NHS England

Clinical Commissioning Policy Proposition:

Rituximab for cytopaenia complicating primary immunodeficiency

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Clinical Commissioning Policy Proposition: Rituximab for cytopaenia complicating primary immunodeficiency

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Plain Language Summary

This policy confirms NHS England's commissioning approach to rituximab for the treatment of adults and children with autoimmune cytopaenia as a complication of primary immune deficiency (PID).

PID is a rare inherited condition in which the body's immune system does not function properly and attacks itself. The disease can affect a single part of the immune system or it may affect more than one component of the system. Antibodies are proteins that fight infection, and the disease autoimmune cytopaenia occurs when antibodies are produced that do not function properly and attack the body's blood cells. Many people respond to first-line therapy with intravenous immunoglobulin (IVIG) and steroids although a high proportion of patients become sick again and require alternative therapy.

The aim of this policy proposition 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.

On the basis of the evidence considered and the options available to patients, NHS England has concluded that rituximab should be routinely commissioned as a treatment option for people with autoimmune cytopaenia, a complication of primary immune deficiency.

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 document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

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 for autoimmune cytopaenia arising as a complication of primary immune deficiency will 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

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

Autoimmune complications of primary immunodeficiency disease (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.

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

3. Definitions

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. Rituximab can produce durable responses and may help avoid the need for splenectomy in some patients.

4. Aim 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.

5. 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., 2014.). 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., 2014). 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.

6. 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 very 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

• We found no systematic reviews or controlled studies.

• We found two studies of the effectiveness of rituximab in the treatment of immunodeficiency-associated immune cytopenia:

o 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.

o 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
• We found no health economic studies of rituximab for cytopenia from primary immune deficiency.

Safety
• The use of rituximab has been associated with severe infection, pancytopenia and hypogammaglobulinemia.

7. Proposed 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

If a patient responds to treatment then there would be no limit to the number of further courses provided that:
• The patient continues to respond
• The patient continues to require treatment after remission

Starting criteria
• Second, or further courses of treatment would start if platelet count falls to <30 x 109/L, and the patient is symptomatic

Stopping criteria:
• If a patient has not responded to treatment of 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

8. Proposed 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.

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, Gobert et al. (2011) identify standard doses of 375mg/m2 weekly for 4 weeks, and 100mg/m2 weekly for 4 weeks. The latter dose is widely used in a number of centres in the UK. The decision around dosage will need to be taken locally by the clinician treating the patient as part of a MDT.

Rituximab is normally administered 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).

9. Proposed 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.

10. Proposed mechanism for funding

Funding for rituximab for autoimmune cytopaenia as a complication of primary immune deficiency will be via the local specialised commissioning team.

11. Proposed 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.

12. Documents which have informed this policy proposition

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

Rituximab for the treatment of ANCA-associated vasculitis in adults, NHS England, 2015

Autoimmune haemolytic anaemia: Rituximab, NICE Advice, ESUOM39, 2015

Immune (idiopathic) thrombocytopenic purpura: Rituximab, Nice Advice, ESUOM35, 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

13. Date of review

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