NHS England

Clinical Commissioning Policy: The use of Rituximab as a second line agent for the eradication of inhibitors in patients with Acquired Haemophilia

Reference: NHS England F02/P/a

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Publications Gateway Reference:	**03727**
Document Purpose	Policy
Document Name	F02/P/a Rituximab for Acquired Haemophila
Author	Specialised Commissioning Team, NHS England
Publication Date	July 2015
Target Audience	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists
Additional Circulation List	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
Description	NHS England will routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	
Superseded Docs (if applicable)	
Action Required	
Timing / Deadlines (if applicable)	
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Document Status

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1 Executive summary

Policy Statement

NHS England will commission rituximab for second line treatment in the eradication of inhibitors for patients with acquired haemophilia 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

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

Acquired haemophila A is a rare condition caused by abnormal break-down of factor VIII in the blood stream. Without factor VIII the blood cannot clot normally, and this can result in spontaneous, uncontrolled bleeding.

The high risk of serious or even fatal bleeding means that acquired haemophilia must be treated as soon as it is diagnosed. Treatment includes controlling bleeding episodes and attempting to stop production of the abnormal antibody (called an inhibitor) which is destroying factor VIII.

If first line treatment for removal of the inhibitor is not successful then rituximab may be used. There is a reasonable level of research evidence to suggest that rituximab is usually effective in removing factor VIII inhibitors where first line treatments have failed.

The agents used to control bleeding episodes in acquired haemophilia are very high cost. This means that the use of rituximab is as a second line treatment is likely to be highly cost-effective, because effective inhibitor removal will avoid the need for further use of these agents.

2 Introduction

Acquired haemophilia A (AHA) is a rare condition caused by production of autoantibodies which inactivate factor VIII (known as inhibitors). It must be distinguished from congenital haemophilia A, which is an inherited disorder caused by mutations in the FVIII gene.

AHA is characterised by spontaneous haemorrhage or by bleeding induced by surgery, trauma or other invasive procedures in patients with no previous family or personal history of haemophilia. The pattern of bleeding varies from superficial bruising that requires no haemostatic therapy in approximately one-third of patients to fatal bleeding, for example, intracranial, retroperitoneal, and gastrointestinal in between 8% to 22% of patients.

Although approximately one-third of patients with AHA will experience a spontaneous remission, the high risk of a fatal haemorrhage necessitates immediate treatment once the condition is diagnosed. The management of AHA is directed to the control of bleeding episodes and the eradication of the inhibitor. Patients remain at risk of severe and fatal haemorrhage until the inhibitor has been eradicated, irrespective of the initial factor VIII level and inhibitor titre, and even if they present with mild bleeding. For this reason, treatment guidelines recommend that patients are treated with immunosuppression as soon as the diagnosis has been made, with the aim of eradicating the inhibitor and normalising the factor VIII level.

Immunosuppressive therapies commonly used for the eradication of inhibitors include prednisolone with or without cyclophosphamide, azathioprine, immunoglobulins and ciclosporin. More recently rituximab has been used in the treatment of AHA especially in patients who relapse after first line treatment.

Management of bleeding episodes caused by AHA also involves the use of high-cost bypassing agents such as activated prothrombin complex concentrate or recombinant activated factor VII (rFVII) to control bleeding episodes. Effective inhibitor eradication will therefore reduce the use of activated prothrombin complex concentrate or rFVII in these patients.

3 Definitions

Rituximab: a monoclonal antibody directed against B lymphocytes (a type of whiteblood cell). Rituximab causes depletion of B lymphocytes, including those producing the autoantibodies. It is used in a range of autoimmune disorders, including various haematological diseases.

4 Aim and objectives

The aim of this policy is to prevent severe and potentially fatal bleeding episodes in patients with AHA.

The objectives are to:

- support the cost-effective use of NHS resources.
- ensure equitable access to rituximab as a second line treatment for patients with AHA who have failed first line immunosuppressive treatment.
- avoid the long term costs associated with the use of haemostatic agents in patients with a persistent inhibitor.

5 Epidemiology and needs assessment

The incidence of AHA is about 1.5 per million population per year; it is considerably rarer than the inherited form. It is mainly a disease of older people, with a median age at presentation of 75-80 years. The incidence in males and females is similar, with an exception in the 20-40 year age interval where rate is higher in females due to pregnancy-related cases[11-14].

The cause of inhibitor development in AHA is unknown in about 50% of patients affected. In the remaining 50% a causative underlying condition such as malignancy or rheumatological diseases can be identified.

Activity and cost

As of March 2012, 345 patients with acquired haemophilia were recorded on the UK National Haemophilia Database, 76 of whom received treatment between April 2011 and March 2012.

Modelling has been undertaken to compare data on the cost of the current treatment pathway for AHA including the cost of treating bleeding episodes with the cost of treatment using rituximab as a second line treatment to eradicate the inhibitor.

Treatment of AHA involves the use of bypassing agents such as activated prothrombin complex concentrate or recombinant activated factor VII (rFVII) to control bleeding episodes as well as the eradication of the inhibitor with immunosuppressants. Patients remain at risk of severe and fatal haemorrhage until

the inhibitor has been eradicated. Effective inhibitor eradication will therefore reduce the use of activated prothrombin complex concentrate or rFVII in these patients.

The cost of treating a single bleeding episode with activated prothrombin complex concentrate (2 treatment doses) or recombinant factor VII (three treatment doses) in an inpatient setting is significant and more costly than day case administration of rituximab.

6 Evidence base

Clinical effectiveness

Due to the rarity of the condition there is a paucity of literature on the use of rituximab in the management of AHA, and prospective randomised trials assessing its efficacy have not been performed. The literature search undertaken for the purposes of developing this policy found two systematic reviews of case reports, case series and open-label trials. The most recent systematic review, by Franchini, includes all the studies included in the earlier review.

The Franchini review included 27 studies (19 case reports, 7 case series and 1 open label trial). Complete remission was reported in 57 of the 65 participants, partial response in 2, minor response in 1 and no response in 5 participants. This suggests that rituximab appears to be an effective option for patients with AHA for who established therapies have failed. . However the data were not derived from prospective studies but mainly from case reports describing isolated cases, and positive outcomes were likely to be preferentially reported. The data are also confounded by the concomitant immunosuppressive agents administered in the majority of cases, making it difficult to determine the specific effect or contribution of rituximab. The follow-up in most of the included studies was too short (less than 12 months) to make firm conclusions regarding the long term efficacy of rituximab.

Cost effectiveness

No published analyses of the cost-effectiveness of rituximab in AHA have been identified.

Safety

Data from the European Acquired Haemophilia Registry (EACH2) show that 37% of patients treated with rituximab report at least 1 adverse event which is similar to that reported for the treatment with steroids and cyclophosphamide. The most commonly reported side effect was diabetes (22%) followed by neutropenia (18%) and infection (12%).

7 Rationale behind the policy statement

There is reasonable evidence for the clinical effectiveness of rituximab as a second line treatment for the eradication of inhibitors in AHA.

- Patients with AHA are at high risk of severe and fatal haemorrhage until the inhibitor has been eradicated.
- The cost of inpatient care and bypassing drug treatments to control bleeding in patients with a persistent inhibitor generally exceeds the investment required for day-case administration of rituximab.

Rituximab appears to have a safety profile similar to first line and other agents used to treat AHA inhibitors, and considerably safer than the risks associated with a persistent inhibitor.

8 Criteria for commissioning

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

Rituximab will be routinely commissioned for patients with confirmed AHA where

- All patients should have undergone a 3-5 week trial of first line treatment before rituximab is considered, and
- Rituximab is given only as second line treatment for patients who fail first line immunosuppressive treatment for AHA, and who have no clinical

contraindication to rituximab (e.g. allergic reaction, history of cardiovascular disease), and

- Treatment is provided in specialised haemophilia centres, as defined by the NHS England service specification for specialised haemophilia services.

Exclusion criteria

Rituximab will not be routinely commissioned

- For patients without confirmed AHA
- As a first line immunosuppressive treatment for AHA
- Prescribed at providers who are not commissioned as specialised haemophilia centres, as defined by the NHS England service specification for specialised haemophilia services.

Cost

This policy has been agreed on the basis of NHS England's understanding of the likely price of care associated with enacting the policy for all patients for whom NHS England has funding responsibility, as at the time of the policy's adoption. Should these prices materially change, and in particular should they increase, NHS England may need to review whether the policy remains affordable and may need to make revisions to the published policy.

9 Patient pathway

The clinical care of patients with AHA will be provided by, or under the supervision of, a specialised haemophilia centre.

10 Governance arrangements

The management of patients with AHA is governed by the national service specification for patients with haemophilia and other bleeding disorders.

11 Mechanism for funding

Funding to the provider will be in accordance with their agreed tariff arrangements.

12 Audit requirements

Data for all patients with AHA, including details of rituximab and other treatment must be submitted to the National Haemophilia Database.

Specialised haemophilia services must be able to provide audit data which demonstrate compliance with the criteria for the use of rituximab.

13 Documents which have informed this policy

Collins PW, Chalmers E, Hart DP et al. Diagnosis and management of acquired coagulation inhibitors: a guideline from UKHCDO. British Journal of Haematology 2013; 162:758-773.

14 Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

15 Date of review

This policy will be reviewed in 2016/17 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

1. Wiestner A, Cho HJ, Asch AS et al. Rituximab in the treatment of acquired FVIII inhibitor. Blood 2002;100:3426-3428.
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