NHS England

Clinical Commissioning Policy Proposition:

A13X03 Rituximab for the treatment of Primary Sjogren's Syndrome (PSS) in adults

First published:

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

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

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

Primary Sjögren's syndrome (PSS) is a rheumatic condition in which inflammation in the secretory glands – particularly the tear and salivary glands, means they stop working leading to severe dry eyes and mouth. These are unpleasant and disabling symptoms. Patients also suffer from disabling fatigue and limb/joint pain, lung, neurological and other internal organ disease including B-cell lymphoma
Description of Intervention: Rituximab is a type of drug called a monoclonal antibody which works by dampening down the body's immune system by reducing the numbers of a type of white cell called B-cells. Rituximab is licenced for the treatment of certain non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis (GPA; Wegener's) and microscopic polyangiitis.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission rituximab for primary sjogren's syndrome.

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 primary Sjogren's syndrome will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

The Primary Sjögren's syndrome (PSS) is an autoimmune rheumatic disease in which inflammation of the tear producing (lachrymal) and salivary glands leads to dryness which can be severe and disabling. Symptoms of fatigue and limb/joint pains are found in circa 70% of patients. Systemic features include inflammatory arthritis, vasculitis with purpura, salivary gland inflammation, neuropathies, interstitial lung disease and a 5-10% lifetime risk of B-cell lymphoma. There are no effective therapies and immunosuppressant drugs such as prednisolone, hydroxychloroquine, azathioprine, methotrexate and mycophenolate are generally of modest benefit. Rituximab is licensed for the treatment of certain non-Hodgkin's lymphomas, and some immune related diseases. It is not licensed for PSS but is considered to have some efficacy as a treatment for this condition.

4 Definitions

Rituximab is a chimeric monoclonal anti CD-20 antibody

PSS is defined according to the American-European Consensus Group (AECG) criteria (Vitali et al, Ann Rheum Dis. 2002 Jun;61(6). American College of

Rheumatology / European League Against Rheumatism Consensus Criteria are under development.

The AECG criteria require:

Anti-Ro/La antibodies or an inflammatory focus score >1 on labial salivary gland biopsy. Either 4 out of 6 of:

1. Dry eye symptoms
2. Dry mouth symptoms
3. Objective oral dryness (unstimulated salivary flow rate <0.1ml/min)
4. Objective ocular dryness (Schirmer's test <5mm in 5 mins/van Bijsterveld score >4)
5. Anti-Ro/La antibodies 6. Labial salivary gland focus score >1, or, 3 out of items 3-6. Severe fatigue/dryness/pain is defined as >5/10 on a 0-10 Likert scale or > 50/100 on a visual analogue scale (these 3 components together comprise the ESSPRI).

Systemic disease is defined by an ESSDAI >5

Severe systemic disease is defined by an ESSDAI >14

The minimum clinically important change in ESSDAI is >3 (Seror et al Ann Rheum Dis. 2014 Dec 5. pii: annrheumdis-2014-206008)

The minimum clinically important change in ESSPRI is>1 (Seror et al Ann Rheum Dis. 2014 Dec 5. pii: annrheumdis-2014-206008)

Impaired health-related quality of life in PSS is defined for this purpose as an EQ-5D utility value of <0.5 (Lendrem et al, Ann Rheum Dis. 2014 Jul;73(7):1362-8. doi: 10.1136/annrheumdis-2012-202863)

5 Aims and Objectives

This policy proposition considered:

The evidence to define NHS England's commissioning position on rituximab as part of the treatment pathway for patients with PSS.

The objective was to ensure evidence based commissioning for patients with PSS.

6 Epidemiology and Needs Assessment

PSS is 13 times commoner in women than men. It is estimated to have a prevalence in the UK of 0.1-0.6% of adult women. Most of these patients will have mild disease not requiring systemic therapy. In a UK wide study, the UK Primary Sjögren's Syndrome Registry (UKPSSR), over 700 patients with PSS attending hospital clinics were recruited from 30 centres in the UK with an interest in Sjögren's syndrome over a two year period. These are not incident cases. This prevalence data from centres participating in the UKPSSR allows us to estimate that approximately 400 new patients will present to rheumatology units/year in England. The prevalence of specific features in the UK Primary Sjögren's Registry in the 688 patients recruited by June 2012 is as follows:

Severe fatigue $\geq$ 5/10 = 64%

Severe dryness $\geq$ 5/10 = 72%

Severe pain $\geq$ 5/10 = 52%

Constitutional symptoms = 23%

Salivary gland swelling = 19%

Lymphadenopathy/splenomegaly = 5%

Articular disease= 32%

Cutaneous disease = 8%

Myositis = 2%

Interstitial lung disease = 9%

Central neurological disease = 0.3%

Peripheral neurological disease = 4%

Renal disease= 3%

Haematological abnormalities = 16%

High Immunoglobulins/low complement levels = 47%

ESSDAI≥5 = 42%

ESSDAI>14 = 5%

The majority of these cases may have some level of response to conventional immunosuppressant therapy. 9% of the above cohort were on one of the following conventional immunosuppressant therapies (Azathioprine, Methotrexate, Sulfasalazine, Leflunomide, Ciclosporin, Mycophenolate, Tacrolimus). 2% were on Rituximab, cyclophosphamide, intravenous immunoglobulins, chlorambucil or other chemotherapeutic agent.

Currently patients may be receiving therapies such as azathioprine or mycophenolate requiring frequent hospital monitoring visits associated with an existing cost and a small number receiving rituximab through an IFR or by local arrangement (data not known).

Cyclophosphamide may be used as sequential therapy for patients with progressive neurological disease or vasculitis or ILD but the risk/benefit analysis would not support its use for alleviating severe symptomatic disease or systemic involvement other than the above examples.

7 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Rituximab is licensed for the treatment of certain non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis (GPA; Wegener's) and microscopic polyangiitis. It is not licensed for PSS but has been shown to have some efficacy as a treatment for this condition.

Overall, there was very limited and low quality evidence relevant to the specifically defined subgroup of patients and outcomes. With exception of one prospective study, the evidence base comprises of retrospective observational studies. The overall lack of evidence could be to some extent explained by the small number of patients who fit the definition. Furthermore, the interpretation of the results needs to

take into account potential variation amongst studies as the composite outcome measures include subjective components modelled on physician and patient's judgment of disease activity.

In addition, while most studies report on improvement of ESSDAI score, the link between changes in score and the actual clinically significant impact remains unclear.

In summary, from the current weak body of evidence, rituximab appears to be clinically effective in patients with severe and systemic presentation of primary Sjögren's syndrome. While there is evidence from one prospective study indicating better response to rituximab than standard disease modifying anti-rheumatic drugs, given the small study size and lack of further corroborative evidence, this review is unable to conclude on the effectiveness of rituximab compared with conventional chemotherapeutic and immunosuppressant therapies. There were no relevant cost-effectiveness studies available for review.Recent randomised, placebo-control trials have not been able to demonstrate sufficient efficacy of rituximab in PSS to support its use in the wider population of PSS patients including those with milder symptoms (Carubbi et al, 2014. Devouchelle-Pensec et al , 2014). A case series of 688 PSS patients found a mean UK ESSDAI of 4.8±4.9, with approximately 5% suffering from severe PSS (Oni et al., 2015). Given such small number of patients with severe and progressive disease globally, most studies do not specifically focus on this subgroup.

A prospective study in Italy compared patients treated with rituximab (n=19) with those on disease modifying anti-rheumatic drugs (DMARDs) (n=22) (Carubbi et al., 2013). The authors report inclusion criteria as baseline ESSDAI score ≥ 6. However, the enrolled patients were found to have unusually high mean ESSDAI scores, 19.8±3.1 for DMARDS and 20.3±2.9 for rituximab group. Rituximab treatment resulted in a faster and more pronounced decrease in ESSDAI, all four VAS scores, unstimulated salivary flow and the Schirmer eye test. While improvement was also seen with DMARDs, the impact in the rituximab group was significantly greater than the DMARD group for all measurements except the pain score. ESSDAI for rituximab group fell to 5.2±0.9 at week 120 from 20.3±2.9 at baseline, compared to 8.8±1.7 at week 120 in DMARD group from a baseline of 19.8±3.1. In addition, the

rituximab group appeared to experience significantly more sustained relief in symptoms with the impact of rituximab improving progressively throughout the 120 weeks follow-up. The principal limitation of this study were the small sample size, non-randomised patient allocation between two intervention groups and potential patient selection bias given the higher than norm baseline ESSDAI scores.

The French Autoimmunity and Rituximab (AIR) registry, which includes data on patients with autoimmune disorders treated with rituximab was the basis of two studies included in this review, with potentially overlapping population and hence some double counting of impact.Gottenberg et al (2013) reported improvement in systemic complications of PSS on retrospective analysis of data on 78 patients from AIR registry over 3 to 5 years. 74 patients had systemic involvement and 4 had severe glandular involvement. 60% of patient responded within first treatment cycle of rituximab, majority of the others needed 2-3 cycles while 12 out of 78 patients needed between 4-12 cycles. 17 patients were concomitantly treated with another immunosuppressant agent. Median ESSDAI decreased significantly from 11 (2-31) to 7.5 (0-26) ($p<0.0001$). The median dosage of corticosteroid decreased from 17.6 mg/day (3-60) to 10.8 mg/day but it was not statistically significant ($p=0.1$).

Mekinian et al. (2012) retrospectively analysed data from the AIR registry for efficacy of rituximab in PSS patients with systemic lymphoproliferative symptoms . There were two groups of patients, Group 1 (n=10) with established cryoglobulinaemia and/or vasculinaemia and Group 2 (n=7), without cryoglobulinaemia and/or vasculinaemia. Group 1 had a high median ESSDAI score (24, range 17-44) and demonstrated a significant improvement after 6 months on rituximab with a median ESSDAI down to 14.5 (range 7-21) ($p=0.008$). Group 2 had a lower baseline median ESSDAI score (12, range 10-18) and did not demonstrate significant improvement after 6 months. This study demonstrates a role for rituximab in severe systemic PSS (ESSDAI >17) with majority (>90%) of patients experiencing good symptomatic response and complete resolution of cryoglobulinaemia and vasculitis. The small number of patients, and the single arm retrospective analysis study design limit the wider generalisability of this evidence.

Some studies specifically reported on salivary gland response to rituximab in PSS. In a series of 28 patients recruited as part of TEARS randomised control trial,

significant improvement was reported in salivary gland echostructure on ultrasonography in patients with primary SS, 6 months after the first infusion of rituximab. However, there was no changes in salivary gland size or vascularization (Jousse-Joulin et al, 2015). Ciccia et al (2014) demonstrated the physiological impact on rituximab on salivary gland inflammation in a case series of 15 PSS patients with mixed results. Expression of IL-17 was significantly lower after rituximab treatment, but not expression of IL-23p19 and p-STAT3. Mean salivary flow rate improved from baseline 0.22±0.13ml/min to 0.5±0.2ml/min at week 48. Schirmer's test baseline mean 5.1±2.1 mm/5 min shifted to 9.3±2.3 mm/5 min at week 48. The clinical significance of these observed differences is not established.

Patients with severe progressive Sjögren's syndrome can develop lymphomas. Pollard et al. (2011) reported 35 patients with Sjogren's syndrome who developed lymphoma. In this retrospective clinical study with varied therapeutic interventions, out of 13 patients treated on rituximab, 5 reported to be on complete remission and 8 in partial remission or stable disease. However, the small size of the study and even smaller rituximab intervention group, overlap of therapeutic interventions and retrospective study design prevent any conclusive deduction from this evidence.

In an even small case series of 16 patients, Seror et al (2007) reported on efficacy of rituximab on systemic features and glandular swelling in PSS. There was improvement in 4 of 5 patients with lymphomas and in 9 of 11 patients with systemic involvement (thrombocytopenia, mononeuritis multiplex refractory pulmonary disease with polysynovitis, severe polysynovitis , cryoglobulinaemia) after median 14.5 months of rituximab therapy that was generally well tolerated. Corticosteroid dose was reduced in 11 patients. Concomitant changes were also observed in serum biomarker including decreased rheumatoid factor, c-globuli, Immunoglobulin G (IgG) n and b2-microglobulin levels, and increase in the level of B cell activating factor of the tumour necrosis factor family (BAFF).

In summary the evidence to date demonstrates that;

a) In patients with PSS and B-cell lymphoma chemotherapeutic regimes that include Rituximab are effective and are currently standard of care.

b) The safety of Rituximab has been established across a broad range of

disease indications. Frequent side effects include, infusion reactions and increased frequency of infections. A rare but serious or fatal side effect of Rituximab and other biologic therapies is PML (progressive multifocal leukoencephalopathy).

c) Many studies are relatively small case series. An RCT of 120 patients did not meet the primary outcome target (that is, the predetermined degree of improvement in fatigue at week 24). There was greater improvement at earlier time points but these earlier measures were not the primary end points. Another RCT of 30 patients showed mixed results regarding improved saliva production. A recently completed and not yet published UK RCT of over 100 patients is understood not to have shown significant benefit.

d) The studies included patients with a range of severity of PSS. This added to the difficulty of demonstrating effectiveness of rituximab in those more severely affected as described in the eligibility criteria of the policy. It is recognised the significant morbidity in this group of patients and the lack of treatment options.

e) The evidence for severe cases (that is ESSDAI>=14) patient group is undeveloped. Patients only received two doses of rituximab in most studies (doses differed but most commonly used was 1g given twice) whereas policy allows for subsequent doses for which there is very limited evidence.

f) Some beneficial impact on fatigue and to a lesser extent on dryness features and quality of life has been reported in observational studies and small RCTs. One RCT of 120 patients in France (TEARS study) has demonstrated short-term improvement in fatigue after one course of rituximab however the results of a similar RCT in the UK have not demonstrated symptomatic benefit but did demonstrate modest improvement in salivary flow.

g) Cost effectiveness of Rituximab in PSS has not been assessed (but is being evaluated as part of the UK TRACTISS study at least in relation to fatigue and oral dryness)

Patients with severe or progressive systemic features currently have no effective

therapeutic options.

8 Proposed Criteria for Commissioning

Not applicable.

9 Proposed Patient Pathway

Not Applicable.

10 Proposed Governance Arrangements

Not Applicable.

11 Proposed Mechanism for Funding

Not Applicable.

12 Proposed Audit Requirements

Not Applicable.

13 Documents That Have Informed This Policy Proposition

Not Applicable.

14 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 July 2016).

END