

**Clinical  
Commissioning  
Policy: Rituximab for  
cytopenia  
complicating primary  
immunodeficiency**

Reference: NHS England: 16044/P



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**Additional Circulation List**

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# Clinical Commissioning Policy: Rituximab for cytopaenia complicating primary immunodeficiency

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**Prepared by NHS England Specialised Services Clinical Reference Group for  
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## **Policy Statement**

NHS England will commission rituximab for cytopenia complicating primary immunodeficiency 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 autoimmune cytopenia**

Primary immune deficiency (PID) is a rare inherited illness where the body's immune system does not work properly and attacks itself. The illness can affect one part or many parts of the immune system.

One of the complications of PID is 'autoimmune cytopenia'. This happens when antibodies are produced that do not work properly. Normally, anti-bodies fight infection in the body. In autoimmune cytopenia, the anti-bodies attack the blood cells in the body.

### **About the current treatment**

Current treatments include:

- anti-bodies given into a vein called 'intravenous immunoglobulin' (IVIG)
- steroids - a type of medicine that reduces the immune response ('immunosuppressants')

A high number of patients become sick again and need other treatments.

### **About the new treatment**

Rituximab is a biological medicine that is already used to treat other types of cytopenia ('primary' or 'idiopathic'). It could also be used in patients with PID that leads to autoimmune cytopenia.

### **What we have decided**

NHS England has carefully reviewed the evidence to treat autoimmune cytopenia 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 for autoimmune cytopaenia arising as a complication of primary immune deficiency.

This policy considers commissioning the anti-CD20 agent rituximab for the management of autoimmune cytopaenia arising as a complication of primary immune deficiency (PID).

Autoimmune complications of PID are protean, debilitating and expensive in terms of morbidity and mortality. Many of these autoimmune complications are similar to those of other cohorts for which policies exist such as rheumatoid arthritis, systemic lupus erythematosus (SLE), autoinflammatory conditions and sarcoidosis.

Rituximab, an anti-CD20 agent, is licensed in adults to treat two forms of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, severe rheumatoid arthritis and two forms of severe vasculitis (EMA/614203/2010). It is not licensed for the management of the proposed indication.

## 2 Definitions

Primary immune deficiency (PID) is a rare condition resulting from the failure of the immune system to produce sufficient antibodies or mount an adequate cellular immune response to fight infections.

PID has more than 250 subgroups of chronic disorders in which part of the body's immune system is missing or functions improperly, caused by hereditary or genetic defects. Although some disorders present at birth or in early childhood, the disorders can affect anyone, regardless of age or gender. Some affect a single part of the immune system; others may affect one or more components of the system and patients with PID commonly have an increased susceptibility to infection.

The autoimmune cytopaenias are characterised by the production of antibodies against blood cells and include autoimmune haemolytic anaemia (AIHA),

autoimmune neutropenia (AIN), autoimmune thrombocytopenia (ITP) or various combinations of these conditions. They may be idiopathic (primary) or associated with an underlying malignancy, other systemic autoimmune disorders or may be drug-induced. Many patients respond to first-line therapy with corticosteroids although a high proportion relapse and require alternative therapy.

Rituximab (trade name MabThera), an anti-CD20 agent, is a genetically engineered chimeric monoclonal antibody that depletes the B-cell population by targeting cells bearing the CD20 surface marker.

### **3 Aims and Objectives**

This policy proposition aims to define NHS England's commissioning position on rituximab as part of the treatment pathway for patients with autoimmune cytopaenia arising as a complication of primary immune deficiency.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for people with of autoimmune cytopaenia arising as a complication of primary immune deficiency.

### **4 Epidemiology and Needs Assessment**

Data from the UKPID Register (2008-2012) shows the prevalence of PID is approximately 3.5/100,000 of the UK population (Edgar et al., 2013.). The number of patients on the UK PID register in 2012 was 2,222, of whom 1,328 had predominant antibody deficiencies, the minimum prevalence of predominantly antibody deficiency is 2.1/100,000 of the UK population (Edgar et al., 2013). The majority of these patients will be on immunoglobulin therapy for antibody replacement.

The UKPID Register does not have a breakdown of antibody deficiencies into subgroups, so it has not been possible to ascertain the number of patients with cytopaenia. However, a large longitudinal US study over four decades showed that 120 of 473 patients with common variable immune deficiency (the commonest form

of primary antibody deficiency) had autoimmune cytopaenia in the form of ITP and AIHA, either singly or in combination (Resnick et al., 2012).

According to expert clinical opinion, approximately 30% of patients with predominant antibody deficiency (c.398 patients) may develop autoimmune/autoinflammatory complications with high morbidity and mortality from respiratory and gastrointestinal failure. In these patients, first line immunosuppressive treatment is not always successful.

## 5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of rituximab for autoimmune cytopaenia as a complication of primary immune deficiency.

Whilst there is limited evidence in this specific subgroup of patients with cytopaenia as a complication of primary immune deficiency, there is a clear rationale for routine commissioning as rituximab is already widely commissioned for refractory autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) outside the setting of PID by CCGs (South Central, North West). An aim of this policy is to address the issue of inequality of access for patients with cytopaenia secondary to PID and to bring their treatment options in-line with patients with primary or idiopathic cytopaenias where rituximab is routinely commissioned by CCGs.

The small amount of low quality evidence, due to the rarity of the condition, also means there are unlikely to be randomised control trials in this specific cohort. The available evidence has been identified in this evidence review and is sufficient to demonstrate equivalent efficacy of the effect of rituximab in primary or idiopathic cytopaenia.

When compared to other treatments, rituximab will avoid splenectomy in already immunocompromised patients and there will be significant offset costs from many patients being able to step back down to their background IVIG dose.

The evidence review sought to answer the following question:

**What is the evidence for the clinical and cost effectiveness for rituximab for the management of auto-immune cytopenia arising as a complication of primary immune deficiency?**

**Summary:**

### **Background**

A number of primary autoimmune disorders can result in diminished numbers of circulating blood cells. One treatment of this is rituximab, but there is uncertainty about the clinical and cost effectiveness of this approach.

### **Clinical effectiveness**

The evidence review found no systematic reviews or controlled studies and two studies of the effectiveness of rituximab in the treatment of immunodeficiency-associated immune cytopenia:

- Gobert et al reported a study of 33 people (29 adults) with common variable immunodeficiency complicated by cytopenia. The participants experienced 34 episodes of immune thrombocytopenia and/or autoimmune haemolytic anaemia, of which 24 (74%) responded completely to rituximab, and four (12%) responded partially. Half of the responses lasted more than a year.
- Kim et al reported a smaller study of eight children with various primary immunodeficiency disorders and cytopenia. Seven (88%) responded fully, and the eighth child's haemolytic anaemia responded, though the thrombocytopenia did not. During follow-up, participants nearly all relapsed, but their relapses responded to a further course of rituximab.

### **Cost effectiveness**

No health economic studies of rituximab for cytopenia from primary immune deficiency were found.

## **Safety**

The use of rituximab has been associated with severe infection, pancytopenia and hypogammaglobulinaemia.

## **6 Criteria for Commissioning**

Rituximab will only be commissioned for those patients who meet the following criteria:

- Patients with intractable cytopaenia who have failed to respond to standard therapies (steroids and higher doses of intravenous immunoglobulin (IVIG)), or are contraindicated for standard therapies; AND
- Patients have been provided with information on potential adverse effects.
- Second, or further courses of treatment would start if platelet count falls to  $<30 \times 10^9/L$ , and the patient is symptomatic.

### **Stopping criteria:**

- If a patient has not responded to treatment with rituximab.
- If splenectomy becomes the more beneficial treatment option for the patient.

### **Contraindications**

- Rituximab is contraindicated in people with severe heart failure or severe and uncontrolled cardiac disease.

## **7 Patient Pathway**

Autoimmune cytopaenias are diagnosed with blood tests measuring levels of platelets and haemoglobin. A specialist such as a clinical immunologist, haematologist or oncologist typically evaluates patients for these disorders. Sometimes a bone marrow sample needs to be obtained to determine whether there is a problem with production of blood cells.

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First line treatment is focused on steroids and higher doses of intravenous immunoglobulin (IVIG). Some patients with mild autoimmune cytopaenias may require little to no treatment.

All patients are regularly monitored, measuring platelet count (patients with ITP) and haemoglobin (patients with AIHA). Approximately 30% of patients develop complications or do not respond to first line treatment. If this happens, the dose of IVIG is increased, and second line treatment options are considered including immune suppression with conventional immunosuppressants or corticosteroids. Failure to respond to these treatments will lead to consideration of rituximab, and patients will be provided with information on potential adverse effects. Of patients with autoimmune cytopaenia, less than 10% of patients are treated with rituximab.

The current standard dose is not clear from the literature. The decision around dosage will need to be taken locally by the clinician treating the patient as part of an MDT. Healthcare professionals may refer to the Summary Product Characteristics for further prescribing information.

Rituximab is normally administered intravenously on a day case basis. If this treatment is successful, the dose of IVIG is reduced back to the usual maintenance dose. The patient's condition is monitored by regular blood tests.

If treatment with rituximab does not work, further treatment options include other anti CD20 agents, splenectomy or cytotoxic immunosuppressive agents, which are non-selective in their mechanism of action and can be associated with considerable toxicity. For ITP, further treatment options include romiplostim and eltrombopag.

Most patients can be treated successfully and have no major restrictions on their daily activities. However patients with chronic resistant disease who do not respond to first or second line treatment are at particular risk of life threatening bleeding (severe ITP), life threatening anaemia (severe AIHA) or systemic sepsis (severe AIN).

## **8 Governance Arrangements**

The decision to use rituximab would be subject to an agreed specialist MDT that must include a haematologist and an immunologist, and in discussion with the patient.

Treatment takes place in a specialist centre, and continued use would be subject to evidence of effectiveness at a patient level.

The provider shall have access to support from other clinical specialties for complications of PID including: ear, nose and throat medicine, respiratory medicine, gastroenterology, infectious diseases, haematology, oncology, paediatrics, clinical genetics, and rheumatology.

## **9 Mechanism for Funding**

Rituximab is no longer listed on the NHS Payment Scheme Annex A (high-cost drugs), so use of this drug is in-tariff.

## **10 Audit Requirements**

All centres are expected to participate in national registry data collection, training, examination, peer inspection and guideline development for UKPIN and research into PID as an orphan disease.

Data on these patients should be submitted to the UKPIN registry including follow-up data and time to relapse after each rituximab dose.

## **11 Documents which have informed this Policy**

NHS England Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults. 2013

NHS England Clinical Commissioning Policy. Rituximab for the treatment of ANCA-associated vasculitis in adults. 2015

Autoimmune haemolytic anaemia: Rituximab, NICE Advice [ESUOM39], February 2015

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Immune (idiopathic) thrombocytopenic purpura: Rituximab, Nice Advice [ESUOM35], October 2014

Rituximab for the treatment of Immune (Idiopathic) Thrombocytopenic Purpura (ITP), NHS Northern Treatment Advisory Group, 2015

Rituximab therapy for refractory autoimmune haemolytic anaemia or idiopathic thrombocytopenic purpura, Stockport CCG, 2009.

## **12 Date of Review**

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

## References

Edgar JD et al. Clinical Experimental Immunology (2013) The United Kingdom Primary Immune Deficiency (UKPID) Registry: Report of the first 4 years' activity 2008-2012.

Gobert D, Bussel JB, Cunningham-Rundles C, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol 2011; 155: 498-508.

Kim JJ, Thrasher AJ, Jones AM, et al. Rituximab for the treatment of autoimmune cytopenias in children with immune deficiency. Br J Haematol 2007; 138: 94-6.