Clinical Commissioning Policy
Rituximab for the treatment of IgM paraproteinaemic demyelinating peripheral neuropathy in adults [211001P] [URN: 1910]

Publication date: November 2021 **version number:** 1.0

Commissioning position

Summary

Rituximab is recommended to be available as a routine commissioning treatment option for IgM paraproteinaemic demyelinating peripheral neuropathy in adults within the criteria set out in this document.

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.

Executive summary

The aim of this document is to provide an updated review of the evidence for the use of rituximab for treating people who have IgM paraprotein-associated demyelinating peripheral neuropathy.

Plain language summary

About paraproteinaemic demyelinating peripheral neuropathy

Paraproteinaemic demyelinating peripheral neuropathy (PDPN) is associated with a range of pre-cancerous and cancerous blood conditions. Paraproteins are antibodies produced by white blood cells, which bind to the myelin sheath surrounding the body's nerve fibres resulting in neuropathy which manifests as sensory disturbance, imbalance, tremor and weakness of muscles.

About current treatment

Treatments for PDPN involve the suppression of the blood cancer which is the underlying cause of PDPN or attempts at physical removal of IgM antibodies from the blood. In the past treatments have included corticosteroids, plasmapheresis, interferon-2-alpha, cyclophosphamide and chlorambucil. None of these treatments in isolation has been found to be effective and most have significant or serious side effects. There is limited evidence for the use of intravenous immunoglobulin (IVIg) in the short-term for treating numbness, unsteadiness and weakness associated with PDPN.

About Rituximab

Rituximab belongs to a group of drugs known as 'biologics' which are themselves usually monoclonal antibodies. These drugs are also sometimes called 'targeted biological therapies' as they work by targeting specific receptors on the surface of cells relevant to the cause of the disease. Rituximab targets and attaches to CD20 proteins found on the surface of B cells (a type of white blood cell that produce the disease-causing antibodies), leading to their destruction.

What we have decided

NHS England has carefully reviewed the evidence to treat PDPN with rituximab. We have concluded that there is enough evidence to make the treatment available at this time.

Links and updates to other policies

As a result of the publication of this policy the not for routine commissioning policy for rituximab for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), vasculitis of the peripheral nervous system and IgM paraprotein-associated demyelinating neuropathy (adults) NHS England Reference: 170026/P has been updated. The reference to IgM paraprotein-associated demyelinating neuropathy has been removed.

Committee discussion

Clinical Panel discussed that the evidence was weak but acknowledged some improvements were demonstrated in a specific small subgroup of patients. There is limited evidence for the efficacy in current treatments and rituximab is considered to have a direct action on antibody producing cells with longer term clinical benefits.

See the committee papers (link) for full details of the evidence.

The condition

A peripheral neuropathy is a disease, damage or degenerative process affecting the structure and function of the axons or the myelin of peripheral nerve manifesting itself clinically most commonly as muscle weakness or sensory disturbance.

A range of peripheral neuropathies are associated with the presence of an abnormal level of a single antibody in the blood (called a paraprotein) and in some of these neuropathies this high-level antibody directly binds to one of several targets on the myelin or the axon. These conditions are termed paraproteinaemic peripheral neuropathies.

Paraproteins are immunoglobulins (antibodies) produced by clonal proliferation of one type of immune system white cell in the B-lymphocyte or plasma cell classes. B-lymphocytes are characterised by having a specific identifier protein termed CD20 on their cell surface. There are different classes of immunoglobulins that can normally be produced by B-lymphocytes and plasma cells at different stages of an immune response, or for different functional purposes, and these are termed IgM, IgG, IgA, IgE and IgD. Multiple conditions on a spectrum of malignancy can cause the clonal expansion of B-lymphocytes or plasma cells and are associated with paraprotein production.

Paraproteinaemic peripheral neuropathies represent the 'end-organ damage' of the primary problem, that is a haematological malignancy that elaborates a paraprotein which targets the nerves as its 'end-organ'. Only some types of this malignancy and some immunoglobulin classes of antibody are associated with paraproteinaemic peripheral neuropathy. Treatments for paraproteinaemic neuropathy are therefore primarily targeted at suppressing or 'curing' the

primary haematological malignancy and thus form a subset of the treatments that would be used for the treatment of that malignancy alone.

The range of pre-malignant and malignant haematological conditions associated with PDPN includes monoclonal gammopathies of undetermined significance (MGUS), the most benign of the associated haematological conditions), low grade lymphomas, low-grade Non-Hodgkin lymphoma and occasionally higher-grade disease. The majority of paraproteins in people with PDPN are IgM and are produced by the lower grade conditions above. These IgM antibodies, in approximately 50% of cases, react with a specific myelin protein, called myelin-associated glycoprotein or MAG, and are called anti-MAG antibodies. MAG is on the myelin sheath that insulates nerve fibres. Myelin attacked by these antibodies causes myelin damage (demyelination) of the nerve fibres resulting in the abnormal function and eventually the destruction of the nerve. There are likely to be other IgM targets, as yet unknown.

The clinical presentation of anti-MAG IgM PDPN consists of a slowly progressive distal sensorimotor neuropathy with disabling ataxia and a prominent tremor (Chassande *et al.* 1998). The sensory loss, imbalance, tremor and eventual loss of distal power and muscle wasting is the source of progressive impairment, disability and a decline in quality of life. A wide range of haematological and immunological tests, imaging studies, neurophysiological studies, and muscle and/or nerve biopsies can be required to diagnose anti-MAG IgM PDPN.

Current treatments

The current standard treatment for PDPN focuses on the management of the underlying cause of PDPN, suppressing the malignancy. Generic symptomatic treatments for the positive symptoms of tingling or pain (a range of membrane stabilisers, analgesics and anti-depressants) can be used but these cannot and do not address the progressive and disabling numbness, unsteadiness and weakness. Intravenous immunoglobulin (IVIg) has some very low certainty evidence of short-term effectiveness from a single 4 week crossover study (Comi *et al.* 2002), but clinical consensus is that IVIg is seldom effective in the long-term. Other agents used to try to suppress or modulate the immune response (corticosteroids, plasmapheresis and interferon-2-alpha) or reduce the levels of antibody by targeting the haematological problem (including chemotherapeutic agents such as cyclophosphamide, corticosteroids and chlorambucil) have been used in the past and studied in a few trials. None of these treatments has been shown to be effective alone and most have a range of serious adverse effects.

The new treatment

Rituximab is a therapeutic monoclonal antibody which targets the CD20 surface marker present on the majority of B cell subsets, leading to their destruction and subsequent reduction in immunoglobulin production. Rituximab was initially developed for the treatment of B-cell lymphoma. However, it is now also used in a variety of B-cell driven autoimmune diseases, including rheumatoid arthritis (Edwards *et al.* 2004; Gurcan *et al.* 2009). The use of rituximab to treat PDPN is off-label. Rituximab is licensed for the treatment of lymphoplasmacytic lymphoma and low-grade Non-Hodgkin lymphoma. It is not licensed for the treatment of MGUS.

As well as treating patients who are newly diagnosed with PDPN, there is also a strong case to give rituximab to antibody positive patients who have already been established on regular IVIg and whose symptoms are worsening. There is limited evidence for the efficacy of IVIg for treating PDPN and rituximab may be a more cost-effective alternative for treating PDPN compared to IVIg. Rituximab is very likely to negate the need for any further IVIg to be given.

The use of four doses of rituximab of 375 mg/m^2 body surface area produces benefits lasting at least 10-12 months conferred by its biological effect compared to one cycle of IVIg. In clinical practice, compared to rituximab IVIg produces lesser improvement, and as the half-life of IgG is 3 weeks and the effect non sustained, cycles of IVIg are repeated every 4-6 weeks indefinitely.

It is anticipated that one cycle of rituximab will last for the duration of action (10 to 12 months) and in clinical practice, some patients need no further subsequent treatment because of immunological resetting and indefinite remission. Given the direct mechanism of action on antibody producing cells and the longer term benefits and efficacy conferred by treatment with rituximab supported in clinical practice, it is proposed that rituximab should be the first line treatment for PDPN.

Epidemiology and needs assessment

PDPN with the presence of anti-MAG IgM antibodies is a rare condition with a prevalence of 0.42[1] per 100,000 in a southeast England[2] population of 3,557,352 people on 1st January 2008 (Mahdi-Rogers & Hughes, 2013) . The condition results in the significant accumulation of disability, occurs in a male to female ratio of approximately 60:40[3] and has a peak decade of onset of 70-79 years (Mahdi-Rogers & Hughes, 2013) . The mean age of onset is 58.2 years (Mahdi-Rogers & Hughes, 2013). Of those diagnosed with PDPN, approximately 50 people a year might be newly identified and deemed appropriate for rituximab treatment.

Evidence summary

NHS England has concluded that there is sufficient evidence to support a proposition for the routine commissioning of this treatment for the indication. The evidence reviews which inform this commissioning position can be accessed here: (link)

[1] Mahdi-Rodgers & Hughes found that there were 1.04 (95% CI 0.73–1.43) per 100 000 population with paraproteinaemic demyelinating neuropathy in southeast England. 15 of the 37 patients had anti-MAG IgM antibodies giving a prevalence of 0.42 patients with anti-MAG antibody positive paraproteinaemic demyelinating neuropathy.

[2] The study area comprised of the administrative areas of South-East London, Kent and East Sussex.

[3] Mahdi-Rodgers & Hughes found that the male gender-specific prevalence per 100 000 was 1.28 (95% CI 0.80–1.94) and that for females was 0.82 (95% CI 0.45–1.34) giving a male to female ratio of approximately 60:40.

Implementation

Criteria

Inclusion criteria

The decision to treat patients who have PDPN with rituximab will be made by the multi-disciplinary team including a haematology consultant and a neurology consultant from a tertiary neuroscience centre. The infusion would be given in a local hospital following approval by the tertiary centre. Rituximab should be given to patients with:

1. IgM paraprotein; and
2. Demyelinating peripheral neuropathy clinically consistent with anti-MAG IgM PDPN

WITH EITHER

3. <5 years disease or ongoing disease progression; and
4. disability as measured by an I-RODS score of less than 42/48.

OR

5. Progression of haematological disease (MGUS, lymphocytoplasmic leukaemia or non-Hodgkin's lymphoma) with a significant increase in plasma paraprotein trending over time.

Starting criteria

The decision to commence treatment with rituximab must be made in conjunction with the patient and by the relevant multi-disciplinary team (MDT). Individual Trusts will have policy documents for rituximab prescription, which should be followed.

Reference should be made to the Summary of Product Characteristics (SmPC) when considering treating patients with rituximab, in particular section 4.3 Contraindications, section 4.4 Special warnings and precautions for use and section 4.6 Fertility, pregnancy and lactation.

Baseline investigations should include a full blood count, liver function tests serum creatinine levels and immunoglobulin subsets (IgG, IgM and IgA) and a baseline CD-19[4] count.

HIV and hepatitis B/C virus Ab screening should also be performed.

TB Screening[5] should take place to rule out active and latent TB before starting treatment.

Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV.

Consideration can be given to a VZV vaccination in antibody-negative patients, 6 weeks before starting treatment.

Immunisation records should be reviewed and where possible any relevant outstanding vaccines administered prior to initiating treatment with rituximab. The green book recommendations should be followed.

[4] A CD-19 count is a surrogate marker for the CD-20 count.

[5] TB screening involves a TB symptom screen and one of the TB Elispot or the Quantiferon tests depending on whether or not the patient is immunosuppressed/on immunosuppressants. This would be followed by a chest x-ray if they have either a reactive TB Elispot/two indeterminate TB Elispot results or a positive quantiferon/two borderline quantiferon results. Treatment with rituximab can proceed if chest X-ray is normal and the patient is asymptomatic (no cough, weight loss, fever, night sweats etc.)

As per manufacturer guidance, patients with positive hepatitis serology should be referred to a liver specialist for monitoring and initiation of antiviral therapy before treatment initiation; treatment should not be initiated in patients with evidence of current hepatitis B infection until the infection has been adequately treated.

HIV infection is not an absolute contraindication to the use of rituximab, and the risk-benefit of rituximab in this setting should be evaluated on a case-by-case basis. In individuals with well controlled HIV infection and normal CD4 counts are unlikely to be at significantly increased risk of adverse events from rituximab.

Chest x-ray for TB screening, hepatitis C virus Ab screening and HIV screening need not be repeated before the second dose and subsequent doses of rituximab unless there is new pertinent history or findings (e.g.; cough with fever; jaundice, sex without contraception, behaviour putting the patient at risk).

Dosing criteria

The rituximab biologic with the lowest acquisition costs should be used. This is likely to be a rituximab biosimilar. Four doses of rituximab of 375 mg/m^2 body surface area should be given intravenously once a week for four weeks.

It is possible that only 1 cycle of rituximab may be required to achieve disease remission. Further cycles of treatment will be considered after at least 6 months guided by clinical relapse and serological monitoring of CD-19 count.

Stopping criteria

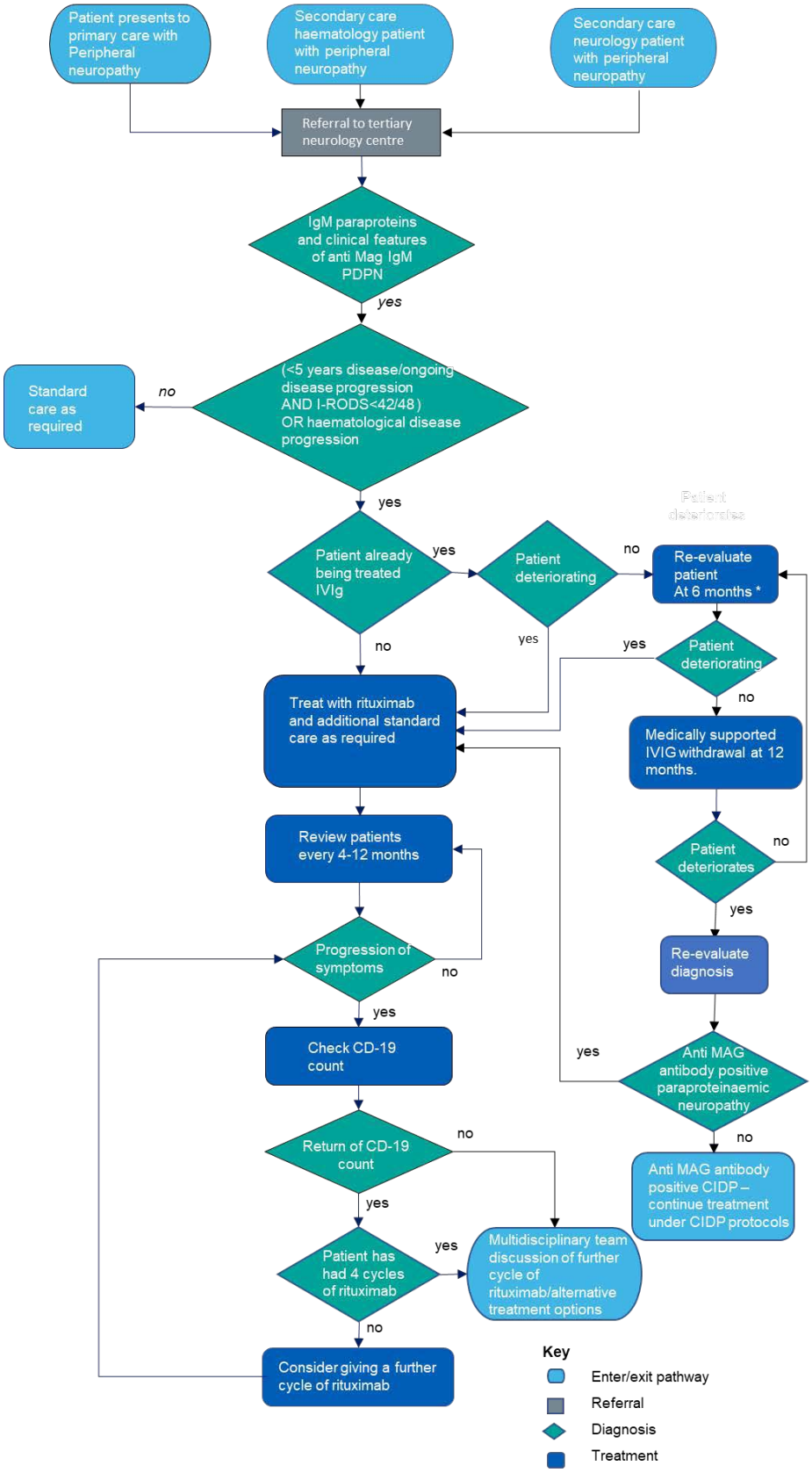
Reference should be made to the SmPC, in particular section 4.4 'Special warnings and precautions for use', for the criteria for permanent discontinuation of treatment with rituximab.

Treatment with rituximab should be stopped if:

- Neuropathy symptoms fail to stabilise or improve after 2 cycles of treatment as assessed using a validated outcome measure.
- A patient develops an infusion-related reaction including cytokine release syndrome.
- The patient is unable to tolerate the side effects of treatment.
- There should be permanent discontinuation of treatment for:
    - Patients who have developed progressive multifocal leukoencephalopathy [6] after treatment with rituximab.
    - Patients who develop severe skin reactions such as Toxic Epidermal Necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome.

[6] Progressive multifocal leukoencephalopathy (PML) is a disease that attacks part of the brain and occurs in people whose immune system is weakened. People with PML have difficulty moving, thinking, and feeling sensations.

Patient pathway



Governance arrangements

The use of rituximab in the treatment of paraproteinaemic demyelinating peripheral neuropathy is outside its Marketing Authorisation i.e. it is off label, any provider organisation treating patients with this intervention will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using approved online prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Mechanism for funding

Reimbursement for the use of rituximab for the treatment of adults with PDPN meeting the criteria within this policy will be managed, through local contract agreements and terms, by the local NHS England Specialised Commissioning Teams. It is expected that new funding will be required to commission rituximab for the treatment of adults with PDPN.

The cost will depend on the rituximab product used, the price of which is commercial in confidence. Only the rituximab product with the lowest acquisition cost will be reimbursed under this policy (likely to be a biosimilar).

Audit requirements

Patients treated for PDPN will be assessed at 6 months, 12 months and thereafter based on clinical need. An appropriate disability measurement score will be used to assess the efficacy of treatment with rituximab. Remission rates following treatment with rituximab will also be monitored.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

analgesics	Medicines used for pain relief.
anti-depressants	A type of medicine used to treat clinical depression.
chemotherapeutic agents	Drugs which are used to treat cancer. They work by targeting cells in the body at different points in the cell formation cycle.
chlorambucil	A medicine which is used to treat some types of cancer and certain blood problems. It works by reducing the number of abnormal cells your body makes.
Corticosteroids	Anti-inflammatory medicines used to treat a range of conditions.
cyclophosphamide	A type of chemotherapy used to treat a number of different types of cancer.
interferon-2-alpha	This medication is the same as a protein that your body naturally produces. Treatment with interferon may improve a person's immunity against cancer or virus infections.
Immunoglobulin M (IgM)	Antibody produced as part of your immune response.
low grade lymphomas	A type of blood cancer where the cells divide slowly so that the cancer develops over a long period of time.
lymphoplasmacytic lymphoma	A rare slow growing cancer of the lymph system, a part of the immune system which helps to fight off infections. In LPL, abnormal B cells (white blood cells) reproduce in the bone marrow and displace healthy blood cells.
Membrane stabilisers	Inhibit the conduction of electrical impulses across the cell wall of nerve cells and thereby produce a nerve block. They are used for pain relief.
monoclonal antibodies	Laboratory-made proteins that mimic the immune system's ability to fight off harmful pathogens such as viruses.
monoclonal gammopathies of undetermined significance (MGUS)	A non-cancerous condition where the body makes an abnormal protein, called a paraprotein. This paraprotein does not do anything useful, and for most people it does not cause any problems.
myelin	A fatty substance that insulates nerve fibres in the body and increases the rate at which electrical impulses are passed along the nerves.
plasmapheresis	This is a medical procedure performed outside the body whereby the liquid part of the blood, or plasma, is separated from the blood cells. The plasma is treated and then returned to the body.
Waldenström macroglobulinaemia	A type of lymphoplasmacytic lymphoma (see definition above).

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