NHS England

Clinical Commissioning Policy: Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocus motor neuropathy (MMN), vasculitis of the peripheral nervous system & IgM paraprotein-associated demyelinating neuropathy (adults)

NHS England Reference: 170026/P

Publications Gateway Reference:	05527s
Document Purpose	Policy
Document Name	Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocus motor neuropathy (MMN), vasculitis of the peripheral nervous system & IgM paraprotein-associated demyelinating neuropathy (adults)
Author	Specialised Commissioning Team
Publication Date	15 December 2017
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	Not for Routine Commissioning - NHS England will not routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	N/A
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	**N/A**
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Document Status

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Clinical Commissioning Policy: Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocus motor neuropathy (MMN), vasculitis of the peripheral nervous system & IgM paraprotein-associated demyelinating neuropathy (adults)

First published: December 2017

Prepared by NHS England Specialised Services Clinical Reference Group for Neurosciences

Published by NHS England, in electronic format only.

Policy Statement

NHS England will not routinely commission rituximab for chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy **i**n 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 chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy

It is estimated that over 10 million people in the UK live with a neurological condition which has a significant impact on their lives. Of these people, around 350,000 will require help for most of their daily activities.

Peripheral neuropathy describes damage to, or a disease affecting, nerves which can impair sensation, movement, gland or organ function, or other aspects of a person's health depending on the type of nerve affected. Immune-mediated peripheral neuropathies include chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy.

About current treatments

Many people with immune mediated peripheral neuropathy which is impacting on their daily activities will respond to conventional treatments such as steroids, intravenous immunoglobulin or cyclophosphamide. Individuals who do not respond to these treatments can be referred to a specialist neurology centre for alternative treatments.

About the new treatment

Rituximab belongs to a group of drugs known as monoclonal antibodies. These drugs are sometimes called targeted biological therapies as they work by targeting specific receptors on the surface of cells relevant to the cause of the disease.

What we have decided

NHS England has carefully reviewed the evidence to treat chronic inflammatory demyelinating neuropathy, multifocal motor neuropathy, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy with rituximab**.** We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

Peripheral neuropathy is damage to, or disease affecting, nerves which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

Immune-mediated peripheral neuropathies represent a spectrum of peripheral nerve disorders that can be classified according to time course, predominant involvement of motor/sensory fibres, distribution of deficits and clinically related parameters such as electrophysiology and serum antibodies. They include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and immunoglobulin M (IgM) paraprotein-associated demyelinating neuropathy.

This document considers the evidence for the use of rituximab in the treatment of immune-mediated peripheral neuropathies. Rituximab is a type of biological medication called a monoclonal antibody. It works by attaching to certain blood cells from the immune system (B cells) and destroying them.

2 Definitions

CIDP is a neurological disorder characterised by progressive weakness and impaired sensory function in the legs and arms. The disorder is sometimes called chronic relapsing polyneuropathy. Chronic indicates that condition occurs over a long period of time. Inflammatory indicates that the nerve damage occurs due to the presence of inflammation, a complex process involving the immune system. Demyelinating indicates the damage affects the protein coating (myelin) around the nerve fibres. Polyradiculoneuropathy means that the condition affects more than one nerve.

MMN is an immune-mediated neuropathy that affects the body's motor nerves. These are the nerves which control the muscles and the condition makes it hard for them to send electrical signals resulting in arms and legs feeling weak, causing muscle cramps, spasms and twitches. MMN is not fatal and, in most cases,

treatment can make muscles stronger, although the condition remains slowly progressive.

Vasculitis (inflammation of the blood vessels) of the peripheral nervous system, also referred to as non-systemic vasculitic neuropathy (NSVN), is vasculitis restricted to the peripheral nervous system - the part of the nervous system that consists of the nerves and ganglia on the outside of the brain and spinal cord.

IgM paraprotein-associated demyelinating neuropathy refers to neuropathies associated with a paraprotein. It results in mainly sensory disorders.

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities.

3 Aims and Objectives

This policy proposition considered: NHS England's commissioning position on rituximab as part of the treatment pathway for adult patients with immune mediated peripheral neuropathy including CIDP, MMN, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy who do not respond to conventional therapy.

The objectives were to: ensure evidence based commissioning in the use of rituximab for the treatment of immune mediated peripheral neuropathy including CIDP, MMN, vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy.

4 Epidemiology and Needs Assessment

It is estimated that over 10 million people in the UK (adults and children) live with a neurological condition which has a significant impact on their lives. Of these, around 350,000 will require help for most of their daily activities due to a neurological condition (The Neurological Alliance, 2003). A small minority will require treatment from a specialist neurology team.

5 Evidence Base

NHS England has concluded that rituximab should not be routinely commissioned as an option in the treatment of adult patients with immune mediated peripheral neuropathy.

The evidence review sought to provide a response to three key questions:

Question 1: Is rituximab clinically effective to treat adult patients with immune mediated peripheral neuropathy including CIDP, MMN (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy?

Two double blinded randomised placebo trials (level 1/-1) evaluating the effectiveness of rituximab in IgM anti-myelin associated glycoprotein antibody demyelinating neuropathy (Dalakas et al., 2009; Leger et al., 2013) showed no significance in outcomes in intention to treat analysis. There is level 3 evidence which has reported improvements in CIDP, MMN and IgM paraprotein associated demyelinating neuropathy. The majority of these studies have been case series/case reports providing low level evidence. There have been no recent studies evaluating the role of rituximab in NSVN. To date there has been no collective consensus on primary end points, and numerous sensory/motor/functional scores have been adopted across all studies.

i) CIDP: There is low level evidence (level 3) showing clinical improvement following use of rituximab in CIDP. Rituximab has been used in patients with CIDP following partial or complete lack of response from conventional therapies (intravenous immunoglobulin, corticosteroids and plasma exchange). Three case series have been identified to date (level 3 evidence), of which two series showed a functional improvement (functional scales utilised MRC, INCAT, ONLS, RODS) following treatment with rituximab. The medium follow-up was one year in all three case series. Benedetti et al. (2011) reported 13 cases, of which 8 patients had a co-occurring haematological condition, and this patient cohort were particularly

responsive to rituximab, which has also been observed in case reports (Cochrane Review 2013).

Side Effects: Gorson et al. (2007) reported two cases that required increased doses of IVIG following treatment with rituximab. No side effects were otherwise reported in the studies.

ii) MMN: IVIG is widely recognised as first line therapy in MMN, with both corticosteroids and plasma exchange shown not to be beneficial. There are two low level evidence (level 3) studies evaluating the use of rituximab in MMN. Chaudhry et al., (2010) (n=6) showed no reduction in IVIG usage and function (measured using 4 score scales) post rituximab treatment. Steiglbauer et al. (2009) (n=3), showed a clinical improvement following treatment. No side effects were reported in these studies.

iii) Vasculitis of the peripheral nervous system: The Peripheral Nerve Society (2010) have extrapolated data from small to medium vessel primary systemic vasculitides for rituximab and recommended that it remains an unproven treatment option. First line therapy in NSVN is based upon level 3 studies and recommends corticosteroids with tapering over months. In rapid progressive neuropathy cyclophosphamide for short term, bridging with long-term methotrexate or azathioprine has been recommended (level 4, Peripheral Nerve Society, 2010).

iv) IgM paraprotein-associated demyelinating neuropathy with or without anti-MAG antibodies: Two recent double blinded randomised trials (Dalakas et al., 2009; Leger et al., 2013) have shown no significant benefit. Dalakas et al. (2009) (n=50) used INCAT disability score, and found with removal of one patient in the rituximab group with a normal score at baseline from analysis, the findings were significant p=0.0036. Leger et al. (2013) (n=54) evaluated the absolute change in the INCAT sensory score (ISS) with no significance. However secondary outcomes included INCAT disability score which showed a significant difference when compared to placebo (p=0.037). The authors note a variability in other motor, sensory and functional scores. Two case series (level 3) have shown an improvement following rituximab therapy. Niermeiger et al. (2009) evaluated 17 patients with disabling IgM

MGUS polyneuropathy and found improvement in strength and sensory function although this did not translate to overall improvement in disability. Benedetti et al. (2008) studied the long term effects of rituximab in anti-MAG polyneuropathy patients (n=10) and found all patients improved at 12 months (sensory, ataxia and muscle scores), 80% maintained improvement at 24 months and 60% at 36 months.

Side Effects: The two case series did not report any side effects. The randomised controlled trials reported significant side effects varying from 7-23%, including bronchospasm, erythematous rash with severe itching, anaemia, bradycardia, dyspnoea and diplopia. A recent case series (n=3) of reported patients experienced clinical deterioration following administration of rituximab at the second or third dose. Benedetti et al. (2008) conducted a long term study (up to 36 months) and 4/10 patients had deteriorated further. The effect of rituximab both short and long term requires further evaluation in this cohort of patients.

Dosing Administration: There is no established evidence-based protocol for the administration of rituximab in peripherally demyelinating conditions and variations in dose and interval has been noted. Rituximab administration is commonly given at a dose of 375mg/m^2 weekly, for four consecutive weeks, or 1g every 2 weeks for a month, with variable continuation of rituximab following induction therapy.

Question 2: Is rituximab cost effective as a treatment for adult patients with immune mediated peripheral neuropathy including CIDP, multifocal motor neuropathy (MMN) (with or without block), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (with or without anti-MAG antibodies) who do not respond to steroid therapy or who do not respond to steroid therapy as an alternative or in addition to treatment with IVIG?

To date there have been no studies evaluating cost effectiveness of rituximab as a treatment for adult patients with immune mediated peripheral neuropathy including CIDP, MMN, vasculitis of the peripheral nervous system, and IgM paraprotein-associated demyelinating neuropathy with or without anti–MAG antibodies.

Question 3: Should rituximab be used as a second line treatment instead of IVIG or as an adjunct to IVIG?

To date there has been no specific study protocols evaluating the use of rituximab as a second line treatment instead of IVIG or as an adjunct to IVIG specifically. The patient cohort has been variable from severe disease to mild/moderate disease, including patients who have been non-responsive towards conventional treatment.

6 Date of Review

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

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