Evidence Review:

Rituximab for Primary Sjögren's Syndrome (PSS) in adults

Reference: A13X03/01

NHS England

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First published:	February 2016
Updated:	Not applicable
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Contents

1. Introduction

Primary Sjögren's syndrome (PSS) is a chronic autoimmune condition where the immune system attacks the tear and saliva glands, and other secretory glands throughout the body without an underlying disease. Inflammation of glands reduces the production of tears and saliva causing dry eyes and dry mouth which are the main symptoms of PSS. B lymphocyte cells play a key role in the disease pathophysiology and are also linked to more systemic presentation of PSS such as cryoglobulinaemia (with or without vasculitis), thrombocytopenia, polysynovitis, and increased risk of cancer of lymph nodes (non-Hodgkin lymphoma).

There are no effective therapies and immunosuppressant drugs such as prednisolone, hydroxychloroquine, azathioprine, methotrexate and mycophenolate are generally of modest benefit. Oral and ocular dryness can be treated symptomatically with artificial tears (and other unlicensed topical therapies) and saliva but these are only partially effective for many patients. In patients with some residual tear or saliva production, stimulants such as pilocarpine can be helpful in some patients and blocking the tear (outlet) ducts to retain tears on the surface of the eye can also help selected patients.

PSS is associated with significant morbidity and reduced health-related quality of life and individuals with PSS consume considerable healthcare resources. 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. It is not licensed for PSS but has been shown to have efficacy as a treatment for this condition.

2. Summary of results

In clinical practice, PSS is assessed using a combination of objective tests including salivary flow and tear gland tests, and subjective tests, such as functioning questionnaires and visual analogue scales (VAS). These have recently been combined into two measures, the EULAR Sjögren's Syndrome disease activity index (ESSDAI) and the EULAR Sjögren's Syndrome patient report index (ESSPRI). The ESSDAI gives a weighted score to 12 disease features. Patients with an ESSDAI in the range of 5-13 are classified as having moderate PSS, while those with ESSDAI ≥ 14 are classified as having severe PSS.

This evidence review is focussed on the subgroup of patients with systemic and severe Primary Sjögren's syndrome, defined as follows
- Patients with severe and progressive PSS (ESSDAI ≥ 14) despite prolonged use of hydroxychloroquine and at least two other immunosuppressant therapy/therapies (prednisolone >=10mg/day, azathioprine, methotrexate, mycophenolate, cyclosporine or leflunomide) or those in whom cyclophosphamide is contraindicated or not tolerated.
- Patients where high activity in at least one ESSDAI domain that has not responded to conventional therapies and is associated with impaired health-related quality of life

The review was undertaken address the following questions for this patient group:
1) Is rituximab clinically effective in improving outcome measures (as listed below) in the defined group of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?
2) Is rituximab more effective in improving outcome measures (as listed below) in the defined group of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?
3) Is rituximab cost effective in the treatment of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?

To ensure all current evidence was scrutinised within the review framework, the literature search was kept wide and input from clinical experts was sought to highlight any additional relevant studies.

Overall, there was very limited and low quality evidence relevant to the specifically defined subgroup of patients and outcomes to directly answer the above questions. 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.

Clinical effectiveness

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).

Dosage and safety

Rituximab has been available for clinical use in Europe since 1998 and its dosage and side-effects are well established. However, the use in PSS is limited and largely off label and in a smaller number of cases. Rituximab was administered in dose of 375 mg/m^2/week or 1g/ week in most studies included in the review. Studies report varying rates of side-effects which could also be a reflection of the differences in inclusion criteria, classification of adverse events and length of follow up time. TEARS randomised trial (Devauchelle-Pensec et al., 2014) reported that rituximab used alone at low infusion rates of 100 mg/hour was generally well tolerated in PSS patients, although fatigue and headache were common during the first infusion but not for repeat infusions. None of the patients had severe side effects during the trial duration and the overall complication rates for the rituximab arm was lower at 87% compared with 93% in the placebo arm after 48 weeks. One patient required hospital admission and low-dose corticosteroid treatment for arthralgia and purpura occurring 7 days after the last infusion. Arthralgia developed in 2 patients and previously unknown arthritis was reported in 2 patients. No infections or other adverse events were detected. There were no changes in hepatic, renal, or hematologic tests during the trial. Authors report that adverse events with rituximab in PSS are likely to be lower compared with that in patients with lymphoma potentially explained by a lower risk for cytokine release syndrome caused by B cell lysis than those with lymphoma.

Mekinian et al. (2012) reported adverse events in 6 out of 17 patients in 6 months including one case each of severe acute infusion reaction, severe cutaneous infection and hypogammaglobinaemia. The data from AIR registry which is largest study population and long term follow-up in the review reported 5 (6.4%) serious infusion reactions occurred in a total of 78 patients. There were 3 serious infections (1.3/100 patient-years) which included 2 bronchopulmonary infections (cytomegalovirus and Staphylococcus aureus) after 4 years of initiation of rituximab and 2 cancers (0.9/100 patient-years).

Cost effectiveness

There were non-cost-effectiveness data available and none of the studies compared rituximab with conventional chemotherapy and immunosuppressant.

3. Research questions

1) Is rituximab clinically effective in improving outcome measures (as listed below) in the defined group of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?

2) Is rituximab more effective in improving outcome measures (as listed below) in the defined group of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?

3) Is rituximab cost effective in the treatment of patients with Primary Sjögren's syndrome compared with conventional chemotherapeutic and immunosuppressant therapies?

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	Study design and			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
-	Other	110 patients	Rituximab	Clinical effectiveness of the intervention	30 % reduction in either fatigue or oral dryness at 48 weeks, measured by VAS.	Not reported yet see summary.	Global assessment of pSS pain, salivary and lachrymal flow rates, quality of life, EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient Reported Index (ESSPRI)	Not reported yet see summary.	Brown, Sarah; Navarro Coy, Nuria; Pitzalis, Costantino; Emery, Paul; Pavitt, Sue; Gray, Janine; Hulme, Claire; Hall, Frances; Busch, Robert; Smith, Pete; Dawson, Luke; Bombardieri, Michele; Wan-Fai, Ng; Pease, Colin; Price, Elizabeth; Sutcliffe, Nurhan; Woods, Clodagh; Ruddock, Sharon; Everett, Colin; Reynolds, Catherine; Skinner, Emma; Poveda-Gallego, Ana; Rout, John; Macleod, Iain; Rauz, Saaeha; Bowman, Simon; TRACTISS trial team. The TRACTISS protocol: a randomised double blind placebo controlled clinical trial of anti-B-cell therapy in patients with primary Sjögren's Syndrome. BMC Musculoskelet Disord 2014;15(0):21.	-	-	This is the study design for a large UK based RCT, TRACTISS, that has now been completed but the results have yet to be published. The results are scheduled for Autumn 2015 and a preprint of these results has been seen, but the paper is currently at the peer review. Hence, while we will summarise the results here, it should be stressed that these have not gone through the peer review, however it is anticipated that these results will be published shortly. The patients involved in the study had a mean ESSDAI of 5.7 and there was no significant difference between placebo arm and rituximab arm. This paper has not been graded.

2-	Other	41 patients	Rituximab 1g at day 1 and day 15, course repeated every 24 weeks for 120 weeks.	Clinical effectiveness of the intervention compared to existing interventions	Change from baseline in VAS and ESSDAI scores, salivary flow and Schirmer 1 test.	ESSDAI: rituximab: 20.3±2.9 (baseline), 14.2±2.8 (wk. 12), 9.8±2.0 (wk. 24), 9.4±1.6 (wk. 48), 5.7±1.0 (wk. 72), 5.2±0.9 (wk. 120) DMARD: 19.8±3.1 (baseline), 17.6±3.2 (wk. 12), 14.2±2.8 (wk. 24), 9.8±2.0 (wk. 48), 10.2±2.0 (wk. 72), 8.8±1.7 (wk. 120) Analogous results exist for global disease activity, Pain, Fatigue, Dryness and physical GA VAS., all demonstrating a statistically significant reduction, with rituximab having a larger reduction than DMARD. Unstimulated salivary flow also demonstrated an analogous reduction but it was not statistically significant until week 48.. The Schirmer 1 test demonstrated a steady increase from baseline, but it was not statistically significant until week 120.	Safety of rituximab.	No patient showed a systemic or infusion-related side effect. No patients developed humoural immunodeficiency.	Carubbi F, Cipriani P, Marrelli A, Benedetto P, Ruscitti P, Berardicurti O, Pantano I, Liakouli V, Alvaro S, Alunno A, Manzo A, Ciccia F, Gerli R, Triolo G, Giacomelli R.. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study.. Arthritis. Res. Ther. 2013;15(5):R172.	-	-	This is a small prospective before and after study comparing the use of rituximab with the use of Disease modifying anti-rheumatic drugs (DMARD) (such as hydroxychloroquine, methotrexate, cyclosporine). The study inclusion criteria was 2 out of 4 VAS scores >50mm and ESSDAI>6. The baseline ESSDAI was found to be unusually high, 19.8±3.1 range (6-41) for DMARD arm and 20.3±2.9 range (6-41) for rituximab arm. It is not clear if this was due to planned inclusion of higher ESSDAI patients . It provides evidence for the possible efficacy of rituximab, with a significant reduction in ESSDAI score from week 24. The principle limitation of this study are the sample size, allocation bias due to non-randomised allocation between two intervention groups and potential patient selection bias given the higher than norm baseline ESSDAI scores.

3	Systematic	392 total.	Rituximab predominantly 375 mg/m^2/week Also, 1g/ week	Clinical effectiveness of the intervention	A wide variety of different outcomes	The review summarises the results of the 21 studies (including 3 RCTs, 1 cohort study and 17). Only one study specifies an exclusion based on ESSDAI (Carubbi et al., 2013) that required ESSDAI > 6 and found rituximab resulted in faster and more pronounced decrease in ESSDAI, than disease modifying anti-rheumatic drugs. Paper concludes that rituximab treatment in pSS should represent good starting point to evidence based guidelines.	-	-	Carubbi, F.; Alunno, A.; Cipriani, P.; Bartoloni, E.; Ciccia, F.; Triolo, G.; Gerli, R.; Giacomelli, R.. Rituximab in primary Sjögren's syndrome: a ten-year journey. Lupus 2014;23(13):1337-1349.	-	-	This review is not specifically directed toward the population and outcome of interest.The review methodology is more narrative instead of systematic. The key studies from the review are included individually in the CER. The method of systematic literature reveiw is not clear. Hence, the evidence graded as 3.
3	Case series	15 patients	Rituximab (rituximab) four infusions	Clinical effectiveness of the intervention	Salivary gland expression of IL-17, IL-23p19 and p-STAT3	Expression of IL-17 was significantly lower after rituximab treatment, but not expression of IL-23p19 and p-STAT3.	Saliva flow rate Schirmer's test	Saliva flow rate: baseline mean 0.22±0.13ml/min week 48 mean 0.5±0.2ml/min Schirmer's test: baseline mean 5.1±2.1 mm/5 min week 48 mean 9.3±2.3 mm/5 min	Ciccia, Francesco; Guggino, Giuliana; Rizzo, Aroldo; Alessandro, Riccardo; Carubbi, Francesco; Giardina, AnnaRita; Cipriani, Paola; Ferrante, Angelo; Cannizzaro, Alessandra; Giacomelli, Roberto; Triolo, Giovanni. Rituximab modulates IL-17 expression in the salivary glands of patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2014;53(7):1313-1320.	-	-	The motivation for this case series is that during pSS, salivary gland inflammation occurs in the presence of altered adaptive immune responses seen as, for example, the expression of the IL-23p19/IL-17 pathway. Hence the neutralisation of IL-17 appears to be a promising therapeutic approach. This case series demonstrated in the salivary gland biopsies of 15 patients that rituximab significantly reduces the expression of IL-17. The small number and non-comparator study design are key limitations.

1-	RCT	120	Rituximab 1g (at weeks 0 and 2)	Clinical effectiveness of the intervention	A composite endpoint Sjorgen Syndrome responder index (SSRI) based on changes in Visual Analogue Scale (VAS) scores of five outcome measures (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow and erythrocyte sedimentation rate (ESR)). SSRI-30 response is defined as a >30% change in two out of five VAS scores.	Derivation of a new primary outcome (SSRI-30) designed to test efficacy in treating pSS. SSRI-30 at 6 weeks:47% rituximab vs 21% placebo p<0.01 SSRI-30 at 16 weeks: 50% rituximab vs 7% placebo p<0.01 SSRI-30 at 20 weeks: 55% rituximab vs 20% placebo p<0.01 The outcome is validated by applying SSRI-30 outcome to two smaller RCT: - (Meijer et al., 2010): 68% rituximab vs 40% at week 12 and 74% rituximab vs 40% at week 24 -(Dass et al., 2013): 40% rituximab vs 35% at week 10 and 41% rituximab vs 37% at week 22. The paper found a statistically significant difference in the number of responders, in TEARS trial, when SSRI was based on changes in 2, 3 or 4 of the 5 outcomes. This always favoured rituximab over placebo.	-	-	Cornec, Divi; Devauchelle-Pensec, Valérie; Mariette, Xavier; Jousse-Joulin, Sandrine; Berthelot, Jean-Marie; Perdriger, Aleth; Puéchal, Xavier; Le Guern, Véronique; Sibilia, Jean; Gottenberg, Jacques-Eric; Chiche, Laurent; Hachulla, Eric; Hatron, Pierre Yves; Goeb, Vincent; Hayem, Gilles; Morel, Jacques; Zarnitsky, Charles; Dubost, Jean Jacques; Seror, Raphaèle; Pers, Jacques-Olivier; Meiners, Petra M.; Vissink, Arjan; Bootsma, Hendrika; Nowak, Emmanuel; Saraux, Alain. Development of the Sjögren's Syndrome Responder Index, a data-driven composite endpoint for assessing treatment efficacy. Rheumatology (Oxford) 2015;54(9):1699-1708.	-	-	This paper was a post hoc analysis of the TEARS RCT data to attempt validate the composite index SSRI-30 used in that trial. SSRI-30 has not been commonly used by other study in the CER, hence limited relevance.

1-	RCT	17 patients	Rituximab 1g	Clinical effectiveness of the intervention	Number of patients that had >20% improvement in fatigue VAS. Social functioning:	Mean change from baseline in fatigue VAS score at six months: rituximab: 36.8±17.9 mm (baseline vs 6 months p<0.001), placebo: 17.6±32.2mm (TRX vs placebo p=0.147) Social functioning at 6 months: Mean improvement in SF-36 score was 4 vs -24 (for placebo) (p=0.06), from a baseline level of 43.6 vs 36.7.	Adverse Events	Two patients had three adverse events (headaches, urticarial rash, fever and meningism) One patient had two adverse events. Two patients treated with rituximab had infusion reactions.	Dass, S.; Bowman, S. J.; Vital, E. M.; Ikeda, K.; Pease, C. T.; Hamburger, J.; Richards, A.; Rauz, S.; Emery, P.. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann. Rheum. Dis. 2008;67(11):1541-1544.	Median disease duration 7.25 years (rituximab) vs 8.25 (placebo) years range(1-19). Baseline fatigue VAS score 76mm (rituximab) vs 69mm (placebo)	-	This is a very small RCT is based primarily on the change in the fatigue VAS score. There was a statistically significant improvement in the fatigue VAS score, compared to the baseline value. However there was also an improvement in the placebo arm such that rituximab vs placebo impact was not statistically significant. There was improvement in social functioning in rituximab arm vs placebo arm with p=0.06. Principle limitations are very small sample size, use of fatigue VAS only and absence of ESSDAI scoring. However, patients studied did have high fatigue VAS (approx. 70mm) and approximately 8 years disease duration.

1-	RCT	120	Rituximab 1g (at weeks 0 and 2)	Clinical effectiveness of the intervention	Decrease of at least 30mm in 2 of 4 VASs at 6 weeks, 16 weeks and 24 weeks. Decreases in individual VAS scores	2 of 4 VAS: 6 weeks: 22.4% (rituximab) vs 9.1% (placebo) p=0.036 16 weeks: 26.3% (rituximab) vs 17.0% (placebo) p=0.091 24 weeks: 23% (rituximab) vs 22% (placebo) p=0.91 Statistically significant differences between rituximab and placebo in number of patients with >30mm change in the following VAS score: Fatigue at 6 weeks (34.7% vs 8.2% p<0.001) and 16 weeks (27.2% vs. 8.9% p=0.012), but not at 24 weeks	Adverse Events	Rituximab used alone at low infusion rates of 100 mg/hour was well tolerated, although fatigue and headache were common during the first infusion. Adverse events did not occur during the second infusion. First 2 patients experienced infusion-relatednreactions when the infusion rate was increased to 200 mg/hour, but these side effects improved when the rate was decreased to 100 mg/hour. None of the patients had severe side effects. In most	Devauchelle-Pensec, Valérie; Mariette, Xavier; Jousse-Joulin, Sandrine; Berthelot, Jean-Marie; Perdriger, Aleth; Puéchal, Xavier; Le Guern, Véronique; Sibilia, Jean; Gottenberg, Jacques-Eric; Chiche, Laurent; Hachulla, Eric; Hatron, Pierre Yves; Goeb, Vincent; Hayem, Gilles; Morel, Jacques; Zarnitsky, Charles; Dubost, Jean Jacques; Pers, Jacques Olivier; Nowak, Emmanuel; Saraux, Alain. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann. Intern. Med. 2014;160(4):233-242.	Mean baseline ESSDAI score: 10.0±6.9 (rituximab) vs 10.2±6.8 (placebo)	-	This paper presents the principal results of the large TEARS RCT. The paper found a significant difference in the improvement in VAS scores between the rituximab arm and the placebo arm at week 6. However, this difference had reduced by week 24. The difference was largely being driven by fatigue score. It is important to note that the majority of the baseline ESSDAI scores were below 14 and no subgroup analysis, on patients with ESSDAI > 14, was completed. There was no significant reduction in ESSDAI score. There was no comparison with existing treatment options. Overall, not relevant to the review.
3	Case series	16 patients	Rituximab (rituximab) 375 mg/m^2	Clinical effectiveness of the intervention	VAS scores at week 12 and week 36	At week 12 significant improvement in VAS scores in fatigue, dryness (p<0.05), tender point count (p<0.035). At week 36 significant improvement in global disease activity, pain, fatigue, dryness, tender point count, tender joint count VAS scores (p<0.05)	Quality of Life questionnaires	36 questionnaire was significantly improved at week 12.	Devauchelle-Pensec, Valérie; Pennec, Yvon; Morvan, Johanne; Pers, Jacques-Olivier; Daridon, Capucine; Jousse-Joulin, Sandrine; Roudaut, Anne; Jamin, Christophe; Renaudineau, Yves; Roué, Isabelle Quintin; Cochener, Béatrice; Youinou, Pierre; Saraux, Alain. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum. 2007;57(2):310-317.	-	-	This case series examines the improvement in 15 patients following treatment with rituximab. Improvement in a number of VAS scores. Inclusion based on 2 of 4 VAS scores > 50mm, no calculation of ESSDAI or subgroup analysis, hence of little relevance to this review.

3	Case series	1120	Either systemic drugs: Hydroxychloroquine (25.2%) Corticoids (65%) Immunosuppressive agents (13%) Intravenous immunoglobulins (2.2%) Rituximab (rituximab) (3%)	Clinical effectiveness of the intervention	Hazard Ratio (HR), adjusted for age, gender and levels of ESSDAI activity of death and Lymphoma.	Only Death HR significantly different from 1.0 was for Hydroxychloroquine, 0.57 (95% CL 0.34-0.95), i.e. reduced chance of death. rituximab: 0.44 (95% CL 0.14-1.4) i.e. while there was a reduce risk of death with rituximab therapy, this was not statistically significant	Baseline ESSDAI score	Baseline ESSDAI score = 5.91±6.77.	Gheitasi, H.; Kostov, B.; Solans, R.; Fraile, G.; Suárez-Cuervo, C.; Casanovas, A.; Rascón, F. J.; Qanneta, R.; Pérez-Alvarez, R.; Ripoll, M.; Akasbi, M.; Pinilla, B.; Bosch, J. A.; Nava-Mateos, J.; Díaz-López, B.; Morera-Morales, M. L.; Retamozo, S.; Ramos-Casals, M.; Brito-Zerón, P.; SS Study Group, Autoimmune Diseases Study Group (GEAS), Spanish Society of Internal Medicine (SEMI). How are we treating our systemic patients with primary Sjögren syndrome? Analysis of 1120 patients. Int. Immunopharmacol. 2015;27(2):194-199.	-	-	This is a retrospective case series hence the potential for selection bias. The sample size of patients using rituximab was small (35/1120) . There was no subgroup analysis on ESSDAI>14 and the baseline ESSDAI score was 5.91±6.77.

3	Case series	78 patients	Rituximab (rituximab) 1g followed by 375 mg/m^2 x 4.	Clinical effectiveness of the intervention	ESSDAI	mean ESSDAI at baseline: 11.0 (range 2-31) mean ESSDAI at 6 month: 7.5 (range 0-26) p<0.0001.	Efficacy assessed by global opinion of clinicians Adverse events.	Efficacy assessed by global opinion of clinicians: 47 /78 (60%) patients. 5/78 (6.4%) patients had serious infusion events 3/78 (3.8%) patients had serious infections. Two deaths occurred both related to cancers.	Gottenberg, Jacques-Eric; Cinquetti, Gael; Larroche, Claire; Combe, Bernard; Hachulla, Eric; Meyer, Olivier; Pertuiset, Edouard; Kaplanski, Guy; Chiche, Laurent; Berthelot, Jean-Marie; Gombert, Bruno; Goupille, Philippe; Marcelli, Christian; Feuillet, Séverine; Leone, Jean; Sibilia, Jean; Zarnitsky, Charles; Carli, Philippe; Rist, Stephanie; Gaudin, Philippe; Salliot, Carine; Piperno, Muriel; Deplas, Adeline; Breban, Maxime; Lequerre, Thierry; Richette, Pascal; Ghiringhelli, Charles; Hamidou, Mohamed; Ravaud, Philippe; Mariette, Xavier; Club Rhumatismes et Inflammations and the French Society of Rheumatology. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. Ann. Rheum. Dis. 2013;72(6):1026-1031.	-	-	This large multi centre case series attempted to evade the challenges of defining primary endpoints by using the ESSDAI score and a subjective questionnaire of efficacy to the clinician. The ESSDAI score indicated a statistically significant improvement, while the questionnaire indicated a 60% efficacy ratio. No subgroup analysis was available and the mean baseline ESSDAI was 11.0.

3	Case series	247 patients, of which 84 had Sjogren's syndrome	57% of patients received local therapy, 37% of patients received systemic therapy, of whom 47% received rituximab.	Clinical effectiveness of the intervention	Overall Survival	Median overall survival was 9.3 years, with no significant difference between those receiving local or systemic therapy (e.g. Rituximab).	-	-	Jackson, Amie E.; Mian, Michael; Kalpadakis, Christina; Pangalis, Gerassimos A.; Stathis, Anastasios; Porro, Elena; Conconi, Annarita; Cortelazzo, Sergio; Gaidano, Gianluca; Lopez, Armando; Guillermo, null; Johnson, Peter W.; Martelli, Maurizio; Martinelli, Giovanni; Thieblemont, Catherine; McPhail, Ellen D.; Copie-Bergman, Christiane; Pileri, Stefano A.; Jack, Andrew; Campo, Elias; Mazzucchelli, Luca; Ristow, Kay; Habermann, Thomas M.; Cavalli, Franco; Nowakowski, Grzegorz S.; Zucca, Emanuele. Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue of the Salivary Glands: A Multicenter, International Experience of 248 Patients (IELSG 41). Oncologist 2015;20(10):1149-1153.	-	-	This retrospective case series examines patients with mucosa-associated lymphoid tissue (MALT) lymphomas, of which a sub group had pSS (33%) and a further sub group was treated with Rituximab (17%). No subgroup analysis was done on those just receiving Rituximab, although there was no significant difference in overall survival rate, between those receiving local or systemic treatments. The retrospective, non-comparator study design are key limitations.

3	Case series	28 patients	Rituximab 1g (at weeks 0 and 2)	Clinical effectiveness of the intervention	Salivary gland ultrasonography. The number of patients who had statistically significant changes from baseline after 24 weeks. For echo-structure score - looked at aggregated score based on size of left, right and worse parotid gland. In addition to left, right and worse submandibular gland.	Aggregated parotid parenchyma echo-structure score: 7/14 patients in rituximab arm had significant changes vs 1/14 in placebo arm p=0.03. Submandibular glands also demonstrated improvement, but not statistically significant, 5/14 patients in rituximab arm had significant changes vs 1/14 in placebo arm p=0.16. There was no significant difference between rituximab and placebo arm in the mean surface area changes on longitudinal section of parotid glands from baseline .	A pulsed Doppler was used on the transverse facial artery to provide a spectral blood flow analysis and the computation of a resistive index.	No significant different was seen in the resistive index between rituximab arm and placebo arm.	Jousse-Joulin, Sandrine; Devauchelle-Pensec, Valérie; Cornec, Divi; Marhadour, Thierry; Bressollette, Luc; Gestin, Simon; Pers, Jacques Olivier; Nowak, Emmanuel; Saraux, Alain. Brief Report: Ultrasonographic Assessment of Salivary Gland Response to Rituximab in Primary Sjögren's Syndrome. 0 2015;67(6):1623-1628.	-	-	A subset of 28 subjects from the TEARS randomised control trial were given an ultra-sonographic assessment of salivary gland response to rituximab. Ultrasonography showed improved salivary gland echostructure in patients with primary SS receiving rituximab, with no changes in salivary gland size or vascularization, 6 months after the first infusion. The validity and clinical significance of salivary gland echo-structure scores need further scientific scrutiny especially given the lack of concomitant changes in the gland size and vascularisation .There was no comparison with existing treatment options. In addition, this is a post hoc analysis , with the potential for significant bias.

1-	RCT	30 patient, 20 rituximab (rituximab) and 10 placebo	Rituximab 1g	Clinical effectiveness of the intervention	Whole Saliva Flow (ml/minute), unstimulated and stimulated, measured at weeks 5, 12, 24, 36, 48. VAS score for Oral dryness and ocular dryness.	Stimulated whole saliva flow: rituximab arm saliva flow significantly improved at week 5 (p=0.018), 12 (p=0.004), but in placebo arm saliva flow decrease. However started at different mean baseline values (placebo: 0.42±0.26 range 0.36, rituximab: 0.70±0.47 range 0.47) In week 12 there was a statistically significant difference in improvement, from baseline values, between the placebo arm and rituximab arm. Oral and ocular VAS scores for rituximab arm demonstrate a significant improvement from baseline at weeks 5, 12, 24, 36 and 48. Although not significantly different from placebo arm except at week 36 and 48.	Lacrimal Gland function Adverse events	Significant differences in absolute B cell count from baseline to weeks 5,12,24, 36 and 48 in rituximab arm. Adverse Events: One patient in the rituximab group developed mild serum sickness-like disease.	Meijer, J. M.; Meiners, P. M.; Vissink, A.; Spijkervet, F. K. L.; Abdulahad, W.; Kamminga, N.; Brouwer, E.; Kallenberg, C. G. M.; Bootsma, H.. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62(4):960-968.	Hypothesise that improvements in placebo arm may be due to treatment with prednisolone.	-	This is a small RCT principally focussed on using whole saliva flow rate as a measure of pSS. The study found a significant improvement in stimulated whole saliva flow rate, from baseline level, when measured at 5 and 12 weeks after initial treatment. After this the improvement reduces until at week 48 a decrease in flow rate is measured. While in the placebo arm a decrease is measured. This leads to a significant difference between placebo arm and rituximab arm at week 12. However, the principal concern with such a conclusion is that the rituximab arm and the placebo arm appear to be starting at very different levels of saliva flow rates. It is not clear if rituximab had some outliers leading to a difference in mean and rang which would invalidate a comparison between mean values. There was no subgroup analysis by B cell count or saliva flow rate. ESSDAI was not calculated.

3	Case series	28 patients	Rituximab 1g at day 1 and 15.	Clinical effectiveness of the intervention	EULAR Sjorgen Syndrome Patient report index (ESSPRI) EULAR Sjorgen Syndrome disease activity index (ESSDAI)	Mean ESSDAI (p value comparison with baseline) Baseline 8±5, week 16 3±3 (p<0.001), week 24 3±3 (p<0.001), week 36 3±3 (p<0.001), week 48 5±7 (p=0.064), week 60 8±6 (p=0.662) Mean ESSPRI (p value comparison with baseline) Baseline 6.3±2.2, week 16 4.6±2.0 (p<0.001), week 24 5.3±2.0 (p<0.001), week 36 5.3±2.0 (p=0.007), week 48 5.8±1.9 (p=0.068), week 60 5.6±2.2 (p=0.043)	Patients and Physicians global disease activity index IGM-Rf rheumatoid factor Stimulated whole salivary flow	Patients and Physicians global disease activity index both demonstrated statistically significant drops from week 16, which maintained until week 60. IGM-Rf rheumatoid factor demonstrated significant drop from baseline level in weeks 16, 24 and 36. Mean stimulated whole salivary flow demonstrated no statistically significant decrease.	Meiners, P. M.; Arends, S.; Brouwer, E.; Spijkervet, F. K. L.; Vissink, A.; Bootsma, H.. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann. Rheum. Dis. 2012;71(8):1297-1302.	-	-	This is a prospective single centre case series with 60 week follow up of 28 patients treated with rituximab. The mean baseline ESSDAI score was 8, and no subgroup analysis of high baseline ESSDAI scores was conducted. The results indicate improvements in ESSDAI from week 16 until week 48. Improvement is also seen in ESSPRI, global disease activity index and IGM-Rf rheumatoid factor, but not saliva flow. Key limitation of this study is absence of a comparator group.
3	Case series	17 patients	Rituximab	Clinical effectiveness of the intervention	ESSDAI	Overall. Median ESSDAI: Baseline: 18 (10-44), 3 months: 11 (5-20), 6 months: 11 (5-29), 9 months: 12 (5-30) (p<0.05) group 1 Median ESSDAI: Baseline: 24 (17-44), 6 months: 14.5 (7-21) p=0.008 group 2: baseline 12 (10-18) with no significant change.	Safety of rituximab.	6 of 17 patients had adverse events, including 2 mild arterial hypertension, 1 severe acute infusion reaction, 1 severe cutaneous infection and 1 hypogammaglobinaemia.	Mekinian, A.; Ravaud, P.; Hatron, P. Y.; Larroche, C.; Leone, J.; Gombert, B.; Hamidou, M.; Cantagrel, A.; Marcelli, C.; Rist, S.; Breban, M.; Launay, D.; Fain, O.; Gottenberg, J. E.; Mariette, X.. Efficacy of rituximab in primary Sjogren's syndrome with peripheral nervous system involvement: results from the AIR registry. Ann. Rheum. Dis. 2012;71(1):84-87.	-	-	This prospective small case series with group 1 (n=10) that included patients with cryogloulinaemia or vasculinaemia and group 2 (n=7) , which didn't. Group 1 had a higher baseline ESSDAI score (median 24) and saw a significant reduction. While group 2 had a lower ESSDAI (median 12) and saw no reduction. Small sample size and retrospective design are significant limitations.

3	Case series	688 patients	Not relevant.	Other	Proportion of patients eligible for different exclusion criteria, according to EULAR Sjogren's syndrome disease activity index (ESSDAI) and EULAR Sjogren's syndrome Patient Reported Index (ESSPRI)	Mean ESSDAI = 4.8±4.9. Proportion of patients with ESSDAI >5: 41.7% Proportion of patients with ESSDAI >9: 17.3% Proportion of patients with ESSDAI >14: 5.1% Mean ESSPRI = 5.3±2.2 Mean ESSPRI >5: 60.2% 2 of 3 ESSPRI scores >5 : 65.1% Fatigue and Dryness score >5: 54.7%	-	-	Oni, Clare; Mitchell, Sheryl; James, Katherine; Ng, Wan-Fai; Griffiths, Bridget; Hindmarsh, Victoria; Price, Elizabeth; Pease, Colin T.; Emery, Paul; Lanyon, Peter; Jones, Adrian; Bombardieri, Michele; Sutcliffe, Nurhan; Pitzalis, Costantino; Hunter, John; Gupta, Monica; McLaren, John; Cooper, Annie; Regan, Marian; Giles, Ian; Isenberg, David; Saravanan, Vadivelu; Coady, David; Dasgupta, Bhaskar; McHugh, Neil; Young-Min, Steven; Moots, Robert; Gendi, Nagui; Akil, Mohammed; Barone, Francesca; Fisher, Ben; Rauz, Saaeha; Richards, Andrea; Bowman, Simon J.; UK Primary Sjögren's Syndrome Registry*. Eligibility for clinical trials in primary Sjögren's syndrome: lessons from the UK Primary Sjögren's Syndrome Registry. Rheumatology (Oxford) 2015;0(0):0.	-	-	This case series is a retrospective analysis of patients in the UK pSS Registry. The study was designed to collect information to allow for effective future study design, however it does contain some information of relevance to the PICO. In particular, the proportion of the population with an ESSDAI >14 is found to be 5.1%.
3	Case series	15 patients	Rituximab (rituximab) 375 mg/m^2	Clinical effectiveness of the intervention	Salivary tests eye tests (Schirmer's, Rose Bengal, Tear break up time) Subjective scores for general fatigue, physical fatigue, reduced fatigue, reduced motivation.	In early pSS: significant improvement at week 12 in Rose Bengal test, Tear break up time and all subjective scores. In MALT/pSS: only significant improvement in Rose Bengal test.	Safety of rituximab.	2 of 8 patients had mild in fusion reactions in early pSS group HACAs developed in 4 of 8 patients with early pSS. No adverse events in MALT/pSS group.	Pijpe, J.; van Imhoff, G. W.; Spijkervet, F. K. L.; Roodenburg, J. L. N.; Wolbink, G. J.; Mansour, K.; Vissink, A.; Kallenberg, C. G. M.; Bootsma, H.. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum. 2005;52(9):2740-2750.	-	-	This case series examines the safety and efficacy in two small groups, one with early stage pSS (n=8) and the other with mucosa-associated lymphoid tissue (MALT) and pSS (n=7). More adverse events were recorded in early pSS group. Clinical efficacy noted in both groups. There was no further subgroup analysis of relevance to PICO. The small number and non-comparator study design are key limitations.

3	Case series	35 patients	Rituximab 375 mg/m^2	Clinical effectiveness of the intervention	Clinical remission of lymphoma	13 patients were on rituximab alone and 5 on rituximab with Chemotherapy. Out of 13 patients treated with rituximab 5 went into complete remission and 8 into partial remission or stable disease.	-	-	Pollard, Rodney P. E.; Pijpe, Justin; Bootsma, Hendrika; Spijkervet, Fred K. L.; Kluin, Philip M.; Roodenburg, Jan L. N.; Kallenberg, Cees G. M.; Vissink, Arjan; van Imhoff, Gustaaf W.. Treatment of mucosa-associated lymphoid tissue lymphoma in Sjogren's syndrome: a retrospective clinical study. J. Rheumatol. 2011;38(10):2198-2208.	-	-	This retrospective observational case series of 35 patients with MALT and pSS. 13 were treated with rituximab, with varied success. There was no calculation of ESSDAI or subgroup analysis by severity of disease. The small size of the study and even smaller rituximab intervention group, overlap of therapeutic interventions and retrospective study design limit the generalisability of the findings from this study.
3	Case series	16 patients	Rituximab (rituximab) 375 mg/m^2	Clinical effectiveness of the intervention	Efficacy of rituximab	rituximab was prescribed for lymphoma (n = 5), refractory pulmonary disease with polysynovitis (n = 2), severe polysynovitis (n = 2), mixed cryoglobulinaemia (n = 5), thrombocytopenia (n = 1) and mononeuritis multiplex (n = 1). At median follow-up of 14.5 (range 2-48) months, improvement in 4 of 5 patients with lymphomas and in 9 of 11 patients with systemic involvement. Dryness was improved in only a minority of patients. Corticosteroid dose was reduced in 11 patients. rituximab induced decreased rheumatoid factor, gamma-globulin and beta2-microglobulin levels, and the level of B cell activating factor of the tumour necrosis factor family (BAFF) increased concomitantly with B cell depletion. Five patients were re-treated, with good efficacy and tolerance, except for one with probable serum sickness-like reaction.	Safety of rituximab.	3 of 15 patients had mild adverse effects.	Seror, Raphaèle; Sordet, Christelle; Guillevin, Loic; Hachulla, Eric; Masson, Charles; Ittah, Marc; Candon, Sophie; Le Guern, Véronique; Aouba, Achille; Sibilia, Jean; Gottenberg, Jacques-Eric; Mariette, Xavier. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann. Rheum. Dis. 2007;66(3):351-357.	-	-	There was no further subgroup analysis of relevance to PICO. The small number and non-comparator study design are key limitations.

3	Case series	53 patients retrospectively studied	Rituximab	Clinical effectiveness of the intervention	Overall Survival (OS) Event Free Survival (EFS)	OS: Patients with a non-Hodgkin Lymphoma 96% (95% CL 83%-99%) at 3 years. EFS: Patients with a non-Hodgkin Lymphoma 81% (95% CL 61%-91%) at 3 years.	Adverse events	Of 35 patients, 12 had adverse events, 3 deaths 1 treatment failure, 5 relapses, 3 histological transfers.	Voulgarelis, Michael; Ziakas, Panayiotis D.; Papageorgiou, Aristea; Baimpa, Evangelia; Tzioufas, Athanasios G.; Moutsopoulos, Haralampos M.. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjögren syndrome. Medicine (Baltimore) 2012;91(1):42248.	-	-	This retrospective observational case series examined 35 patients with non-Hodgkin lymphoma, 59% of which were Mucosa-associated Lymphoma. The primary endpoints were survival rates and ESSDAI was not calculated. There was no indication of the severity of the pSS, hence little of relevance to the PICO.

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	sjogren's OR Sjögren's OR sjogren OR Sjögren AND primary
Updated search terms - Intervention	rituximab OR Rituxan OR Mabthera
Updated search terms - Comparator	Hydroxychloroquine OR Prednisolone OR Azathioprine OR Methotrexate OR Mycophenolate OR Ciclosporin OR Leflunomide
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
	Published, peer-reviewed articles identified by Simon Bowman (provided by email); this includes case reports with small numbers of patients as relevant to specific population.
Exclusion criteria	**General 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
	Articles published before 2014 and included in previous Evidence Review, unless specifically identified by Simon Bowman (see inclusion criteria above)