



Clinical Commissioning Policy Proposition:

Rituximab for immunoglobulin G4-related disease (IgG4-RD)

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

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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

The policy proposition aims to confirm NHS England's commissioning approach to rituximab for patients with immunoglobulin G4-related disease (IgG4-RD).

IgG4-RD is a recently discovered condition which provides a link between diseases previously regarded as unrelated and affecting only one organ. It is caused by cells in the blood stream which produce harmful substances that attack the body's own tissues. In doing so, IgG4-RD can cause many different disorders that affect multiple organs at the same time. Although symptoms may be mild (some patients have no symptoms at all), it can cause severe organ damage and even death if not treated.

Rituximab is a type of drug called a biological therapy. It works by removing the cells which are directly harmful by 'targeting' specific proteins on the surface of cells relevant to the cause of the disease. It may be used to treat IgG4-RD in cases where a patient cannot receive or experiences significant side-effects from other treatments or when the latter have ceased to be effective. Although rituximab is licensed in the UK for other diseases, it is not licensed for the treatment of IgG4-RD.

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of rituximab for patients with IgG4-RD for a small number of highly selected patients.

1. Introduction

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

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 IgG4-RD 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

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognised immunemediated 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 proposed 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.

3. Definitions

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

Immunoglobulin G4 (IgG4): 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 immunosuppresive disease-modifying antirheumatic drugs (DMARDs) that dampen the underlying disease process rather than simply treating symptoms.

4. Aim and objectives

This policy proposition 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.

5. Epidemiology and needs assessment

IgG4-RD is rare (estimated incidence 60 per million / 0.28 – 1.08 per 100,000 population (Uchida et al., Int J Rheumatol, 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, Lancet, 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 pseudotumor, 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 which 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 etc (Stone J, Lancet, 2015).

6. Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal 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, for which it is likely to be difficult to gain funding;

- 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 (RTX) 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.

7. Proposed criteria for commissioning

Inclusion criteria:

Rituximab will be prescribed to patients who meet all criteria below as assessed by MDT

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

<u>a) Tissue diagnosis</u>

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

<u>c) Serology</u>

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

<u>d) Clinical</u>

(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 1st or 2nd 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

8. Proposed patient pathway

Once diagnosis is confirmed, corticosteroids is a first line treatment, unless the treatment is contra-indicated or the patient is corticostereoid 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 proposed as third line treatment.

Dosage: 1g infusion adminstered 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.

9. Proposed 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. A national specialised network of clinicians and providers with specialist interest in IgG4-RD should be developed and a rotating clinical lead identified.

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 requires a highly specialised governance structure and it is proposed that the governance arrangements of Behçet's Syndrome are replicated in this disease area [A13/S(HSS)a].

10. Proposed mechanism for funding

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

11. Proposed 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. It is proposed this is modelled on the national registry for biologic therapy in systemic lupus erythematous (BILAG-BR) (A13/PS/a).

Regarding Rituximab treatment, information on the following outcomes should be collected 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/Discontinuation in steroids/immunosuppressants;
- Frequency of re-treatment;
- Total immunoglobulin levels pre-, and post-treatment; and
- Serious adverse effects.

Specific audit reports on the use of rituximab and specific outcomes in this patient group will be requested by the commissioner. It is proposed that the above data be collected and audited annually.

12. Documents which have informed this policy proposition

NHS Specialised services specification for Behçet's Syndrome Service (Adults and Adolescents), A13/S(HSS)a

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).