NHS England

Evidence Review:

Rituximab for the treatment of dermatomyositis and polymyositis (Adults)

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Prepared by	Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Dermatomyositis and polymyositis are two types of idiopathic inflammatory myopathies (IIMs) - a heterogeneous group of diseases that result in inflammation of muscle tissue (myositis) which can lead to weakness, fatigue and disability. Idiopathic inflammatory myopathies may also impact on the skin, joints, lungs, heart and gastrointestinal tract, contributing to added disease burden. There is also increased long-term cardiovascular risk.

There are four main types of idiopathic inflammatory myopathies:

1. Dermatomyositis (DM)
2. Polymyositis (PM)
3. Sporadic inclusion body myositis
4. Myositis which occurs in association with other diseases such as Systemic Lupus Erythematosus

This document considers dermatomyositis and polymyositis only.

There are no national guidelines for the treatment of dermatomyositis or polymyositis. Conventional treatment comprises physical therapy to improve muscle strength and high dose steroid therapy, prednisolone in severe cases and a short course of intravenous methylprednisolone which may be used in severe disease at induction of therapy.

There is a significant group of around 15% of patients (Allenbach et al., 2015) who are inadequately controlled by conventional therapy. These patients may also be resistant or refractory to several immunosuppressive drugs such as azathioprine, ciclosporin, tacrolimus, methotrexate and mycophenolate mofetil, which may also be used to reduce the need for steroids. Other treatment options currently considered include immunoglobulin therapy and topical therapies for the skin manifestations. Severe disease may also be treated with cyclophosphamide, however this is highly toxic and while it can quickly control the disease, it should be discontinued as soon as possible.

Rituximab is a type of biological therapy that reduces circulating B-cells and prevents their maturation into antibody-secreting plasma cells. Rituximab is administered either as four infusions, each 375mg/m2, given at weekly intervals infusions over 4 weeks (the lymphoma protocol) or 2 infusions of 1g, two weeks apart (the rheumatoid arthritis protocol) for the treatment of autoimmune diseases such as rheumatoid arthritis. As with all immunosuppressive therapy there is a risk of infection following infusion and appropriate patient selection and counselling is important prior to treatment.

2. Summary of results

The evidence review undertaken sought to answer the following questions:

Question 1: Is rituximab a clinically effective treatment for adult patients with dermatomyositis and polymyositis?
Question 2: Is rituximab safe to use in the treatment of dermatomyositis and polymyositis in adults?
Question 3: Is rituximab a cost-effective treatment option for use in adult patients with dermatomyositis and polymyositis?

In summary, the current evidence is characterised primarily by small case series type studies and the data from the US National Institute of Health Rituximab in Myostis (RIM) study. This is not unexpected given the rarity of the condition. The studies reviewed generally reported the effectiveness of rituximab, although their size and design is recognised.

Invariably, where it was actually reported, the dose of rituximab used was 1g, two infusions, 2 weeks apart.

Question 1: Is rituximab a clinically effective treatment for adult patients with dermatomyositis and polymyositis?

Oddis (2013) provides data from the US National Institute of Health Rituximab in Myositis (RIM) study. The objective of the study was to assess the safety and efficacy of rituximab in a randomised, double-blind, placebo-

phase trial in adult and paediatric myositis patients, comparing a “start early” strategy to later commencement of rituximab. "Refractory myositis" was defined as the intolerance to or an inadequate response to glucocorticoids and at least one other immunosuppressive (IS) or immunomodulatory agent (e.g. azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, leflunomide or IVIG). This was a large, well conducted study of a rare group of conditions and while it was not set up to demonstrate efficacy of rituximab compared to other therapies, it did indicate that 83% of randomised patients met the definition of improvement (DOI) demonstrating very high clinical impact in a group of chronic recalcitrant patients. In this respect, the study could be characterised as a large, well conducted observational study of 200 patients in which 83% of the cohort achieved clinically relevant improvement following rituximab.

Aggarwal (2014), in a further analysis, explored the importance of myositis autoantibodies to identify phenotypically distinct subsets of myositis patients. The study which analysed data from the RIM study in 195 patients who met the definition of improvement (DOI), establishes that the presence of autoantibodies is predictive of response to rituximab – both in terms of shorter time to improvement and 2-3 fold higher chances for improvement.

Rider (2014) concluded in a small case series of patients taken from the RIM study that a significant proportion did have a clinically relevant response to rituximab, although the lack of a comparator makes it difficult to ascribe outcomes to the treatment.

There are no systematic reviews or meta analyses specific to rituximab in the treatment of patients with myositis. Vermaak (2015) published a literature review on the evidence for a range of biologics in myositis. This review highlights the lack of good quality evidence and the heterogeneous nature of patients treated, the prior treatments, study design, outcomes assessed and methodological quality of a great deal of the research. The review concludes that some agents can be recommended, and some not. The studies included patients with active polymyositis (PM) and dermatomyositis (DM). It was not possible to draw conclusions as to whether the patients included in the studies would definitively meet PM and DM diagnostic criteria in England; the studies were small, mostly observational, and often of variable quality with heterogeneous populations. All patients included had active disease and were heavily pre-treated.

Unger (2014) published a small case series and concluded that objective improvement was seen in most patients (a heavily pre-treated group having received prior immunomodulating agents). The study observed that DM patients appeared to respond better than patients with anti-synthetase syndromes who required retreatment. This finding of differential response between different sub-groups was noted by others, for example Muñoz-Beamud (2013).

In summary, the observational evidence does suggest that there is a clinically relevant response in a large proportion of the cohort treated.

Question 2: Is rituximab safe to use in the treatment of dermatomyositis and polymyositis in adults?

While a number of papers indicated that rituximab was well tolerated, for example Couderc et al., 2011, some side effects, particularly infections are well recognised as a risk associated with rituximab and need to be considered in the context of the severity of the disease (Taborda et al., 2014).

Question 3: Is rituximab a cost-effective treatment option for use in adult patients with dermatomyositis and polymyositis?

No cost-effectiveness studies were found.

3. Research questions

• Is rituximab a clinically effective treatment for adult patients with dermatomyositis and polymyositis?

• Is rituximab safe to use in the treatment of dermatomyositis and polymyositis in adults?

• Is rituximab a cost-effective treatment option for use in adult patients with dermatomyositis and polymyositis?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Level	Study design and intervention			Outcomes					Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Systematic	NA - no meta analysis conducted.	This was a study considering multiple immunotherapies. It is not possible to comment on specific treatments.	Other	Improvement in muscle strength, ideally after 6 months.	Miscellaneous	Improvements in patient and physician global scores, physical function and muscle enzymes, and adverse events, in addition to achieving the International Myositis Assessment and Clinical Studies group (IMACS) Definition of Improvement (DOI) after at least 6 months.	NA	Vermaak, Erin; Tansley, Sarah L.; McHugh, Neil J.. The evidence for immunotherapy in dermatomyositis and polymyositis: a systematic review. Clin. Rheumatol. 2015;0(0):0.	NA	NA	Population: Age range 36-55 years. Summary comments: This review highlights the lack of good quality evidence and the heterogeneous nature of patients treated, the prior treatments, study design, outcomes assessed and methodological quality of a great deal of the research. The review concludes that some agents can be recommended, and some not. Caution is recommended in interpretation of the finding.
3	Case series	18	Rituximab administered early (as per RIM protocol). 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention	Percentage change in individual measures and in the definitions of improvement (DOIs) and standardised response means were examined over 44 weeks. The results were in-depth testing of muscle strength and cutaneous assessments, patient-reported outcomes, and laboratory tests.	Fifteen patients met the definition of improvement (DOI) at week 44, 9 patients met a DOI 50% response, and 4 met a DOI 70% response.	-	-	Rider, Lisa G.; Yip, Adrienne L.; Horkayne-Szakaly, Iren; Volochayev, Rita; Shrader, Joseph A.; Turner, Maria L.; Kong, Heidi H.; Jain, Minal S.; Jansen, Anna V.; Oddis, Chester V.; Fleisher, Thomas A.; Miller, Frederick W.. Novel assessment tools to evaluate clinical and laboratory responses in a subset of patients enrolled in the Rituximab in Myositis trial. Clin. Exp. Rheumatol. 2014;32(5):689-696.	Not stated.	Not stated.	Population: Age information not given. 5 patients with dermatomyositis, 8 patients with polymyositis and 5 patients with juvenile dermatomyositis. Summary comments: This was a small sub-analysis of a sub-group of patients from the Rituximab in Myositis (RIM) study. How this group of patients were selected is not clear. 15 (of the 18) were reported to have had clinically significant improvement (meeting the DOI) at 44 weeks, 9 (of 18) had a 50% improvement and 4 had a 70% response. Patient reported outcomes improved by up to 28%. The "up to" may disguise a mean improvement in patient reported outcome, which may be less than 28%. The lack of a comparator also makes it difficult to ascribe outcomes to the treatment.

2-	Cohort	195 myositis patients [75 adult polymyositis/72 adult dermatomyositis/48 juvenile dermatomyositis (JDM)] in the RIM RCT	Rituximab administered early. 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention compared to existing interventions	Time to achieve the preliminary International Myositis Assessment and Clinical Studies Group definition of improvement (DOI) between the 2 groups.	No difference in the time to DOI between the rituximab late (n=102) and rituximab early (n=93) groups.	Time to achieve ≥20% improvement in muscle strength, and the proportion of early and late rituximab patients achieving DOI at week 8.	No significant difference between the two groups.	Aggarwal, Rohit; Bandos, Andriy; Reed, Ann M.; Ascherman, Dana P.; Barohn, Richard J.; Feldman, Brian M.; Miller, Frederick W.; Rider, Lisa G.; Harris-Love, Michael O.; Levesque, Marc C.; RIM Study Group; Oddis, Chester V.. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile dermatomyositis and adult polymyositis. 0 2014;66(3):740-749.	NA	Eighty percent of the cohort (157/195) possessed at least one auto antibody by immunoprecipitation. The presence of a myositis auto antibody was most strongly associated with improvement and had a relatively constant effect on the time to DOI throughout the trial. After controlling for other factors in the multivariable model, patients with anti-Syn (primarily anti-Jo-1) and anti-Mi-2 showed a 2 to 3 fold higher chance of improvement as compared to the 'no auto antibody' group.	Population: Adults with refractory polymyositis and adults and children with refractory dermatomyositis. Mean age 40 in the rituximab early group and 43 in the rituximab late group. Summary comments: The aim of this study was to provide further insight into the predictors of response to rituximab in this cohort. The importance of myositis auto antibodies to identify phenotypically distinct subsets of myositis patients was already well recognised. This study further establishes that the presence of auto antibodies is predictive of response to rituximab. This may be important in determining priorities for commissioning.

2-	RCT	200	Rituximab administered early. 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention	Time to achieve the preliminary International Myositis Assessment and Clinical Studies Group definition of improvement (DOI) between the 2 groups.	No difference in the time to DOI between the rituximab late (n=102) and rituximab early (n=93) groups.	Time to achieve ≥20% improvement in muscle strength, and the proportion of early and late rituximab patients achieving DOI at week 8.	No significant difference between the two groups.	Oddis, Chester V.; Reed, Ann M.; Aggarwal, Rohit; Rider, Lisa G.; Ascherman, Dana P.; Levesque, Marc C.; Barohn, Richard J.; Feldman, Brian M.; Harris-Love, Michael O.; Koontz, Diane C.; Fertig, Noreen; Kelley, Stephanie S.; Pryber, Sherrie L.; Miller, Frederick W.; Rockette, Howard E.; RIM Study Group. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum. 2013;65(2):314-324.	Adverse events are clearly reported in table 2 of the study. There were 136 common drug-related adverse events (frequency >2), and 136 drug-related infectious adverse events in the entire RTX treated cohort. Note these are events not people.	The study was reported to have not met the primary endpoint - i.e. a difference in time to achieve a (pre-specified) clinically significant response between early and late start.	Population: Age information not given. Adults with refractory polymyositis and adults and children with refractory dermatomyositis. Summary comments: This was a study was comparing early and late start for rituximab rather than as a comparator to treatments in the PICO scope. This was a large and well conducted study. Steroid and immunosuppression were allowed in both groups, thus the study compared a "start early" strategy to later commencement of rituximab. Though the study did not meet the primary endpoint, 161 (83%) of randomised patients did achieve clinically significant improvement (met the DOI and individual core measures improved in both groups throughout the 44-week trial). In this respect, the study might also be characterised as an observational study of 200 patients in which 83% of the cohort achieved clinically relevant improvement. Defining the cohort randomised (to either arm) thus becomes important - "Refractory myositis" was defined by the intolerance to or an inadequate response to glucocorticoids and at least one other immunosuppressive (IS) or immunomodulatory agent (e.g. azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, cyclophosphamide, leflunomide or intravenous immunoglobulin (IVIG)). It may be noted that some prior immunosuppressants may have a more powerful impact than others - for e.g. comparing the potency of mycophenolate to cyclophosphamide. This is not well explored within the main RIM study. The authors themselves agree that this trial suffers from statistical failure and was underpowered to study the effect of early and late start of rituximab. On this basis, there is level 2- evidence that 83% of a refractory cohort of myositis having failed glucocorticoids and additional immunosuppressive agents in the course of their disease met the defined improvement by the end of the trial.
3	Case series	44 (only 18 of which were treated with rituximab)	Rituximab 1g, two infusions, 2 weeks apart.	Other	Response of MRI to rituximab treatment.	The response of MRI measures to rituximab was variable, and did not significantly agree with a standardised clinical definition of improvement.	NA	NA	Yao, Lawrence; Yip, Adrienne L.; Shrader, Joseph A.; Mesdaghinia, Sepehr; Volochayev, Rita; Jansen, Anna V.; Miller, Frederick W.; Rider, Lisa G.. Magnetic resonance measurement of muscle T2, fat-corrected T2 and fat fraction in the assessment of idiopathic inflammatory myopathies. Rheumatology (Oxford) 2015;0(0):0.	NA	NA	Population: Age information not given. 18 patients with idiopathic inflammatory myopathies (IIM). Summary comments: Small study. Low quality, methodologically speaking. Included to highlight the seeming discrepancy between clinical measures of response and objective MRI measures. What isn't reported, and wasn't included in the study, was the agreement between objective / clinical / patient reported response.

3	Other	19	Rituximab 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention	Change to steroid dose and creatine phosphokinase (CPK).	Under rituximab, both CPK and daily prednisolone dose were reduced by week 18. Six of eight patients with alveolitis improved under rituximab. Overall, 9 of 13 polymyositis (PM) patients responded. Six of the responders and two patients without documented response, all anti-synthetase syndrome patients, were re-treated. In contrast, all five dermatomyositis (DM) patients responded and none required retreatment.	NA	NA	Unger, Leonore; Kampf, Susanne; Lüthke, Kirsten; Aringer, Martin. Rituximab therapy in patients with refractory dermatomyositis or polymyositis: differential effects in a real-life population. Rheumatology (Oxford) 2014;53(9):1630-1638.	One case of fatal pneumonia, six more severe infections were seen. One patient developed hypogammaglobulinemia. Two patients had mild infusion reactions.	NA	Population: Age range 19-77 years. Mean age 57 years. Patients predominately with myositis. Summary comments: Objective improvement was seen in the majority of patients with regard to CPK and lung function tests, and glucocorticoids could be reduced. DM patients appear to respond better than patients with anti-synthetase syndromes who required retreatment. Infections were common. This was a small chart audit study, with no comparison group. It was a heavily pre-treated group with a large number of patients having received prior immunomodultating agents, many of the patients included having already received prior cyclophosphamide. In this context, rituximab might be considered a last in line treatment. There is a differential response, in terms of the need for retreatment between PM and DM patients. Of the DM (n=5) patients, all were perceived to have objective response and none had need for rituximab re-treatment out to 27 months; in contrast in the PM cohort (n=13), nine patients had objective response and 8 of these required retreatment with rituximab.
2-	Cohort	90	Rituximab 1g, two infusions, 2 weeks apart.	Other	NA	NA	NA	NA	Taborda, A. L.; Azevedo, P.; Isenberg, D. A.. Retrospective analysis of the outcome of patients with idiopathic inflammatory myopathy: a long-term follow-up study. Clin. Exp. Rheumatol. 2014;32(2):188-193.	NA	NA	Population: Age information not given. Mixed study of patients on a registry with a range of myopathies. Summary comments: This is a long-term epidemiological study of a mixed group of myopathies (n=90). As such caution is warranted when drawing any conclusions. 11% of the group were treated with rituximab. Use of rituximab was reported to be associated with death (HR 3.5), however this may be a marker for severity of disease.

3	Case series	16	Rituximab 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention	Myositis Intention to Treat index (MITAX) and the serum creatine kinase (CK) levels - baseline, 6 months, 12months. The primary efficacy outcome was 20% improvement in the MITAX index and 30% reduction in CK.	Eight patients responded to treatment and achieved both the MITAX and CK levels objectives within 6 months of rituximab therapy. Five out of these 8 responders remained clinically stable at 12 months and CK levels were still reduced or normalised. 4 of the non-responders were probably misdiagnosed.	NA	NA	Muñoz-Beamud, Francisco; Isenberg, David A.. Rituximab as an effective alternative therapy in refractory idiopathic inflammatory myopathies. Clin. Exp. Rheumatol. 2013;31(6):896-903.	-	All patients showed adequate B cell depletion (BCD) with re-population occurring for a 15.4 months average (range 3-42 months). Those simultaneously treated with cyclophosphamide achieved longer lasting depletion (average 18.6 months).	Population: Age information not given. Patients with active dermatomyositis or polymyositis failing to respond to conventional therapy. Summary comments: The definition of "failed conventional therapy" is not clearly defined. It is noted that myositis overlap and anti-synthetase syndromes seem to respond better than other patient subsets - this seems at odds with some of the other reported studies which reported this group did not respond as well.
3	Case series	30	Rituximab 1g, two infusions, 2 weeks apart.	Clinical effectiveness of the intervention	Not clearly reported.	Rituximab was effective in 16 patients (out of 25). Duration of efficacy was 15.5 months. Steroid use decreased in 15 patients, stopped in 4, remained stable in 8 and increased in the remaining 3. The CS dose decreased from 21.2 to 9.9 mg/day. Manual muscle testing was performed in only five patients: it increased from 87 to 91/100 at 6 months.	NA	NA	Couderc, Marion; Gottenberg, Jacques-Eric; Mariette, Xavier; Hachulla, Eric; Sibilia, Jean; Fain, Olivier; Hot, Arnaud; Dougados, Maxime; Euller-Ziegler, Liana; Bourgeois, Pierre; Larroche, Claire; Tournadre, Anne; Amoura, Zahir; Mazières, Bernard; Arlet, Philippe; De Bandt, Michel; Schaeverbeke, Thierry; Soubrier, Martin. Efficacy and safety of rituximab in the treatment of refractory inflammatory myopathies in adults: results from the AIR registry. Rheumatology (Oxford) 2011;50(12):2283-2289.	Thirteen adverse events reported (from 30 in cohort, and 25 receiving rituximab - seven infections and one serious infection (pyelonephritis))	-	Population: Mean age 52. Refractory idiopathic inflammatory myopathies (IIM). Summary comments: Small retrospective study. As such, caution is warranted drawing conclusions. Rituximab was reported to be effective in this population. The population was heavily pre-treated though it might be noted there is limited use of cyclophosphamide in the pre-treatment regimes (and possibly higher use of IVIG than would be the norm in UK clinical practice). Concomitant use of immunosuppressants alongside rituximab was the norm for many patients, raising a question of whether rituximab or the immunosuppressants are the key therapeutic agents, it is impossible to conclude on this. It was reported that rituximab was well tolerated, this finding should be set against a not insignificant proportion of the patients having documented adverse effects.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	-
Updated search terms - Population	Idiopathic Inflammatory Myopathies Dermatomyositis DM Polymyositis PM
Updated search terms - Intervention	Rituximab CD20 antibody, rituximab GP2013 IDEC-C2B8 IDEC-C2B8 antibody Mabthera Rituxan
Updated search terms - Comparator	Intravenous immunoglobulin IVIG Alphaglobin Endobulin Flebogamma DIF Gamimmune Gamimmune N Gamimune Gamimune N Gammagard Gammonativ Gamunex Globulin-N Immune Globulin Intravenous Intravenous immunoglobulins Intraglobin Intraglobin F Intravenous Antibodies IV Immunoglobulins Iveegam Privigen Sandoglobulin Venimmune Venoglobulin Venoglobulin-I Octagam

	Vigam cyclophosphamide Cyclophosphane Cytophosphan Cytophosphane Cytoxan Endoxan Neosar NSC-26271 Procytox Sendoxan Immunoabsorption Plasmapheresis
Updated search terms - Outcome	None
Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	-
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. No relevant outcomes 4. Incorrect study type 5. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 6. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	-