NHS England

Clinical Commissioning Policy: Rituximab for the treatment of dermatomyositis and polymyositis (adults)

Reference: NHS England: 16036/P

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Medical	Operations and Information	**Specialised Commissioning**
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference:	**05527s**
Document Purpose	Policy
Document Name	Clinical Commissioning Policy 16036/P
Author	Specialised Commissioning Team
Publication Date	15 July 2016
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Routinely Commission - NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	This document is part of a suite of policies with Gateway Reference 05527s.
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	**N/A**
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

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Clinical Commissioning Policy: Rituximab for the treatment of dermatomyositis and polymyositis (adults)

First published: July 2016

Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Rheumatology

Published by NHS England, in electronic format only.

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Policy Statement

NHS England will commission rituximab for the treatment of dermatomyositis and polymyositis 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 Dermatomyositis and polymyositis

Dermatomyositis and polymyositis belong to a group of illnesses called 'idiopathic inflammatory myopathies' (IIM). Idiopathic means that the cause of the illness is not known.

- IIMs cause inflammation of muscle tissue (myositis) - this can lead to disability and can cause the patient to feel weak and very tired.
- IIMs may also affect the skin, joints, lungs, heart, stomach and gut.
- Patients with IMM, also have an increased risk of problems such as heart disease and stroke in the long-term.

IMMs are rare, with around 500 new cases per year in England and Wales.

About the current treatment

Current treatment options includes:

- physical therapy to improve muscle strength
- medicines that reduce the immune response ('immuno-suppressants'), including steroids
- anti-bodies given into a vein, called 'intravenous immunoglobulin' (IVIG)
- medicines applied to the skin ('topical treatments').
- a medicine called 'cyclophosphamide' may be given to dampen down the immune system - however this has severe and life-threatening side effects so is not a long-term option and is only used in severe cases.

In around 15% of patients, the current treatments do not control the symptoms well enough.

About the new treatment

Rituximab is a biological medicine that helps to reduce inflammation. It can be used by patients whose symptoms are not controlled by current treatments.

What we have decided

NHS England has carefully reviewed the evidence to treat adult patients with active dermatomyositis or polymyositis (who have auto-antibodies relevant to myositis) with rituximab. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission rituximab in the treatment of adult patients with active dermatomyositis or polymyositis who have autoantibodies relevant to myositis.

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 biological medicine that targets and binds specifically to a protein (CD20) on pre-B and mature B lymphocytes. Once bound, it then depletes peripheral B cells, which are known to play a key role in the inflammation. Rituximab is administered either as four infusions, each 375mg/m2, given at weekly intervals infusions over 4 weeks or 2 infusions of 1g, two weeks apart 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 Definitions

The Idiopathic Inflammatory Myopathies (IIM) are a heterogeneous group of diseases that are characterised by inflammation of muscle tissue (myositis) which can lead to profound weakness, fatigue and disability. There are four main types: dermatomyositis, polymyositis, sporadic inclusion body myositis and myositis which occurs in association with other diseases such as Systemic Lupus Erythematosus.

Dermatomyositis most frequently affects the skin and muscles, however it is a systemic disorder that may also affect the joints, oesophagus, the lungs and the heart.

Polymyositis is a type of chronic inflammation of the muscles closest to the body's midline (i.e. hips, spine, neck), without skin disease, and can be associated with marked pain as well as weakness in these areas.

Rituximab is a biological medicine that targets and binds specifically to a protein (CD20) on pre-B and mature B lymphocytes. Once bound, it then depletes peripheral B cells, which are known to play a key role in the inflammation.

Active disease is defined as a score of <125 (out of 150) on the Manual Muscle Testing 8 (MMT-8) measure in conjunction with two other abnormal Core Set

Measures (CSM). If the MMT-8 score is >125 (out of 150), a third abnormal CSM is necessary. Please see section 7. Proposed Criteria for Commissioning for further details.

3 Aims and Objectives

This policy proposition aims to define NHS England's commissioning position on rituximab as part of the treatment pathway for adult patients with active dermatomyositis or polymyositis who have autoantibodies relevant to myositis.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with active dermatomyositis or polymyositis who have autoantibodies relevant to myositis.

4 Epidemiology and Needs Assessment

Dermatomyositis and polymyositis are rare disorders with an incidence of approximately 500 new cases per year in England and Wales (NHS England Specialised Commissioning Service Specification, 2013/14).

Dermatomyositis has an estimated incidence of 5.5 cases per million people (Callen, 2002) and normally has a short and relatively severe onset. When the characteristic inflammation of the muscles occurs without skin disease, the condition is referred to as polymyositis. Polymyositis most commonly affects adults in their 30s, 40s and 50s. It is more common among women than men and symptoms usually develop gradually over weeks or months.

Allenbach et al., 2015 suggests that 15% of people with dermatomyositis and polymyositis will not respond to conventional therapy with 80% of patients possessing at least one autoantibody (Aggarwal et al., 2014).

The total number of patients that would expect to receive rituximab per year would be circa. 60 (15% of 500 patients per year not responding to conventional therapy, with 80% of those patients having autoantibodies relevant to myositis).

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of rituximab in the treatment of adult patients with active dermatomyositis or polymyositis who have autoantibodies relevant to myositis.

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 Myositis (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 dermato myositis (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.

6 Criteria for Commissioning

Rituximab should be used as part of the treatment regime to achieve disease control and clinical remission in patients with definite dermatomyositis and polymyositis and severe, active disease. Rituximab should be used in patients who have failed (including contraindications or severe adverse effects) with conventional treatment including corticosteroids and at least two immunosuppressive / immunomodulatory steroid-sparing drugs. Patients should also have myositis relevant autoantibodies.

Active disease:

Active disease is defined as a score of <125 (out of 150) on the Manual Muscle Testing 8 (MMT-8) measure in conjunction with two other abnormal Core Set Measures (CSM). If the MMT-8 score is >125 (out of 150), a third abnormal CSM is necessary.

The other CSM needed consists of 1 of the following 6 measures:

(1) Patient's global assessment of disease activity by visual analogue scale (VAS) with a minimum score of 2.0cm out of 10.0cm (Isenberg et al, 2004)

(2) Physician's global assessment of disease activity by VAS with a minimum score of 2.0cm out of 10.0cm (Isenberg et al, 2004)

(3) Health Assessment Questionnaire (HAQ) disability index with a minimum value of 0.25

(4) Elevated level of at least 1 (locally measured) muscle enzyme (creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, or aspartate amino-transferase AST) to a minimum of 1.3 times the upper limit of normal, with the most abnormal muscle enzyme value selected as the target enzyme to be followed

(5) Global extramuscular disease activity score with a minimum value of 1.0cm (based on composite assessment of disease activity on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, and cardiac scales of the Myositis Disease Activity Assessment Tool [MDAAT])

(6) Active interstitial lung disease defined as a decrease of 10% in forced expiratory volume (FVC) and/or 15% of the diffusion capacity of the lung for carbon monoxide (DLCOcor) value

Stopping points would mirror that of the Rituximab in Myositis (RIM) study, namely:

Treatment should stop if patients do not meet the definition of improvement (DOI) criteria after each cycle of therapy (as per the rheumatoid arthritis protocol) or if the disease is no longer active. The DOI is the International Myositis Assessment and Clinical Studies (IMACS) Group preliminary validated response of a ≥ 20% improvement in 3 of any 6 core set measures with no more than 2 core set measures (CSMs) worsening by ≥ 25% [which could not include manual muscle testing (MMT)].

The 6 CSM for this trial were:

(1) Patient global disease activity using a 10 cm visual analogue scale (VAS)

(2) MD global disease activity also using a 10 cm VAS

(3) Health Assessment Questionnaire (HAQ)

(4) Serum muscle enzyme

(5) Global extra-muscular disease activity (based on the investigator's composite assessment of disease activity on the constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiac scales of the Myositis Disease Activity Assessment Tool (MDAAT))

(6) MMT, assessed using a validated measure, the MMT-8.

(7) An improvement in interstitial lung disease is defined as an increase of 10% in forced expiratory volume (FVC) and/or 15% of the diffusion capacity of the lung for carbon monoxide (DLCOcor) value

Re-treatment criteria:

The patient has previously responded to treatment but has had a disease flare. A flare is defined as the patient having active disease (as defined above). Only patients who have responded to treatment the first time can be re-treated.

Contraindications: Contraindications to continuing the use of rituximab as per standard clinical guidelines.

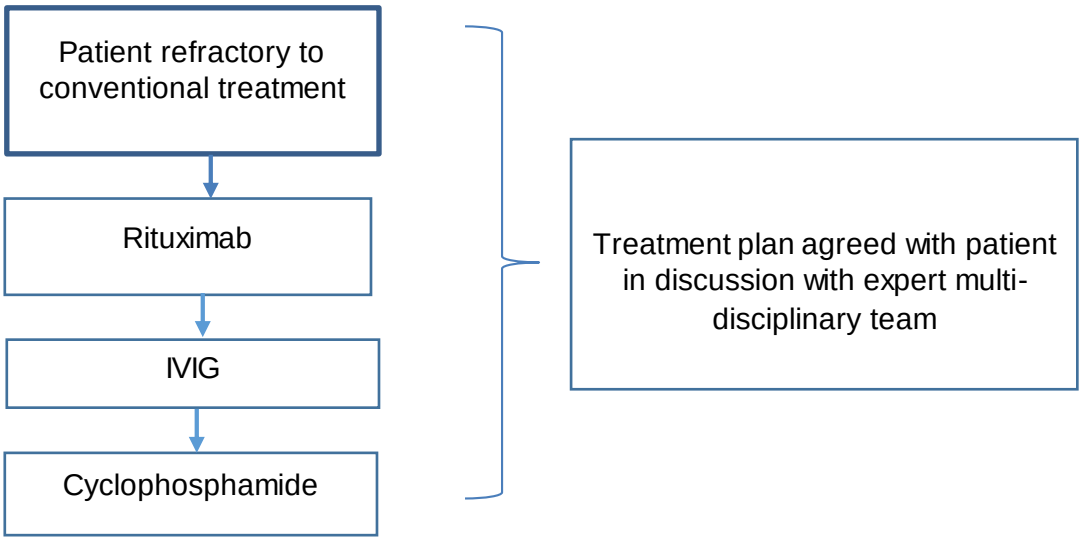
Dosing regimen: 2 infusions of 1g, two weeks apart (the rheumatoid arthritis protocol).

7 Patient Pathway

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. However, there is a significant group of around 15% of patients inadequately controlled by conventional therapy ( ). These patients are additionally resistant or refractory to several immunosuppressive drugs.

Rituximab would be used in this group of patients as a second line treatment, subject to there being no contraindications. IVIG may be considered as a third line treatment, and, recognising its toxicity cyclophosphamide would be considered fourth line. This should not preclude use of IVIG as outlined within existing DOH guidelines.



8 Governance Arrangements

Rituximab must only be used for treatment in specialised centres or in collaboration with specialised centres under the supervision of a multi-disciplinary team.

9 Mechanism for Funding

Funding for rituximab in the treatment of adult autoantibody positive patients with active dermatomyositis and polymyositis would be through the local NHS England specialised commissioning teams.

10 Audit Requirements

Patient data to be mandatorily collected as part of the Myositis Disease Activity Assessment Visual Analogue Scales (MYOACT) Registry to monitor efficacy and safety according to agreed outcomes. An annual audit should report on the following outcomes, collected following the administration of a course of two injections:

- Time to DOI
- Time to Clinical Remission
- Duration of effect
- Timing of re-treatment
- Reduction/Discontinuation in Steroids/Immunosuppressants
- Frequency of Retreatment
- Serious Adverse Effects

All patients receiving rituximab must be registered with the MYOACT registry. Data should be kept locally until MYOACT is set up.

11 Documents which have informed this Policy

NHS England Specialised Commissioning Service Specification for Specialised Rheumatology Services, 2013/14

12 Date of Review

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

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