



Evidence Review:

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

NHS England

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Commissioning

1

Contents

| Summary of results 3 | , |
|--------------------------------------|----|
| Research Questions 4 | ļ |
| Methodology 5 | ; |
| Results 5 | ; |
| References See Appendix | (1 |
| Literature Search Terms See Appendix | (2 |

1. Introduction

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 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.

2. Summary of results

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.

3. Research questions

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

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

| Grade | Ştı | udy d <u>es</u> | ign and | | Outcomes | | | | Reference | e Other | | |
|----------|--------|-----------------|-------------|--------------|-------------------------|-----------------|-----------|-----------|----------------------|-----------|----------|---|
| Grade of | | | | Category | Primary | Primary Result | Secondary | Secondary | Reference | Complic | Benefits | Comments |
| evidence | design | size | | | Outcome | | Outcome | Result | | ations | noted | |
| | _ | | | | | | | | | noted | | |
| 2- | Case | 30 | 1000 mg | Clinical | Disease activity | The primary | none | - | Carruthers, | Two | =. | The authors conclude that this prospective, single- |
| | series | | doses of | | | outcome was | | | Mollie N.; | patients | | arm pilot trial of rituximab (RTX) provide strong |
| | | | RTX, | s of the | by the IgG4-RD | achieved by 23 | | | Topazian, | were | | evidence that B cell depletion is an effective |
| | | | administere | intervention | Responder | participants | | | Mark D.; | hospitali | | treatment for IgG4-RD. 13% of the cohort required |
| | | | d | | Index (IgG4-RD | (77%). Fourteen | | | Khosroshahi | sed for | | retreatment during the 12m after enrollment. At 12 |
| | | | approximate | | RI) and | (47%) were in | | | , Arezou; | infection | | months only 7% of patients required steroids for their |
| | | | ly 15 days | | ' ' | complete | | | Witzig, | s during | | IgG4-RD. Fourteen (47%) and 12 (40%) participants |
| | | | apart | | | remission at | | | Thomas E.; | the trial | | achieved and maintained complete remissions |
| | | | | | | 6 months, and | | | Wallace, | period. | | through 6 and 12 months, respectively. Considering |
| | | | | | ` ' | 12 (40%) | | | Zachary S.; | Four | | the extent of organ involvement, patients with limited |
| | | | | | • | remained in | | | Hart, Philip | addition | | organ involvement were more likely to achieve |
| | | | | | | complete | | | A.; | al | | complete remission within 6 months compared with |
| | | | | | improvement of | | | | | patients | | those with multiorgan involvement (12/16 vs 6/14 |
| | | | | | the IgG4-RD RI | months | | | Vikram; | were | | subjects including serum IgG4 in the assessment; |
| | | | | | by two points. | | | | Smyrk, | hospitali | | p=0.10; 14/16 vs 7/14 subjects if serum IgG4 |
| | | | | | The primary | | | | Thomas C.; | sed. | | excluded; p<0.05). The study concludes that the |
| | | | | | outcome, | | | | Chari, | | | findings from this prospective pilot trial support the |
| | | | | | measured at | | | | Suresh; | | | observations from small retrospective studies |
| | | | | | 6 months, was | | | | Stone, John | | | indicating that B cell depletion is an effective and |
| | | | | | defined as: (1) | | | | H | | | important treatment for IgG4-RD. Gluco-corticoid |
| | | | | | decline of the | | | | Rituximab | | | (GC) should remain the first treatment approach for |
| | | | | | IgG4-RD RI ≥2 points | | | | for IgG4- related | | | most patients at the present time, assuming the absence of major contraindications to GC therapy. |
| | | | | | compared with | | | | disease: a | | | However, the incomplete or unsustained responses |
| | | | | | baseline; (2) no | | | | prospective, | | | to GCs observed in many IgG4-RD patients, coupled |
| | | | | | disease flares | | | | open-label | | | with the fact that many IgG4-RD patients are middle- |
| | | | | | before month 6; | | | | trial. Ann. | | | aged to elderly and have co-comorbidities |
| | | | | | and (3) no GC | | | | Rheum. Dis. | | | contraindicating long-term GCs, indicate that B cell |
| | | | | | use between | | | | 2015;74(6):1 | | | depletion may have a substantial role in a large |
| | | | | | months 2 and 6 | | | | 171-1177. | | | percentage of IgG4-RD patients. This may be |
| | | | | | | | | | | | | particularly true for patients with multiorgan disease. |
| | | | | | | | | | | | | paradading and for parionic with mattergan disease. |
| | | | | | <u> </u> | | | | | | | |

| 2- | Case | 10 | RTX (2 | Clinical | Clinical | Nine of 10 | the IgG4- | not | Khosroshahi | - | none | Treatment with Rituximab led to prompt clinical and |
|----|--------|----|--------------|--------------|-------------------|-------------------|--------------|----------|--------------|---|----------|---|
| | series | | infusions of | effectivenes | improvement - | patients | RD | reported | , Arezou; | | reported | serologic improvement in refractory IgG4-RD in all |
| | | | 1000 mg, 15 | s of the | assessed by | demonstrated | Disease | - | Carruthers, | | | patients with active inflammation. It was reported that |
| | | | days apart | intervention | monitoring the | striking clinical | Activity | | Mollie N.; | | | repeated courses of Rituximab may lead to |
| | | | | | patient's ability | improvement | Index and | | Deshpande, | | | progressive declines in serum IgG4 concentrations |
| | | | | | to taper | within 1 month | Flare Tool | | Vikram; | | | and better disease control. |
| | | | | | prednisone to | of starting RTX. | (retrospecti | | Unizony, | | | |
| | | | | | discontinuation | All 10 patients | vely | | Sebastian; | | | |
| | | | | | and to stop | were able to | applied) | | Bloch, | | | |
| | | | | | | discontinue | | | Donald B.; | | | |
| | | | | | serial | prednisone and | | | Stone, John | | | |
| | | | | | measurements | | | | H | | | |
| | | | | | of total IgG and | | | | Rituximab | | | |
| | | | | | IgG subclasses; | therapy. | | | for the | | | |
| | | | | | and by follow- | | | | treatment of | | | |
| | | | | | up radiologic | | | | IgG4-related | | | |
| | | | | | assessments | | | | disease: | | | |
| | | | | | guided by the | | | | lessons from | | | |
| | | | | | patient's | | | | 10 | | | |
| | | | | | particular | | | | consecutive | | | |
| | | | | | pattern of organ | | | | patients. | | | |
| | | | | | involvement. | | | | Medicine | | | |
| | | | | | | | | | (Baltimore) | | | |
| | | | | | | | | | 2012;91(1):5 | | | |
| | | | | | | | | | 7-66. | | | |

| 2- | Cooo | 14 | DTV (2 | Clinical | Clinical | Among those | 1 | | Khooroohoh: | | nono | This was a small officeau study to access the alinias! |
|----|--------|----|-------------|--------------|------------------|-------------------|----|---|---------------|---|------|--|
| 2- | Case | 4 | | | improvement | Among these | 1- | - | Khosroshahi | - | none | This was a small efficacy study to assess the clinical |
| | series | | | | • | patients, the | | | , Arezou; | | • | and serologic responses to B lymphocyte depletion |
| | | | 1000 mg, 15 | | was assessed | serum IgG4 | | | Bloch, | | | therapy with rituximab in patients with IgG4-RSD. It |
| | | | days apart | intervention | by monitoring | concentrations | | | Donald B.; | | | was reported that treatment with rituximab led to |
| | | | | | the | declined by a | | | Deshpande, | | | prompt clinical and serologic improvement in patients |
| | | | | | tapering/discont | | | | Vikram; | | | with refractory IgG4-RSD. The decline in serum IgG4 |
| | | | | | | within 2 months | | | Stone, John | | | concentrations was substantially steeper than that of |
| | | | | | prednisone and | | | | H | | | the autoantibody concentrations in immune-mediated |
| | | | | | , | administration. | | | Rituximab | | | conditions in which rituximab is effective, such as in |
| | | | | | , | All 4 patients | | | therapy | | | rheumatoid arthritis. In addition, the reduction in IgG- |
| | | | | | the serum | demonstrated | | | leads to | | | subclass levels appeared to be specific for IgG4. |
| | | | | | concentrations | striking clinical | | | rapid decline | | | |
| | | | | | of B | improvement | | | of serum | | | |
| | | | | | lymphocytes, | within 1 month | | | IgG4 levels | | | |
| | | | | | immunoglobulin | of the initiation | | | and prompt | | | |
| | | | | | s, and IgG | of rituximab | | | clinical | | | |
| | | | | | subclasses | therapy, and | | | improvement | | | |
| | | | | | before and after | tapering or | | | in IgG4- | | | |
| | | | | | therapy | discontinuation | | | related | | | |
| | | | | | | of their | | | systemic | | | |
| | | | | | | treatment with | | | disease. | | | |
| | | | | | | prednisone and | | | Arthritis | | | |
| | | | | | | DMARDs was | | | Rheum. | | | |
| | | | | | | achieved in all 4 | | | 2010;62(6):1 | | | |
| | | | | | | patients. A | | | 755-1762. | | | |
| | | | | | | decrease in IgG | | | 100 1102. | | | |
| | | | | | | concentration | | | | | | |
| | | | | | | was observed | | | | | | |
| | | | | | | for the IgG4 | | | | | | |
| | | | | | | subclass only. | | | | | | |
| | | | | | | Subciass only. | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

Appendix Two

Literature search terms

| Assumptions / limits applie | d to search: |
|--|--|
| Original search terms: | n/a |
| Updated search terms - Population | igg4-rd OR immunoglobulin g4 OR igg4-related diesease OR igg4 sclerosing disease OR igg4-related systemic disease OR igg4-related sclerosing disease OR igg4-related sclerosing disease OR igg4-related systemic sclerosing disease OR igg4-related autoimmune disease OR igg4-related autoimmune disease OR igg4-associated multifocal systemic fibrosis OR igg4-associated disease OR hyper-igg4 disease OR systemic igg4-related plasmacytic syndrome OR igg4-positive multiorgan lymphoproliferative syndrome OR igg4 syndrome |
| Updated search terms - Intervention | rituximab OR rituxan OR mabthera |
| Updated search terms - Comparator | steroid OR steroids OR azathioprine OR methotrexate OR mycophenolate mofetil OR prednisolone OR prednisolone OR methylprednisolone OR corticosteroid OR corticosteroids OR glucocorticoid |

| | OR glucocorticosteroid OR glucocorticosteroids |
|-----------------------------------|---|
| Updated search terms - Outcome | n/a |
| Inclusion criteria | General inclusion criteria In order of decreasing priority, articles will be selected based on the following criteria. 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3. All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here Specific inclusion criteria The policy working group asked the following paper to be included in the clinical evidence review: Treatment approaches to IgG4-related systemic disease, Khosroshahi A, Stone JH. Curr Opin Rheumatol. 2011;23(1):67 |
| Exclusion criteria | Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) Specific exclusion criteria n/a |