NHS England

Clinical Commissioning Policy Proposition:

Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (Adults)

Information Reader Box (IRB) to be inserted on inside front cover for documents of 6 pages and over, with Publications Gateway reference number assigned after it has been cleared by the Publications Gateway Team. Publications Gateway guidance and the IRB can be found on the Intranet.

Clinical Commissioning Policy Proposition:
Rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (Adults)

Reference: NHS England D04X09/01

First published: January 2016

Prepared by NHS England Specialised Commissioning Team

Published by NHS England, in electronic format only.

Classification: OFFICIAL

The National Health Service Commissioning Board was established on 1 October 2012 as an executive non-departmental public body. Since 1 April 2013, the National Health Service Commissioning Board has used the name NHS England for operational purposes.

Contents

Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

Plain Language Summary

This policy confirms NHS England's commissioning approach to rituximab in the treatment of adult patients with immune mediated peripheral 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 (PN) 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 (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy.

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

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.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission rituximab in the treatment of adult patients with immune mediated peripheral neuropathy.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether rituximab in the treatment of adult patients with immune mediated peripheral neuropathy will not be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Peripheral neuropathy (PN) 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 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.

3. Definitions

Chronic inflammatory demyelinating polyradiculoneuropathy (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.

Multifocal motor neuropathy (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.

4. Aim 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 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 objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with immune mediated peripheral neuropathy.

5. 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.

6. 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 chronic inflammatory demyelinating polyradiculoneuropathy (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?

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) and (Leger et al, 2013) showed no significance 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 small case series/case reports providing low level evidence. There have been no recent studies evaluating the role of rituximab in non-systemic vascular neuropathies (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) Chronic inflammatory demyelinating polyradiculoneuropathy (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 small 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) Multifocal motor neuropathy (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 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 non systemic vasculitic neuropathy (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).

iv) IgM paraprotein-associated demyelinating neuropathy with or without anti-MAG antibodies: Two recent double blinded randomised trials Dalakas et al, 2009 and 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 significant 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 significant 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/m2 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 chronic inflammatory demyelinating polyradiculoneuropathy (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 (CIDP, MMN, vasculitis of the peripheral nervous, IgM paraprotein-associated demyelinating neuropathy with our 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.

7. Documents which have informed this policy

N/A

8. Date of review

This document will lapse upon publication by NHS England of a commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).