NHS England

Evidence Review:

Rituximab for connective tissue disease associated interstitial lung disease

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Contents

1. Introduction

Interstitial lung disease (ILD) is a potentially fatal complication of a range of connective tissue diseases. The condition occurs in between 10 – 35% of individuals with scleroderma, idiopathic inflammatory myopathy and mixed connective tissue disease (MCTD). The pathogenesis of CTD-ILD is complex with immune system dysfunction and immune-mediated pulmonary inflammation contributing to its progression and development.

Current therapy for CTD-ILD consists of anti-inflammatory and immunosuppressive drugs including cyclophosphamide. For patients who are unresponsive to treatment, and for whom lung transplant is unavailable or inappropriate, palliative care is the remaining option.

Rituximab is a chimeric monoclonal antibody which causes a rapid depletion in B lymphocytes in the peripheral circulation. Rituximab has been successfully used in a number of other systemic autoimmune diseases and has an acceptable safety profile.

CTD-ILD is a complication of a number of different connective tissue diseases. Precise epidemiological data is hard to find as many of the diseases have overlapping symptoms. Scleroderma has an estimated annual incidence of 19 per 1,000,000 population and a prevalence of around 88 per million. Around 25-30% of patients with scleroderma develop clinically significant ILD per year and only a subset of these (less than 20%) patients will be unresponsive to conventional therapies. The estimated incidence of idiopathic inflammatory myopathy is 2 to 8 per million population with up to a third having ILD. The prevalence of idiopathic inflammatory myopathy is estimated to be between 2.2 and 10.6 per million population. The incidence of MCTD is 2 to 5 per million with 10-35% having ILD.

2. Research Questions

This literature review aims to answer the following research questions on the clinical effectiveness, safety and cost-effectiveness of rituximab in the treatment of severe CTD-ILD that is refractory to conventional treatments.

1. Is rituximab clinically effective in the treatment of refractory CTD-ILD?
2. Is rituximab safe to use in the treatment of patients with refractory CTD-ILD?
3. Is rituximab a cost-effective treatment option in the treatment of patients with refractory CTD-ILD?

3. Methodology

Articles were retrieved by electronic searching of MEDLINE, Cochrane, NHS Evidence and CRD databases. The search terms used were “Rituximab”, together

with “CTD-ILD” and their combinations. All articles identified were English-language, original full-text papers. Some articles were also identified from the reference lists of recent publications. For evaluation of studies case series as well as controlled trials were considered.

The search strategy is summarized in Appendix 1. Multiple reviewers examined abstracts to ensure they could inform on efficacy, safety or cost-effectiveness of rituximab for CTD-ILD. Reference tracking was undertaken to identify further papers to review.

No time limits were applied to the search. Only studies on adults in the English language were considered for this review. Studies had to include rituximab treatment for ILD [caused by any CTD].

Table1: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–*	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance
2+	Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance
2–*	Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance
3	Non-analytical studies (eg case reports, case series)
4	Expert opinion, formal consensus
*Studies with a level of evidence (–) should not be used as basis for making recommendations. *Source*: adapted from SIGN (2001).	

Table 2: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence

Grades of recommendations
Grade 'A'   At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or***   A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
Grade 'B'   A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or***   Extrapolated evidence from studies rated as 1++ or 1+
Grade 'C'   A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or***   Extrapolated evidence from studies rated as 2++
Grade 'D'   Evidence level 3 or 4 ***or***   Extrapolated evidence from studies rated as 2+

Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001

4. Results

One systematic review were found which summarised the majority of the studies that have already been considered in the evidence review. No meta-analysis was undertaken. One RCT was found. As the focus of the evidence review was the efficacy, safety and cost-effectiveness of rituximab, individual rituximab studies were obtained for critical appraisal.

Seven studies were found to meet the final inclusion criteria. 5 of these were case series or uncontrolled studies. No cost-effectiveness studies were found. Study characteristics and results are summarized in the following tables.

Table 3

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 3	Study design : Retrospective case series, UK Number of patients and their characteristics 8 patients (5M, 3F), severe-progressive CTD-ILD, previously treated with rituximab, failure to respond to conventional therapy, (5 patients polymyositis/dermatomyositis ILD, 2 patients undifferentiated CTD ILD, 1 patient systemic sclerosis ILD) Intervention Rituximab, 1000mg Day 0 and 14, one patient received 375mg/m2 weekly for 4 weeks Comparator None	Clinical status, pulmonary function tests (PFTs) (DLCO and/or FVC),	Improvement in clinical status and/or PFTs in 7 out of 8 patients (p=0.008) In 6 patients with serial PFTs median improvement in DLCO 22% (range 0-119%, p=0.04), and FVC of 18% (range 0-100%; p=0.03). Up to 9 months follow up data. Improvements occurred within first 2-3 months after treatment	Keir GJ et al (2012)0	Case series. Retrospective analysis.

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 3	Study design Retrospective case series, UK Number of patients and their characteristics 50 patients with severe, progressive ILD, treated with rituximab Intervention Rituximab Comparator None	PFTs (FVC, DLCO), mortality, hospitalisation	Median improvement in FVC of 6.7% (P<0.01), stability of DCLO (0% change, P<0.01), in 6-12 months post treatment. 2 patients required hospitalization following severe infections, 10 patients died from underlying progression of ILD at a median of 5.1 (range1.2-24.5) months after treatment.	Keir GJ et al (2014)	Case series. Retrospective analysis. Not all patients had CTD-ILD.

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 1-	Study design Randomised, controlled proof of principle study, Greece Number of patients and their characteristics 14 patients (2M, 12 F), 8 randomised to receive rituximab and standard treatment, 6 to receive standard treatment alone, diagnosis of systemic sclerosis, significant ILD Intervention Rituximab four weekly pulses (375 mg/m2) at baseline and 6 months, in addition to standard therapy Comparator Standard therapy	PFTs, high resolution CT, skin thickening, skin infiltrating B cells, overall functional activity, adverse events at 1 year	PFT improvement in rituximab group (increase in FVC compared to baseline (mean +/- SD 68.13 +/-19.69 vs. 75.63 +/-19.73 at baseline vs. 1 year, p=0.0018) no change in control group on PFT (mean +/-SD 86 +/-19.57 vs. 81.67+/-20.69 at baseline vs. 1 year respectively p=0.23) (increase in DLCO compared to baseline (mean +/- SD 52.25 +/-20.71 vs. 62 +/-23.21 at baseline vs. 1 year, p=0.0017) no change in control group on PFT (mean +/-SD 65.33 +/-21.43 vs. 60.17+/-23.69 at baseline vs. 1 year respectively p=0.25) No changes on CT in rituximab group HRCT scores were identical at baseline and at 24 weeks in all patients in the rituximab group, control group increase in HRCT score not statistically significant (p=0.170) Improvement in skin thickening in intervention group not statistically significant but linked to a reduction in B cells. No significant change in skin scores in the control group. One patient in intervention group hospitalized 3 months after intervention with respiratory tract infection	Daoussis D et al (2010)	Randomised controlled trial with a high risk of bias, controls on differing drug regimes/types

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 3	Study design Retrospective case series, Norway Number of patients and their characteristics 11 patients (4m, 7F, mean age 52), ILD, treated with rituximab, anti-synthetase syndrome Intervention Rituximab, 8 received 2 infusions 1000mg at day 0 and 14, one patient received 2 doses of 700mg, 2 patients received 4 weekly infusions at 375 mg/m2 Comparator None	Use of immunomodulators, immunological parameters, PFTs, lung imaging, serum creatine kinase, adverse effects	7 patients received immunomodulators after rituximab, 2 patients (n=10) had a decrease in antibody levels, 9 patients had an increase in PFTs, 5 patients showed improvements in CT, normalized creatine kinase in 3 (n=5) patients, one death in follow up period, one infusion related adverse event, 6 patients attended hospital with fever and raised CRP	Sem et al (2009)	Small retrospective case series, all patients remained on steroids throughout the trial, no statistical testing
Level 3	Study design Open label trial, prospective, Italy Number of patients and characteristics Nine patients (8F, 1M) with systemic sclerosis, mean age 40.9, treated with rituximab, worsening despite cyclophosphamide therapy Intervention Rituximab, two infusions of 1000mg, two weeks apart, 100mg prednisolone at each infusion, three patients retreated with rituximab 1g x2 Comparator None	Internal organ involvement, biological marker detection, skin biopsies and analysis	All nine patients reported an improvement in skin scores decreasing from 21.1 +/-9.0 to 12.0 +/-6.1 (p=0.001). FVC and DCLO not statistically significant change. High levels of IL-6 at baseline, permanently decreased at 6 months (0.6 +/- 0.9 pg/ml, P=0.02)	Bosello et al, 2010	Small prospective cohort study, differing treatment regimes

Clinical Effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 3	Study design Case series Number of patients and characteristics One, male, systemic sclerosis ILD, previous cyclophosphamide treatment Intervention Rituximab, 4 weekly infusions (375 mg/m2), remained on baseline therapy followed by another course 6 months later Comparator None	PFTs, HAQ, 6MWD	Baseline – dyspnea NYHA III-IV, FVC 32%, DLCO 18%, HAQ 2, 6MWD 400m HAQ score 1.250, Dyspnoea class 2, 6DMWD 475m, oxygen sat 92%, FVC 34%, DLCO 27% 6 months after second course	Daoussis D et al, 2010	Case series, one individual
Level 2-	Study design Systematic review Number of patients and their characteristics N=8, CTD-ILD (Keir et al 2012), n=50 CTD-ILD (Kier et al 2014), n=22 CTD-ILD (Dodds et al 2014), N=15 (systemic sclerosis CTD-ILD(SSc-ILD))(Lafyatis R et al), n=8 SSC-ILD (Daoussis et al 2010), n=11 (idiopathic inflammatory ILD) (IIM-ILD) (Sem et al 2009), n=8 (IIM-ILD) (Unger et al 2014), n=10 RA-ILD (Matteson et al 2012), n=10, (Palmer et al 2014) Intervention Rituximab Comparator Control group (D Daoussis et al 2010)	Pulmonary function tests, radiographic changes, thoracic HRCT scan, mortality	The authors concluded that the role of rituximab in CTD-ILD remains to be defined and further studies are required to better define its role particularly whether it would be more effective in specific subsets of CTD-ILD	Chartand S, Fischer A. Management of connective tissue disease-associated interstitial lung disease. Rheum Dis Clin North Am. 2015 May;41(2):279-94	The review considered a number of small case series and only one RCT. The doses and frequency of administration are variable and there is a diverse patient cohort.

Table 4

Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
Level 3	Study design Retrospective case series, Norway Number of patients and their characteristics 11 patients (4m, 7F, mean age 52), ILD, treated with rituximab, anti-synthetase syndrome Intervention Rituximab, 8 received 2 infusions 1000mg at day 0 and 14, one patient received 2 doses of 700mg, 2 patients received 4 weekly infusions at 375 mg/m2 Comparator None	Use of immunomodulators, immunological parameters, PFTs, lung imaging, serum creatine kinase, adverse effects	7 patients received immunomodulators after rituximab, 2 patients (n=10) had a decrease in antibody levels, 9 patients had an increase in PFTs, 5 patients showed improvements in CT, normalized creatine kinase in 3 (n=5) patients, one death in follow up period, one infusion related adverse event, 6 patients attended hospital with fever and raised CRP	Sem et al (2009)	Small retrospective case series, all patients remained on steroids throughout the trial, no statistical testing
Level 3	Study design Retrospective case series, UK Number of patients and their characteristics 50 patients with severe, progressive ILD, treated with rituximab Intervention Rituximab Comparator None	PFTs (FVC, DLCO), mortality, hospitalisation	Median improvement in FVC of 6.7% (P<0.01), stability of DCLO (0% change, P<0.01), in 6-12 months post treatment. 2 patients required hospitalization following severe infections, 10 patients died from underlying progression of ILD at a median of 5.1 (range1.2-24.5) months after treatment.	Keir GJ et al (2014)	Case series. Retrospective analysis. Not all patients had CTD-ILD. .

Safety					
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Table 4

Cost-effectiveness					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
	No studies				

5. Summary of Evidence

Clinical effectiveness

Five case series (Level 3) and one RCT (Level 1-) provided information on the clinical effectiveness of rituximab for CTD-ILD.

The RCT (Daoussis et al, 2010) was a small study and had a high risk of bias due to the small number of participants (n=14). The results showed a statistically significant improvement in lung function compare to baseline in those receiving rituximab with no change in the control group. Changes on lung imaging and skin changes in the intervention and control groups did not reach statistical significance.

The remaining studies were case series. Two of the five studies (Kier GJ et al 2012, Kier GJ et al 2014) demonstrated statistically significant improvements in respiratory function in patients treated with rituximab. Two studies reported improvements in respiratory function (Sem et al, 2009) (Daoussis D et al, 2010) but did not test these improvements statistically. One study (Bosello et al, 2010) did not report any statistically significant change in lung function overall in the patient cohort. These studies were uncontrolled and showed a high degree of heterogeneity in the dose/dosing interval/duration of course for the administration of rituximab, whether additional treatment was taken in addition to rituximab and how long patients were followed up. All studies investigated patients who had failed to respond to standard therapy. They also reported on very small numbers of patients. Reporting of case series can be particularly affected by publication bias.

The overall grade of the evidence is D.

Safety

Three studies considered the safety of rituximab for CTD-ILD. The RCT (Daoussis et al, 2010) reported one hospitalization in a patient receiving the drug. The patient was hospitalized for three days with a respiratory tract infection but made a full recovery. Two case series also reported adverse events. One (Kier et al 2013) reported serious lung infection requiring hospitalization following rituximab and the other (Sem et al) reported one fatal lung infection and one infusion related adverse event in the group treated with rituximab.

Cost-effectiveness

No cost effectiveness studies were found.

References

1. Bosello S, De Santis M et al. B cell depletion on diffuse progressive systemic sclerosis: safety, skin score modification and IL-6 modulation in an up to thirty six month follow up open label trial. Arthritis Research and Therapy 2010; 12:RS4
2. Daoussis D, Liossis S-N.C et al. Is there a role for B-cell depletion as therapy for scleroderma? A case report and review of the literature. Semin Arth Rheum 40:127-136
3. Daoussis D, Liossis S-N C et al. Experience with rituximab in scleroderma: results from a 1 year proof of principle study. Rheumatology 2010;49: 271-280
4. Keir GJ, Maher TM et al. Rituximab in severe, treatment refractory interstitial lung disease. Respirology 2014, Vol 19, Issue 3, 353-359
5. Keir GJ, Maher TM et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Resp J 2012; 40: 641-648
6. Sem M, Molberg O et al. Rituximab treatment of the anti-synthetase syndrome – a retrospective case series. Rheumatology 2009; 48:968-971

7. Chartand S, Fischer A. Management of connective tissue disease-associated interstitial lung disease. Rheum Dis Clin North Am. 2015 May;41(2):279-

Appendices

Appendix 1 - Search strategy

Question(s)	
• Is it a specialised service? • Is it in tariff? • Is it, or can it be, adequately covered by the appropriate detail in the service specification? • Is it very low volume or does it have a low number of requests, such as less than 10 per year? If it is low volume then it may not merit a clinical commissioning policy or may be deferred to the next round of policy reviews. • Does it appear too difficult to establish an evidence base or find suitable evidence to support a new clinical commissioning policy? If there is such limited evidence that it will not be possible to answer the review question then it will not be possible to generate a clinical commissioning policy. • Is it a clinical area included within the scope? If not, then a clinical commissioning policy may not be suitable for this	
Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Connective tissue disease interstitial lung disease refractory to conventional therapy
I – Intervention Which intervention, treatment or	Rituximab

approach should be used?	
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Cyclophosphamide, steroids, mycophenolate
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* *Improvement in respiratory function* *Important to decision-making:* Complications of treatment Rates of relapse
Assumptions / limits applied to search *e.g. date limits, inclusion and exclusion criteria (study type or aspect of topic)*	

Appendix 2- Version Control Sheet

Version	Section/Para/Appendix	Version/Description of Amendments	Date	Author/Amended by
1	Whole document	No previous literature review in the standard template	16/10/14	A Ali
2				
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