Clinical Commissioning Policy: Rituximab for immunoglobulin G4-related disease (IgG4-RD)

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Clinical Commissioning Policy: Rituximab for immunoglobulin G4-related disease (IgG4-RD)

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Prepared by NHS England Specialised Services Clinical Reference Group for Specialised Rheumatology

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Contents

Policy Statement

NHS England will commission rituximab for immunoglobulin G4-related disease (IgG4-RD) 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 Immunoglobulin G4-related disease

Immunoglobulin G4-related disease (IgG4-RD) is an illness that has only recently been identified.

- It is caused by cells in the blood stream that make harmful substances – these attack the body's own tissues.
- This can lead to problems that affect multiple organs at the same time.
- The signs can vary - some patients have no signs of illness at all, others may be mild and some can cause severe organ damage and even death if not treated.

About the current treatment

Treatments will usually include medicines that reduce the body's immune response, such as steroids and immuno-suppressants.

About the new treatment

Rituximab is a biological medicine that works by 'targeting' specific proteins (receptors) on the surface of cells relevant to the cause of the disease. It can work to remove the harmful cells in IgG4-RD.

It may be used to treat IgG4-RD in patients:

- who cannot have other treatments
- who have side effects from other treatments
- when other treatments no longer work well enough.

Although rituximab is licensed in the UK for other illnesses, it is not licensed for the treatment of IgG4-RD.

What we have decided

NHS England has carefully reviewed the evidence to treat IgG4-RD with rituximab. We have concluded that there is enough evidence to consider making the treatment available for a small number of highly selected patients with IgG4-RD.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a policy to routinely commission rituximab for patients with IgG4-RD for a small number of highly selected patients.

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognised immune-mediated chronic condition that links several disorders previously seen as unrelated. Recognised as a unified entity only a decade ago, the disease is caused by plasma cells producing the antibody subtype IgG4 which results in mass-forming tissue destructive lesions, with the three key pathologic features of IgG4-RD being lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis.

Conditions once regarded as autoimmune/idiopathic disorders but now recognised to be part of IgG4-RD include: autoimmune pancreatitis, cholangitis, periaortitis, retroperitoneal fibrosis with ureteric obstruction, orbital masses, pulmonary nodules / interstitial or airway involvement, thyroiditis, dacryoadenitis, sialadenitis, renal tubulo-interstitial nephritis or membranous glomerulonephritis, lymphadenopathy, testicular masses, prostatitis, pericarditis, mastitis and perineural disease. Symptoms, if any, are usually mild and include the presence of painless swellings and mass lesions. Nevertheless, IgG4-RD can cause severe organ damage and even death if left untreated.

Rituximab is an anti-CD20 chimeric monoclonal antibody. It depletes circulating B-cells and prevents their maturation into a sub-set of antibody-secreting plasma cells that produce IgG4 autoantibodies. Rituximab has been commissioned in IgG4-RD as a third line therapy to control IgG4- RD and prevent further disease progression to fibrosis and organ damage. The eligible patient group is relapsed patients with active disease that is no longer controlled with conventional therapies who, either fail to respond to primary treatment, or with adverse reactions or contraindications to corticosteroids plus azathioprine or methotrexate or mycophenolate mofetil.

2 Definitions

Immunoglobulin G is a type of antibody which has an important role in human immunity.

Immunoglobulin G4 (IgG4) is a subclass of immunoglobulin G.

Rituximab (trade name MabThera® in the UK) is a biological therapy. It removes a type of cell called B-cells. Some B-cells produce harmful antibodies which attach the body's own tissues (Arthritis Research UK).

Azathioprine (Imuran®), methotrexate (MaxTrex®) and mycophenolate mofetil (CellCept®) are all immunosuppressive disease-modifying anti-rheumatic drugs (DMARDs) that dampen the underlying disease process rather than simply treating symptoms.

3 Aims and Objectives

This policy aims to define NHS England's commissioning position on rituximab as part of the treatment pathway for adult patients with IgG4-related disease.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with IgG4-related disease.

4 Epidemiology and Needs Assessment

IgG4-RD is rare (estimated incidence 60 per million / 0.28 – 1.08 per 100,000 population (Uchida et al., 2012)).

IgG4-RD generally occurs most commonly in middle-aged and older men. This is certainly true for conditions such as type 1 (IgG4-related) autoimmune pancreatitis, retroperitoneal fibrosis, IgG4-related tubulointerstitial nephritis, and many other organ manifestations. However, the gender distribution differs somewhat with regard to patients with involvement of organs of the head and neck. As examples, in patients with IgG4-related sialadenitis and IgG4-related ophthalmic disease, males and females appear to be affected more equally (Stone J, 2015).

IgG4-RD can involve one or multiple organs. Patients often present with subacute development of a mass in the affected organ (e.g. an orbital pseudotumour, a renal mass resembling renal cell carcinoma, nodular lesions in the lung) or diffuse enlargement of an organ (e.g. the pancreas). Multiple organs are affected in 60-90% of patients with IgG4-RD. This is associated with significant morbidity and mortality caused by acute renal failure / obstructive uropathy secondary to retroperitoneal fibrosis, cirrhosis and portal hypertension, aortic aneurysms and dissection, biliary obstruction, diabetes mellitus, and other conditions (Stone J, 2015).

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a policy for the routine commissioning of rituximab for patients with IgG4-RD for a small number of highly selected patients. Although there is presently no level 1 evidence, there is a strong rationale for commissioning rituximab in patients with IgG4-RD for the following reasons:

- An RCT would be difficult to perform on such low patient numbers and would have to be undertaken internationally at a high expense;
- The evidence that does exist suggests rituximab is clinically effective, with almost all study participants having clinical and serological responses. More than 75% met the primary outcome and in just under 50% complete remissions were sustained for at least six months, with 40% having a disease response for a year. Almost all patients were able to discontinue steroids and DMARDs. Repeated rituximab courses maintained their effectiveness and resulted in further decreases in IgG4 concentrations, better disease control and quiescent disease; and
- Rituximab is a definitive treatment where patients, despite having trialled steroid and other immunosuppressive/immunomodulatory therapies, still have active disease and are at risk of further organ damage or death.

The literature search identified 31 papers, of which 28 were excluded because they did not meet the inclusion criteria. The three papers included in the comparative effectiveness reviews had 44 patients included in them collectively. All three studies were observational with no comparator group.

Is Rituximab clinically effective in the treatment of patients with refractory IgG4-RD which has failed to respond to conventional treatment or with adverse reactions or contraindications to corticosteroids or corticosteroid-dependent?

The three studies conclude that Rituximab is clinically effective; however caution should be exercised in light of the very small number of patients and study design.
Carruthers et al. (2015) conclude that their prospective, single-arm safety/efficacy trial of rituximab provides strong evidence that B-cell depletion is an effective treatment for IgG4-RD. Thirty patients were recruited into this study: it is not clear whether these were recruited consecutively or the extent to which there may be some selection bias inherent in the study design. The mean age of the study population was 61, with 28 of the 30 being male. 13% of the cohort required retreatment during the 12 months after enrolment. At 12 months only 7% of patients required steroids for their IgG4-RD. Fourteen (47%) and 12 (40%) participants achieved and maintained complete remissions through 6 and 12 months, respectively. Considering the extent of organ involvement, patients with limited organ involvement were more likely to achieve complete remission within 6 months compared with those with multi-organ involvement (12/16 vs 6/14 subjects including serum IgG4 in the assessment; $p=0.10$; 14/16 vs 7/14 subjects if serum IgG4 excluded; $p<0.05$). The study concludes that these findings support the observations from smaller retrospective studies, indicating that B-cell depletion is an effective and important treatment for IgG4-RD. Gluco-corticoids (GC) should remain the first treatment approach for most patients at the present time, assuming the absence of major contraindications to GC therapy.

Khosroshahi A et al. (2012) reported in a small uncontrolled observational study with 10 patients that treatment with Rituximab led to prompt clinical and serologic improvement in refractory IgG4-RD in all patients with active inflammation. All patients discontinued steroid and disease-modifying anti-rheumatic drugs (DMARD) following rituximab treatment; however, four patients were retreated at 6 months. It was reported that repeated courses of rituximab may lead to progressive declines in serum IgG4 concentrations and better disease control. It was not reported whether the 10 patients were consecutively recruited, nor whether the study was prospective

or retrospective. Outcomes were assessed at one month; there is no reporting of longer term outcomes.

Khosroshahi A et al. (2010) performed a small (n=4) efficacy study to assess the clinical and serologic responses to B lymphocyte depletion therapy with rituximab in patients with systemic IgG4-RD. It was reported that treatment with rituximab led to prompt clinical and serologic improvement in patients with refractory systemic IgG4-RD. The decline in serum IgG4 concentrations was substantially steeper than that of the auto-antibody concentrations in immune-mediated conditions in which rituximab is effective, such as in rheumatoid arthritis. In addition, the reduction in IgG-subclass levels appeared to be specific for IgG4. Given the small number of patients, caution should be warranted in drawing conclusions from this study.

Is there any evidence to suggest that either the lymphoma protocol or the rheumatoid arthritis protocol produces better clinical outcomes in patients with refractory IgG4-RD which has failed to respond to conventional treatment or with adverse reactions or contraindications to corticosteroids or corticosteroid-dependent?

There was no evidence to answer this question.

Is Rituximab more effective than standard treatment in the treatment of patients with refractory IgG4-RD which has failed to respond to conventional treatment or with adverse reactions or contraindications to corticosteroids or corticosteroid-dependent?

The three studies were observational in design with no comparator group. It is not possible to give an answer to a question of whether Rituximab is more effective than another treatment. All of the studies were conducted in refractory (to steroid or standard DMARDS) patients.

Is Rituximab safe to use in the treatment of patients with refractory IgG4-RD which has failed to respond to conventional treatment or with adverse reactions or contraindications to corticosteroids or corticosteroid-dependent?

The three studies did not directly address this question, thus it is not possible to provide an evidence based answer.

Is Rituximab a cost-effective treatment option for use in patients with refractory IgG4-RD which has failed to respond to conventional treatment or with adverse reactions or contraindications to corticosteroids or corticosteroid-dependent?

There were no cost effectiveness studies. It is not possible to answer this question.

6 Criteria for Commissioning

Inclusion criteria:

Rituximab will be prescribed to patients who have features that meet all of the criteria below as assessed through the MDT arrangements as agreed by the Rheumatology Network.

1. Diagnosed cases: cases with a confirmed diagnosis of IgG4-RD based on:

a) Tissue diagnosis

Tissue biopsy with characteristic histopathology:

i. lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, obliterative arteritis.

ii. Immunostaining

- IgG4 positive plasma cells (diffuse presence) + organ specific values/HPF
- Ratio of IgG4 to IgG positive plasma cells ≥ 40%

b) Imaging to define the extent of organ involvement

E.g. Positron emission tomography (PET) scan

c) Serology

Serum IgG4 concentrations (>135mg/dl), blood plasmablast levels (flow cytometry)

d) Clinical

i. Symptoms (general) – weight loss and fatigue specifically related to organ dysfunction
ii. Single and multi-organ involvement
iii. Signs of organ enlargement, inflammation, compression, obstruction, associated lymph node enlargement, aneurysms/dissections, thickening, nodules, interstitial involvement
iv. Symptoms and signs of advanced organ dysfunction and end stage disease including secondary complications (Diabetes mellitus, hormone deficiencies etc.)

e) Clinical, histopathological, serological and radiological correlation

2. Resistant or relapsing cases: patients on maintenance glucocorticoids with additional immunosuppression +/- severe intolerance, adverse effects or dependent on high doses of glucorticoids.

3. Active disease: Patients with:

a) Persistent disease activity
b) Worsened disease activity
c) New or recurrent disease activity
d) Urgent disease within a critical organ that may lead to organ failure or pose a threat to patient's life, if effective therapy is not begun promptly.

4. Disease assessment to measure and take into account:

a) Physicians global assessment score (mm)
b) IgG4-RD Responder Index Score (mean ± SD)

Exclusion criteria:

1. Patients who have not yet tried first or second line therapies
2. Patients with a known hypersensitivity to previous use of rituximab for another indication

Stopping criteria:

1. Serious adverse events e.g. anaphylaxis
2. Non-adherent
3. Evidence of no response or incomplete response on regular monitoring and a 12 months assessment, following one course of treatment with option to re-treat within a year in case of partial or late responders

7 Patient Pathway

Once diagnosis is confirmed, corticosteroid treatment is a first line therapy, unless the treatment is contra-indicated or the patient is corticosteroid dependent. If the patient shows incomplete response, methotrexate is prescribed second line unless contraindicated; azathioprine or mycophenolate mofetil are alternative second line agents.

If the patient shows incomplete response and/or has significant associated adverse effects such as infection, diabetes, osteoporosis or cardiovascular disease, Rituximab is commissioned as third line treatment.

Dosage: 1g infusion administered on day 1 and again on day 15.

Following rituximab administration through intravenous infusion, B-cell and immunoglobulin levels should be monitored at 3-4 month intervals until relapse (typically every 1-2 years) after which the rituximab course is re-administered.

For those patients who show incomplete response, there are no further pharmacological treatments. Medical treatment appropriate to the organ affected is initiated, e.g. dialysis where IgG4-RD presents in the renal system.

8 Governance Arrangements

All cases must be discussed by an MDT including a clinician with an interest and knowledge of IgG4-RD, as well as the relevant specialist for the affected organ systems. This might typically include rheumatologists, radiologists, gastroenterologists and hepatologists.

Providers must have arrangements for appropriate access to investigations including histopathology, serology, immunopathology and specialised radiology investigations (where this is clinically relevant) such as 18FDG PET-CT (fluorodeoxyglucose) scanning.

IgG4-RD prescribing requires oversight and the governance arrangements for MDTs are to be agreed through the relevant Rheumatology Network.

9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

10 Audit Requirements

A specific IgG4-RD registry should be set up to ethically and robustly create a database of patients with IgG4-RD, their clinical course and outcomes at various centres across the UK. Pending development of a registry the rituximab treatment given and information on the following outcomes should be collected locally following the administration of a course of two intravenous infusions two weeks apart:

- Time to defined clinical response;
- Time to clinical remission;
- Duration of effect;
- Timing of re-treatment;
- Reduction/continuation in steroids/immunosuppressants;
- Frequency of re-treatment;
- Total immunoglobulin levels pre-, and post-treatment; and

- Serious adverse effects.

The above data will be collected and audited annually through the Rheumatology Network. The Annual audit reports on the use of rituximab and specific outcomes in this patient group will be available to the commissioner.

11 Documents which have informed this Policy

NHS England Specialised services specification for Specialised Rheumatology

12 Date of Review

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

References

Carruthers, Mollie N.; Topazian, Mark D.; Khosroshahi, Arezou; Witzig, Thomas E.; Wallace, Zachary S.; Hart, Philip A.; Deshpande, Vikram; Smyrk, Thomas C.; Chari, Suresh; Stone, John H.. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann. Rheum. Dis. 2015;74(6):1171-1177.

Khosroshahi, Arezou; Carruthers, Mollie N.; Deshpande, Vikram; Unizony, Sebastian; Bloch, Donald B.; Stone, John H.. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. Medicine (Baltimore) 2012;91(1):57-66.

Stone ,J; Brito-Zerón , P; Bosch, X; Ramos-Casals M. A Diagnostic Approach to the Complexity of IgG4-Related Disease. Mayo Clin Proc. 2015 Jul;90(7):927-39.

Uchida, K; Masamune, A; Shimosegawa, T; Okazaki, K
Prevalence of IgG4-Related Disease in Japan Based on Nationwide Survey in 2009 International Journal of Rheumatology Volume 2012 (2012), Article ID 358371, 5 pages http://dx.doi.org/10.1155/2012/358371