NHS England

Clinical Commissioning Policy: Rituximab for the treatment of Idiopathic Membranous Nephropathy in adults

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Clinical Commissioning Policy: Rituximab for the treatment of Idiopathic Membranous Nephropathy in adults

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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.

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1 Executive Summary

Policy Statement

NHS England will not routinely commission Rituximab for the treatment of Idiopathic Membranous Nephropathy in adults.

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.

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 proposition describes NHS England's commissioning approach for the use of rituximab in the treatment of people with Membranous Nephropathy.

Kidneys are organs that help filter waste products from the blood. Membranous Nephropathy (MN) is a rare kidney disease. It causes distressing symptoms including

severe swelling of the legs and sometimes kidney failure. The worst affected patients eventually require kidney dialysis or a kidney transplant. There are established treatments for Membranous Nephropathy but none are 100% effective and all are associated with side effects. These treatments work by suppressing the body's natural immune system. Their side effects can be serious, such as severe infections requiring admission to hospital. Rituximab is a drug that doctors believe may work to treat some types of kidney disease that are not responding to the usual treatments. The NHS requires more information about how well Rituximab works compared to conventional treatments, how safe it is and how cost-effective it is.

This policy proposition has considered the available evidence and found that there is currently insufficient evidence for NHS England to routinely commission rituximab for the treatment of Membranous Nephropathy.

2 Introduction

The aim of treatment of Membranous Nephropathy (MN) is both supportive and immunomodulatory. Supportive treatment is largely based on medications that block the renin angiotensin aldosterone system (RAAS blockade), using angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). Diuretics are used to address oedema and statins to treat secondary dyslipidaemia. In contemporary observational cohort studies, where patients have received these supportive treatments, up to 70% of patients achieve partial or complete remission at 5 years. Because of this natural history, most UK physicians will adopt a supportive approach for 6-12 months after diagnosis. Clinical features that predict progressive CKD include very heavy proteinuria (>8g/day, especially where this is prolonged), impaired kidney function at diagnosis or early in the course of the disease.

Where supportive therapy has failed to induce partial or complete remission of NS, immunomodulatory treatment is considered. There is evidence from randomized controlled trials (RCT) to support regimes based on alkylating agents (cyclophosphamide or chlorambucil) or calcineurin inhibitors (CNI - cyclosporine or tacrolimus), in combination with corticosteroids. Where there is impairment of kidney function, either at diagnosis or during supportive therapy, alkylating agents are the

preferred therapy. 88-92% of patients with moderate disease will be dialysis free at 10 years if treated by an alkylating agent, compared to 32-47% of controls. Use of alkylating agents is associated with significant complication including leucopoenia, infection, secondary infertility and a late malignancy risk. CNIs are also associated with significant complication including hypertension, progressive CKD, dyslipidaemia and a spectrum of metabolic abnormalities. Corticosteroids add to the morbidity associated with these regimes.

3 Definitions

Membranous Nephropathy (MN) is a rare disease with an incidence of 6-10 per million population per year. 25% of MN cases are secondary to malignancy, infection, medications or systemic autoimmune disease (usually Systemic Lupus Erythematosus). In 75% of cases, no underlying associated pathology can be identified and the disease is termed idiopathic. This policy refers only to idiopathic cases of MN.

MN is the most common biopsy proven cause of nephrotic syndrome (NS) in Caucasian adults. This policy refers only to idiopathic cases of MN. Membranous Nephropathy results in:

1. Debilitating symptoms and complications of NS, the latter of which include hospitalization with infection and venous thromboembolism.
2. There is a risk of progressive chronic kidney disease (CKD), including established renal failure (ERF)

Rituximab is a chimeric monoclonal antibody that depletes human B Cells and is given by intravenous infusion in specialist centres. After therapy, peripheral B Cells are depleted for 6-12 months. It is licensed for the treatment of certain lymphomas / leukaemias, rheumatoid arthritis and ANCA associated vasculitis.

Rituximab is not licensed for the treatment of MN.

4 Aims and Objectives

Rituximab is a potentially promising, unlicensed therapy for a serious disease that is difficult to treat, but at the current time there is an insufficient quality and quantity of

evidence to support routine commissioning by NHS England. Rituximab has been used off-license to treat MN but at the present time there are no published RCTs

The evidence considered the use of rituximab in membranous nephropathy in adults, particularly in patients with relapsing disease, with primary treatment failure or with adverse reactions or contra-indications to cyclophosphamide or calcineurin inhibitors.

5 Epidemiology and Needs Assessment

Membranous Nephropathy (MN) is a rare disease with an incidence of 6-10 per million population per year. 25% of MN cases are secondary to malignancy, infection, medications or systemic autoimmune disease (usually Systemic Lupus Erythematosus). In 75% of cases, no underlying associated pathology can be identified and the disease is termed idiopathic. This policy refers only to idiopathic cases of MN.

6 Evidence Base

Rituximab has been used as immunomodulatory treatment in MN. The evidence for the use of MN is presented in a recent evidence review published by NHS England. There are no RCTs assessing the efficacy, safety and cost-effectiveness or Rituximab in MN. At the time of writing, there were 12 publications describing experience with Rituximab in MN, 10 case series (Scottish Intercollegiate Guidelines Network [SIGN] level 3 evidence) and 2 cohort studies (SIGN level 2 evidence). The majority of the studies are small (7-28 plus one case series of 100) and there is probably some overlap of included patients. The majority assessed Rituximab as a secondary therapy for MN. Most assessed a treatment regime of Rituximab 375mg/m^2, four doses at weekly intervals, but some used the alternative regime of two doses of 1000mg on day 1 and 15. The results can be summarised:

1. Efficacy
    a. Reduction in proteinuria at 12 months 48-66%

b. Remission at 12 months 45-75%
c. Insufficient data to report on progression to ERF

7 Rationale behind the Policy Statement

There is emerging evidence showing there may be benefit in the use of rituximab for the treatment of idiopathic membranous glomerular nephritis (IMN) in native kidney patients. However, this is based on weak study designs (majority of studies are cases series from a single centre) with small sample sizes lacking controls patients who are given other immunosuppressive drugs or conservative therapy alone. Therefore, from the studies, spontaneous remission rather than therapeutic effect of the rituximab cannot be formally ruled out. In addition, there were significant variations in treatment protocols across studies. There are also indications that a significant number of patients in studies followed up for 12 months and above relapsed requiring a second course of rituximab.

8 Criteria for Commissioning

Where an individual's clinician believes that there may be exceptional clinical circumstances that might warrant consideration of funding outside of this policy, an application can be made under NHS England's Individual Funding Request (IFR) procedure. This includes cases that may be considered clinically critically urgent. Please see NHS England's website for more details.

This policy proposition has considered the available evidence and found that there is currently insufficient evidence for NHS England to routinely commission rituximab for the treatment of Membranous Nephropathy.

9 Patient Pathway

Not applicable.

10 Governance Arrangements

Not applicable.

11 Mechanism for Funding

Not applicable.

12 Audit Requirements

Not applicable.

13 Documents which have informed this Policy

Not applicable.

14 Links to other Policies

Not applicable.

15 Date of Review

March 2019

16 References

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