Volume) in five of the six patients observed. In the three patients previously treated with cyclophosphamide the percentage change in DLCO ranged from -15.13 to +50.33. The percentage change in predicted FVC ranged from +8.92 to +28.27. Sem et al. (2009) reported an improvement of >10% FVC in six patients and >15% DLCO in three patients. No statistical testing was undertaken in this study. Sharp et al. (2016) reported a statistically significant change in FVC (mean change 4.1%, 95% CI 0.9, 7.2; $P = 0.01$) but not DLCO (mean change 2.1%, 95% CI -1.0, 5.2; $p = 0.18$). Allenbach et al. (2015) reported an improvement in ILD for five out of their ten patients, four had stable disease and one worsened – however it was not possible to isolate the patient who had previously received cyclophosphamide from the cohort. One study (Bosello et al., 2010) did not show a statistically significant improvement in lung function.

All six case reports (Haroon et al., 2011, Yoo, 2012, Daoussis et al., 2010, McGonagle et al., 2008, Sumida et al., 2014, Koichi et al., 2015) reported some improvement in pulmonary function in the patients treated. Haroon et al. (2011) reported an improvement in oxygen saturation (pre-rituximab saturation 94% baseline, 1 minute 91%, 6 minutes 72%, 7 months post rituximab 96% baseline, 1 minute 96%, 6 minutes 90%) and limited impact on FVC and DLCO. Yoo et al. (2012), Daoussis et al. (2010) and Sumida et al. (2014) observed an improvement in both FVC and DLCO. Koichi et al. (2015) reported a decrease in AaDO₂ (Alveolar – arterial gradient). McGonagle et al. (2008) observed mixed results.

CT Imaging changes

One case series (Fitzgerald et al., 2015) reported on CT imaging changes with ILD severity scale improved or remained stable in six out of seven patients with

interstitial disease in pre-treatment scans, but without sufficient detail to ascertain whether these were patients who were relevant to the policy proposition. Sem et al. (2009) also reported improvement in ground glass appearance on HRCT (High resolution computed tomography) resolution in five patients. One patient in this case series reported increased levels of fibrosis after rituximab treatment. Sharp et al. (2016) reported CT changes which did not reach statistical significance.

Four case reports described CT changes (Yoo, 2012, McGonagle, 2008, Sumida, 2014, Koichi, 2015). All reported improvement in ground glass changes and McGonagle et al. (2008) noted resolution of air bronchograms although none of the reports used a scale for recording lung changes.

Quality of life

The case series by Bosello et al. (2010) measured improvements in the impact of the disease after rituximab administration in all patients but one using the Global Health Status (GH) and Health Assessment Questionnaire (HAQ). HAQ fell from 0.9 +/- 0.7 to 0.4 +/-0.5 ($p=0.01$) and GH improved from 59.4+/- 20.9 to 82.8+/-16.6 ($p=0.01$). These patients had been treated with rituximab for resistant skin rather than lung manifestations of their disease.

None of the case reports reported a formal measure of quality of life although four case reports (Haroon et al., 2011, Daoussis et al., 2010, McGonagle et al., 2008, Sumida et al., 2014) and two case series (Paola et al., 2016, Keir et al., 2012) reported subjective improvement of patients' symptoms and dyspnoea.

6 Minute walk

Haroon et al. (2011) and Daoussis et al. (2010) reported improved 6 minute walk distance from 360m to 570m and 400m to 475m respectively.

Skin changes

Daoussis et al. (2010) reported improvement in modified Rodnan Skin Scores in their patient from 20 to 9 following rituximab treatment. Bosello et al (2010) also reported improvement in skin disease activity, severity and overall score. These changes were statistically significant.

Muscle strength

Allenbach et al. (2015) reported some improvement in muscle testing at month 12 after treatment with rituximab. Sem et al. (2009) also reported improvements in a small subset of patients.

Adverse effects

The main complication reported was respiratory infection, reported by Keir et al. (2013), Fitzgerald et al. (2015), Allenbach et al. (2015) and Keir et al. (2012). Allenbach (2015) reported a patient developing ARDS (Acute Respiratory Distress syndrome) but this may have been linked to methotrexate withdrawal. One patient died following an aspiration pneumonia (Fitzgerald et al., 2015) and another died after developing a Pneumocystis infection (Sem et al., 2009). Sem et al. (2009) also reported one infusion related adverse event and six patients attending hospital with raised CRP and fever. Allenbach (2015) also reported one febrile episode as well as two urinary tract infections and one patient with candida.

Out of the five case reports only Daoussis et al. (2010) reported a significant adverse event. One patient contracted a severe respiratory infection which required hospitalisation and intravenous antibiotics (Daoussis et al., 2010).

6 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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