NHS England

Evidence review: Rituximab for the treatment of refractory Systemic Lupus Erythematosus (SLE) in adults and children

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1 Introduction

Introduction

- Systemic lupus erythematosus (SLE, lupus) is a chronic autoimmune condition that causes inflammation in the body's tissues. It affects the whole body including the skin, joints, internal organs and serous membranes and results in chronic debilitating ill health (Alshaiki et al 2018, Duxbury et al 2013).
- The cause of SLE is unknown though a combination of genetic, environmental and hormonal factors is thought to play a role in disease development and progression. Disease activity varies over time and, at the onset, symptoms are very general and may include unexplained fever, extreme fatigue, muscle and joint pain and skin rash (NICE 2014).
- Active SLE involves frequent flares and more severe symptoms compared with inactive disease which is when the disease is in remission. SLE can lead to arthritis, kidney failure, heart and lung inflammation, central nervous system abnormalities and blood disorders. Long-term damage accrues as a result of persistent disease activity and also due to cumulative effects of steroids often used to control the disease (NICE 2014).
- One of the major complications and the most common mortality-leading cause in more than 75% of SLE cases is lupus nephritis (LN), which causes proteinuria and may progress to end stage renal disease (ESRD) (Alshaiki et al 2018).
- The aim of treatment is to reduce disease activity by reducing inflammation, preventing flares and organ damage and thus improving quality of life. The chosen therapy is determined by the clinical manifestations and their combination/pattern, organ damage, disease severity and previous response to drug therapies (Alshaiki et al 2018, NICE 2014, Duxbury et al 2013)

Existing guidance from the National Institute of Health and Care Excellence (NICE)

- Whilst NICE have published guidance on the use of rituximab for a number of indications, no published guidance on the use of rituximab for SLE was identified.

The indication and epidemiology

- Although the severity of the disease is greater in the male population, SLE is significantly more common in women (90%) than men (10%). SLE most commonly presents in women in the reproductive age group, although lupus is increasingly recognized after the age of 40 years, particularly in Europeans (Gordon et al 2018).
- Lupus affected nearly one in 1000 of the population in the UK in 2012 and was most frequently observed in people of African-Caribbean and South Asian descent (NICE 2014, Gordon et al 2018). The age-standardized incidence in the UK according to the Clinical Practice Research Datalink is 8.3/100 000/year for females and 1.4/100 000/year for males, and the highest incidence rates are seen in those of African-Caribbean descent: 31.4/100 000/year, compared with 6.7/100 000/year for those of white European descent. The mean age at diagnosis is 48.9 years, but it is lower in those of African ancestry in the UK and North America (Gordon et al 2018).
- Over 90% of people with SLE develop problems with their joints and muscles such as arthralgia (joint pain) and myalgia (muscle pain). Renal disease also occurs in 40 to 75% of people with SLE and significantly contributes to morbidity and mortality (NICE 2014).
- The incidence of paediatric SLE (pSLE) is 0.3-0.9/100 000 children per year, with a

prevalence of 3.3-8.8/100 000 children. pSLE is associated with more severe and active disease compared with SLE in adults. In particular, there is a higher incidence of renal and central nervous system involvement (Mahmoud et al 2017).

- About one-third of SLE patients in the UK develop LN. ESRD has been reported to occur in 20% of LN patients within 10 years of diagnosis, and the mean age at death in LN patients was 40.3 years, with an average of 7.5 years between development of LN and death. Death from active lupus is rare in the UK; however, 10% mortality over 20 years and a mean age of death of 53.7 years was recently reported (Gordon et al 2018).

Standard treatment and pathway of care

- The goals of therapy for patients with SLE are to ensure long-term survival, achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, improve quality of life, and educate patients about their role in disease management (Duxbury et al 2013, NICE 2014).
- Standard therapy includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids such as prednisolone and disease-modifying drugs such as hydroxychloroquine to treat milder disease, with stronger immunosuppressant agents such as methotrexate, azathioprine, mycophenolate, or cyclophosphamide used in more severe disease or major organ involvement. Corticosteroids are generally used to treat disease flares, although they are often continued long-term (Oon et al 2018).
- However, despite advances in therapy over the past 20 years, significant numbers of SLE patients remain either refractory to conventional immunosuppressive therapies or require unacceptably high corticosteroid doses to control disease (McCarthy et al 2017).

The intervention (and licensed indication)

- Rituximab (RTX) is a chimeric monoclonal IgG1 kappa antibody that binds specifically to the CD20 antigen and mediates B-cell depletion, thereby preventing the renewal of autoantibodies and antigen presentation by pathogenic B cells (Mahmoud et al 2017).
- Rituximab is licensed for the treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them (in combination with methotrexate). It is also licensed for the treatment of different lymphomas, leukaemias and anti-neutrophil cytoplasmic antibody-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis (BNF 2018).
- Rituximab is currently not licensed for the management of SLE (BNF 2018).

Rationale for use

- B cells have critical roles in the pathogenesis of SLE, including cytokine production, presentation of self-antigen, T cell activation, and autoantibody production. Loss of B cell tolerance may be a pivotal event in the pathogenesis of SLE, providing a strong rationale for targeted treatments that modify the effects of B cells. Rituximab is a chimeric monoclonal antibody that selectively targets CD20-positive B cells while sparing stem cells and plasma cells (Merrill et al 2010).

2 Summary of results

- We found two systematic reviews with meta-analyses and a report of an analysis of the UK British Isles Lupus Assessment Group biologics register (BILAG-BR) fulfilling the PICO criteria for inclusion. One systematic review (Alshaiki et al 2018) included 31 studies (two RCTs and 29 observational studies, N=1,112) and the second systematic review (Shamliyan et al 2017) included three RCTs of adult patients (N=420). The BILAG-BR analysis (McCarthy et al 2017) reported on 178 out of a total of 261 patients over five years old treated with rituximab. Individual studies were excluded if they were already included in systematic reviews. Systematic reviews were excluded if more recent systematic review publications included the same primary studies.
- We did not identify any studies assessing the cost effectiveness of rituximab plus standard treatment compared with standard treatment alone for adult and/or children with refractory SLE.

Clinical effectiveness

- Major clinical response[a] in 18.4% (33 patients) was reported at six months follow-up in patients with SLE by the BILAG-BR analysis (McCarthy et al 2017). However, no comparative results were reported. There was no difference in any clinical response outcome measures between immunosuppressive agents plus adjunctive rituximab versus immunosuppressive agents alone in adult patients with refractory SLE at 52 weeks follow-up in the RCT (n=257) included in the systematic review by Shamliyan et al (2017).
- On the other hand, global response rates [73% (95% CI 67% to 78%), N=206], complete response rates [46% (95% CI 38% to 55%), N=773] and partial response rates [34% (95% CI 28% to 40%), N=928] improved after rituximab therapy in refractory SLE patients. This was also the case in patients with refractory LN with global response rates (N=57) of 70% (95% CI 55% to 81%), complete response rates (N=223) of 51% (95% CI 34% to 68%) and partial response rates of 27% (95% CI 18% to 39%) reported (N=928 for SLE and LN).This is based on the meta-analysis by Alshaiki et al (2018). However, no comparative results were reported as the results are based mainly on non-comparative studies.
- Statistically significant improvements were reported in both BILAG[b] and SLEDAI[c] scores (number of patients was not reported) after rituximab therapy in patient with refractory SLE with or without LN ($p<0.001$ for all) in the meta-analysis by Alshaiki et al (2018). However, these were not relative to any comparators as they are based on pooled results from non-comparative studies. The BILAG-BR analysis also reported that 49% of patients (n=88) had a response in terms of BILAG score[d] [median (IQR[e]) reduced from 15 (10 to 23) at baseline to 3 (2 to 12); $p<0.001$ at 6 months]. A reduction in SLEDAI-2K of greater than one point at six months follow-up was reported in 71.9% of patients (n=128) [median (IQR) reduced from 8 (5 to12) at baseline to 4 (0 to 7) $p<0.001$] (McCarthy et al 2017). Again these were not comparative results. In contrast, there was no difference in low disease activity between immunosuppressive agents plus adjunctive rituximab versus immunosuppressive agents alone in adult patients with refractory SLE at 52 weeks follow-

[a] A major clinical response is defined as BILAG-2004 category C/D or E only with SLEDAI-2K score ≤4 and daily oral glucocorticoid (prednisolone)dose ≤7.5 mg

[b] The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity.

[c] The SLEDAI is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105.

[d] The numeric BILAG-2004 global score was calculated at each time point using the values: A = 12, B= 8, C= 1 and D/E = 0

[e] interquartile range (IQR)

up. Although adjunctive rituximab appears to be better at preventing flares [RR 1.41 (95% CI 1.01 to 1.95) numbers needed to treat (NNT=7)]. This is based on one low quality RCT (n=257) included in the systematic review by Shamliyan et al (2017).

- Adjunctive rituximab plus immunosuppressive agents increased the rates of partial renal response [RR[f] 2.00 (95% CI 1.05 to 3.82) NNT = 7] but not complete renal response [RR 0.9 (95% CI 0.5 to 1.5)] compared with immunosuppressive agents alone in patients with refractory LN at 52 weeks follow-up. This is based on one low quality RCT (n=144) included in the systematic review by Shamliyan et al (2017).
- There were significant renal BILAG domain improvements (NNT=5) with immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory LN at 52 weeks follow-up. This is based on one low quality RCT (n=144) included in the systematic review by Shamliyan et al (2017).
- There was a significant reduction in prednisolone dose (mg/d) from baseline in both LN [mean difference -12.50 (95% CI -6.36 to -18.64), p<0.001] and SLE [mean difference -22.93 (95% CI -0.01 to -45.88), p<0.001)] patients after rituximab therapy. This is based on pooled results from five non-comparative studies (number of patients was not reported) by Alshaiki et al (2018). The BILAG-BR analysis also reported a reduction from baseline in prednisolone dose at six months follow-up (n=149). The median dose reduced from 11.25mg (8.375 to 20 mg) to 7.5mg (5 to 12 mg), p<0.001 (McCarthy et al 2017).
- Proteinuria (g/d) was insignificantly decreased in LN patients [mean difference -2.52 (95% CI 0.22 to -5.27), p=0.07]. The decline in proteinuria was significant in SLE patients [mean difference -2.40 (95% CI -1.39 to -3.42), p<0.001]. These results were based on pooled results from four non-comparative studies (number of patients was not reported) included in Alshaiki et al (2018).
- In patients with refractory LN who have had an inadequate response to immunosuppressive agents, adjunctive rituximab reduced urine protein to creatinine (UPC) ratio[g] by ≥50% compared with immunosuppressive agents alone at 78 weeks follow-up (NNT = 6). This is based on one low quality RCT included in the systematic review by Shamliyan et al (2018)
- All the above results should be interpreted with caution as they are from non-comparative studies as well as low quality RCTs of rituximab when used in addition to conventional treatment in refractory SLE with or without LN.

Safety

- The most common adverse reactions associated with rituximab reported in the systematic review by Alshaiki et al (2018) were infection (urinary or respiratory), acute or delayed infusion reactions, sepsis-like syndrome, thrombocytopenia and serum sickness-like reaction. The authors reported two deaths one from varicella and the other from septicaemia. The BILAG-BR analysis reported 185 infectious episodes in 82 patients during a nine-month period. Fifty-four patients suffered multiple infections and 29 serious infections occurred in 26 patients (McCarthy et al 2017).
- No difference in all-cause mortality or adverse events was reported between immunosuppressive agents plus adjunctive rituximab versus immunosuppressive agents alone in adult patients with refractory SLE including those with LN. This is based on one low quality RCT included in the systematic review by Shamliyan et al (2017).

Cost effectiveness

- No studies that evaluated the cost effectiveness of rituximab plus standard treatment

[f] Relative risk is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group.
[g] Urine protein: creatinine ratio (UPCR) assay is used typically to diagnose proteinuria and monitor patients with established proteinuria.

compared to standard treatment alone for the treatment of refractory SLE in adults and children were found.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources Embase, MEDLINE, Cochrane library, TRIP and NICE Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st October 2008 and 18th October 2018.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review.
- Studies were excluded if they were already included in systematic reviews. Systematic reviews were excluded if more recent systematic reviews included the same primary studies.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4 Results

We found two systematic reviews with meta-analyses and a report of an analysis of the British Isles Lupus Assessment Group biologics register (BILAG-BR) fulfilling the PICO criteria for inclusion. One systematic review (Alshaiki et al 2018) included 31 studies (two RCTs, 16 prospective case series and 14 retrospective case series; N=1,112) and the second systematic review (Shamliyan et al 2017) included three RCTs of adult patients (N=420) but only reported adverse events from one of the studies. The analysis (McCarthy et al 2017) reported on 178 out of a total of 261 patients over five years old treated with rituximab. We did not find any comparative studies published subsequent to the systematic reviews. Individual studies were excluded if they were already included in systematic reviews. Systematic reviews were excluded if more recent systematic reviews included the same primary studies.

We did not identify any studies assessing the cost effectiveness of rituximab for adult and/or children with refractory SLE.

What is the evidence on the clinical effectiveness of rituximab and standard care compared with standard care alone for adults and children with refractory SLE?

The clinical outcomes reported in the systematic reviews include global, overall, complete and partial response rates, complete and partial renal response rates, major and partial clinical responses, change in disease activity, BILAG, renal BILAG and SLEDAI scores, and change in

proteinuria as well as urine protein to creatinine ratio and change is prednisolone dose. The large number of outcomes is due to the number of observational studies included in Alshaiki et al (2018).

Global response rate

Global response to RTX was reported by Alshaiki et al (2018) based on three case series that enrolled 57 LN patients and four case series with 206 SLE patients. The pooled global response rate among LN and SLE patients was 70% (95% CI 55% to 81%) and 73% (95% CI 67% to 78%), respectively. No p values were reported and these were not comparative results.

Overall response

Two RCTs (N=401) included in Shamliyan et al (2017) reported no difference in overall response between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 1.0 (95% CI 0.7 to 1.6)] or with LN [RR 1.2 (95% CI 0.9 to 1.7)] at 52 weeks or those with LN at 78 weeks follow-up [RR 1.3 (95% CI 0.9 to 1.7)].

Complete response rate

Alshaiki et al (2018) reported data on complete remission based on 28 studies (mostly uncontrolled, one RCT); of them, 17 studies (N=773) were on SLE, 10 (N=223) on LN, and one study enrolled 10 patients with NPSLE. The pooled complete response rate was 46% (95% CI 38% to 55%) in SLE patients, 51% (95% CI 34% to 68%) in LN patients and 90% (95% CI 53% to 99%) in NPSLE patients. No p values were reported and these were not comparative results.

Complete renal response rate

One RCT (n=144) included in Shamliyan et al (2017) reported no difference in complete renal response at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory LN [RR 0.9 (95% CI 0.5 to 1.5)]

Major clinical response

One RCT (n=257) included in Shamliyan et al (2017) reported no difference in major clinical response at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 0.8 (95% CI 0.4 to 1.5)]

The BILAG-BR analysis by McCarthy et al (2017) reported that major clinical response[h] was achieved in 33/178 (18.4%) of patients at six months follow-up. However, these were not comparative results and no detailed breakdown or p values were provided.

Partial response rate/ Partial clinical response

Alshaiki et al (2018) reported partial response to RTX based on 25 case series; nine on LN and 16 on refractory SLE (N=928). The number of patients for the individual indications was not given. The pooled partial response rates were 27% (95% CI 18% to 39%) and 34% (95% CI, 28% to 40%) for LN and SLE respectively. No p values were reported and these were not comparative results. In contrast, Shamliyan et al (2017) found that there was no difference at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with SLE [RR 1.4 (95% CI 0.7 to 2.6)] based on one RCT (n=257).

[h] A major clinical response, defined as BILAG-2004 C/D/Es only with SLEDAI-2K ≤4 and daily oral glucocorticoid (prednisolone)dose ≤7.5 mg

Partial renal response rate
Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in partial renal response at 52 weeks compared with standard treatment alone in patients with LN [RR 2.00 (95% CI 1.05 to 3.82) NNT =7].

[i]***Change in BILAG score***
Pooled results from four case series (number of patients was not reported) showed that BILAG score was significantly reduced in both LN [mean difference -10 (95% CI -4.37 to -15.63), p<0.001] and SLE [mean difference -10.16 (95% CI -8.36 to -11.97), p<0.001] patients after rituximab therapy (Alshaiki et al 2018).

The BILAG-BR analysis by McCarthy et al (2017) also reported that Primary response[j] in terms of BILAG score was achieved in 91/178 (51%) and 88/178 (49%) patients at 3 and 6 months respectively. The median (IQR) BILAG-2004 global score at baseline (n=109) was 15 (10 to 23). This reduced to 4 (2 to 13), p<0.001 at 3 months (n=70) and 3 (2 to12), p<0.001 at 6 months (n=56).

Renal BILAG domain improvement
Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in renal BILAG score at 52 weeks compared with standard treatment alone in patients with LN [RR 1.4 (95% CI 1.1 to 1.8), NNT=5].

Change in SLEDAI score
Pooled results from four case series (number of patients was not reported) by Alshaiki et al (2018) showed that SLEDAI score significantly decreased from baseline in both LN [mean difference -10.59 (95% CI -9.40 to -11.78), p<0.001] and SLE [mean difference -6.90 (95% CI -4.17 to -9.63), p<0.001] patients after RTX therapy. Shamliyan et al (2017) found that there was no difference in low disease activity at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with SLE [RR 1.14 (95% CI 0.96 to 1.36)] based on one RCT (n=257). However, they reported a significant difference in low disease activity without flares in these patients [RR 1.41 (95% CI 1.01 to 1.95) NNT = 7]; the RR as well as the confidence interval is greater than one.

The BILAG-BR analysis by McCarthy et al (2017) also reported that 129/178 (72.5%) and 128/178 (71.9%) patients had a reduction in SLEDAI-2K of greater than one point at three and six months follow-up respectively. The median (IQR) SLEDAI-2K reduced from 8 (5 to12) at baseline to 4 (2 to 8), p<0.001 at 3 months and 4 (0 to 7),p<0.001 at six months.

Change in Prednisolone dose (mg/d)
The pooled mean difference from five case series (number of patients was not reported) showed that prednisolone dose (mg/d) was significantly decreased from baseline in both LN [mean difference -12.50 (95% CI -6.36 to -18.64), p<0.001] and SLE [mean difference -22.93 (95% CI -0.01 to -45.88), p<0.001) patients after rituximab therapy (Alshaiki et al 2018).

[i] The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity.
Total BILAG score is obtained by adding the scores from all affected organs using the numerical scoring of the BILAG-2004 of A = 12, B = 8, C = 1, and D and E = 0
[j] Primary definition of response is loss of all A and B BILAG scores to ≤1; B score with no new A/B scores in other organ domains at 6 months

The BILAG-BR analysis also reported a reduction from baseline in prednisolone dose at six months follow-up (n=149). The median dose reduced from 11.25mg (8.375 to 20 mg) to 7.5mg (5 to 12 mg), p<0.001 (McCarthy et al 2017).

Change in Proteinuria (g/d)

Four case series (number of patients was not reported) included in the meta-analysis by Alshaiki et al (2018) reported on the change of proteinuria. Pooled results from these studies showed a significant decline in proteinuria from baseline was in SLE patients (mean difference -2.40 (95% CI -1.39 to -3.42), p<0.001. However, these studies failed to show a significant decrease proteinuria from baseline in LN patients [mean difference -2.52 (95% CI 0.22 to -5.27), p=0.07. Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant reduction in proteinuria demonstrated by a ≥50% reduction in UPC ratio[k] at 78 weeks compared with standard treatment alone in patients with LN [RR 1.31 (95% CI 1.01 to 1.69), NNT=6)] although this was not the case at 52 weeks.

What is the evidence on the safety of rituximab and standard care compared with standard care alone for adults and children with refractory SLE?

Adverse events

Alshaiki et al (2018) reported that in patients with refractory SLE, infections (four case series), acute or delayed infusion reactions (two case series), thrombocytopenia (one case series), sepsis-like syndrome (two case series) and serum sickness-like reactions (one case series) were reported. However, no further details provided.

Shamliyan et al (2017) reported that there was no difference in adverse effects leading to treatment discontinuation between adjuvant rituximab and standard treatment alone in refractory SLE (one RCT, n=257) at 52 weeks [RR 0.8 (95% CI 0.4 to 1.5)] and LN (one RCT, n=144) at 78 weeks [RR 0.3 (95% CI 0.0 to 3.0)]. They found no difference in serious infections between the treatment arms in patients with refractory SLE at 52 weeks [RR 0.3 (95% CI 0.1 to 2.0)]. They also reported no difference in any infection or total adverse events at 78 weeks in patients with refractory LN based one RCT (n=144), [RR 0.9 (95% CI 0.8 to 1.1)] and [RR, 1.03 (95% CI 0.97 to 1.09)] respectively.

The BILAG-BR analysis by McCarthy et al (2017) reported 185 infectious episodes in 82 patients during a nine month period. Fifty-four patients suffered multiple infections and 29 serious infections occurred in 26 patients. The most common infections were respiratory (n=88) and urinary tract infections (n=36). 111 (60%) infections occurred within the first three months, while 60(32%) infections occurred between three and six months and 14(8%) occurred between six and nine months.

All-cause mortality

There was no difference in all-cause mortality between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE with or without LN [SLE (one RCT, n=257) at 52 weeks: RR 2.1 (95% CI 0.2 to18.4) and LN (2 RCTs, n=163) at 52 to 78 weeks: RR 4.9 (95% CI 0.2 to 99.6). This was based on three RCTs (n=420) included in the meta-analysis by Shamliyan et al (2017).

[k] Urine protein: creatinine ratio (UPCR) assay is used typically to diagnose proteinuria and monitor patients with established proteinuria.

What is the evidence in the cost effectiveness of rituximab for adults and children with refractory SLE?
No studies that evaluated the cost effectiveness of rituximab for adults and children with SLE were identified.

5 Discussion

The evidence identified for the clinical effectiveness of adjuvant rituximab in patients with refractory SLE is conflicting in terms of reducing disease activity and improving overall, clinical and partial responses. The evidence however suggests that the treatment offers some benefit in terms of improving partial renal response and reducing proteinuria in adult patients with LN.

The evidence is based on the results from an analysis of UK registry data and two systematic reviews with limitations in the quality of the studies included, the methodologies applied and the generalisability of the study results to the population of interest. These cast uncertainties on the usefulness of the results. In addition, no long-term results were reported.

The analysis of UK registry data by McCarthy et al (2017) suggests that rituximab is safe and is associated with improvement in disease activity in refractory SLE patients with concomitant reductions in corticosteroid use. These findings should be treated with caution as the use of rituximab was not compared to standard therapy alone and without a comparator we cannot be certain of its relative effectiveness. In addition, the unblinded nature of any registry introduces the potential for bias as does the potential for inter-physician variability in assessing disease activity and reporting adverse events. Also complete data was not available for all the patients analysed.

The systematic review by Alshaiki et al (2018) concludes that rituximab improves clinical outcomes and has a good safety profile in SLE patients (age range was not provided) refractory to conventional treatment. These findings should be treated with caution because the authors included non-comparative studies as well as two RCTs in their meta-analysis. Without a comparator we cannot be certain of how adding rituximab to standard treatment compares with standard treatment alone in patients with refractory SLE. There was heterogeneity among the studies included in the systematic reviews in terms of the outcome measures reported and the doses of rituximab used in the studies. In addition the outcome measures reported were not clearly defined and may have been subject to inter-study and or inter-assessor interpretation. P values and confidence intervals were not provided for many of the outcomes reported.

The two clinical effectiveness studies - low quality RCTs of adult patients (as the third study only reported on safety) assessed by Shamliyan et al (2017) did not prove that rituximab when used in addition to conventional treatment in adult patients with SLE with or without LN is superior to standard treatment alone in terms of clinical response, adverse events and all-cause mortality. However, partial renal response and proteinuria outcome measures were reported to improve in patients with LN. These findings should be interpreted carefully as the RCTs assessed by the systematic review were deemed to be of low quality by the authors; there was a risk of bias due to the fact that they were sponsored by the manufacturers and treatment effects reported were imprecise.

The findings of the two SRMAs may not be generalisable to the NHS in England as the immunosuppressant agents or doses used in the primary studies varied and may not be the same as those used in clinical practice in the UK.

The safety profile of rituximab in this setting appears to be good, with no significant difference in overall severe adverse events, adverse events that lead to discontinuation as well as infections compared with control groups. However the absolute numbers were not available.

6 Conclusion

It is uncertain whether adding rituximab to standard care is more effective at improving clinical response than standard care alone in adults and children with refractory SLE. Whilst the evidence from an analysis of registry data and a meta-analysis of RCTs and observational studies combined suggests that adjuvant rituximab is effective, slightly more reliable evidence from a systematic review of low quality RCTs failed to prove its superiority over standard treatment alone. However, it appears that adjuvant rituximab may offer modest clinical benefits in partial renal response and reduction in proteinuria in SLE adult patients with LN.

The administration of rituximab seems to be well tolerated with no increase in risk of adverse events seen in the studies that reported these.

Further large well-designed multicentre RCTs are required to shed light on the comparative effectiveness of adjuvant rituximab in patients with refractory SLE with or without LN.

7 Evidence Summary Table

For abbreviations see list after each table

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Alshaiki et al 2018 Saudi Arabia 31 studies in the meta-analysis - Two RCTs; 14 prospective case series; 16 retrospective case series Studies conducted between 2005 & 2016; No search date reported	S1-meta-analysis	Patients with refractory SLE with/without LN and/or NPSLE N=1112 Age of included patients was not specified Mean follow-up period was 10.6 months (3 to 38)	Rituximab + immunosuppressant agents **VERSUS** Immunosuppressant agents alone in the RCTs No comparator in the observational studies. Dose of RTX varied between studies - 375mg/m^2 qds or 500mg bd or 1g bd, 2 weeks apart. Doses of 500mg qds, 375 mg/m^2 bd or qds and 750mg bd were also infused	Primary Clinical effectiveness	Global response rate (proportion of patients who achieved a global response rate)	**Pooled results (7 case series)** **LN (n=57)** 70% (95% CI 55% to 81%) **No p values reported** **SLE (n=206)** 73% (95% CI 67% to 78%) **No p values reported** **Overall** 72% (95% CI 67% to 78%) **No p values reported**	7/10	Direct	The outcome measures reported were not clearly defined so these could have been interpreted differently by different assessors. In addition different studies may have different criteria for 'the same' outcome. Non-comparative studies were included in this meta-analysis and no comparative overall results reported; without a comparator it is not possible to know the relative effectiveness of adjuvant RTX. It is not clear what the optimum dose of RTX should be as different doses and regimens were used in the studies. Results may not be generalisable as the immunosuppressant agents or doses used in the studies may not be the same as those used in clinical practice in the UK. Data on adverse events were not clearly reported. Effect of RTX on quality of life not reported in the studies so it is unclear what the results mean in terms of activities of daily living or quality of life. No long-term outcomes were reported.
				Primary Clinical effectiveness	Complete response rate (proportion of patients who achieved a complete response rate)	**Pooled results (28 studies – 27 case series + one RCT)** **LN (n=223)** 51% (95% CI 34% to 68%) **NPSLE (n=10)** 90% (95% CI 53% to 99%) **SLE (n=773)** 46% (95% CI 38% to 55%) **Overall** 49% (95% CI 41% to 57%) **No p values reported**			
				Primary Clinical effectiveness	Partial response rate (proportion of patients who achieved a partial response rate)	**Pooled results (25 case series, n=928)** **LN (n=not reported)** 27% (95% CI 18%-39%) **SLE (n=not reported)**			

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						34% (95% CI 28% to 40%) **Overall** 32% (95% CI 27% to 38%) **No p values reported**			
				Secondary Clinical effectiveness	Change in BILAG[l] score[m]	**Pooled results (4 case series)** **LN (n=not reported)** MD -10 (95% CI -4.37 to -15.63), p<0.001 **SLE (n=not reported)** MD -10.16 (95% CI -8.36 to -11.97), p<0.001) **Overall** MD -10.15 (95% CI -8.43 to -11.87), p<0.001			
				Secondary Clinical effectiveness	Change in SLEDAI score[n]	**Pooled results (4 case series)** **LN (n=not reported)** MD -10.59 (95% CI -9.40 to -11.78) p<0.001 **SLE (n=not reported)** MD - 6.90 (95% CI -4.17 to -9.63), p<0.001) **Overall**			

[l] Composite measures of disease activity (increase in score indicates worse severity): The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity.

[m] Total BILAG score was obtained by adding the scores from all affected organs using the numerical scoring of the BILAG-2004 of A = 12, B = 8, C = 1, and D and E = 0

[n] The SLEDAI is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105.

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						MD - 10 (95% CI -8.91 to -11.09), p<0.001			
				Secondary Clinical effectiveness	Change in Prednisolone dose (mg/d) after therapy	**Pooled results (5 t case series)** **LN (n=not reported)** MD - 12.50 (95% CI -6.36 to -18.64), p<0.001 **SLE (n=not reported)** MD - 22.93 (95% CI -0.01 to -45.88), p<0.001 **Overall** MD - 13.20 (95% CI -7.27 to -19.13), p<0.001			
				Secondary Clinical effectiveness	Change in Proteinuria (g/d)	**Pooled results (4 case series)** **LN (n=not reported)** MD - 2.52 (95% CI 0.22 to -5.27), p=0.07 **NS** **SLE (n=not reported)** MD - 2.40 (95% CI -1.39 to -3.42), p<0.001 **Overall** MD - 2.42 (95% CI -1.47 to -3.37), p<0.001			
				Safety	Adverse drug reaction	Infections (4 case series) Acute or delayed infusion reactions (2 case series) thrombocytopenia (1 case series) Sepsis-like syndrome (2 case series) serum sickness-like reaction (1 case series)			

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						No other details provided			
McCarthy et al 2017 Registry data analysis – observational study	S2 – secondary analysis of existing data	Patients with persistent active SLE[o] ≥5 yrs old (proportion or ratio of children to adults was not provided) & commenced biologic therapy within the last 12 months. Assessment was carried out at 6 months. RTX n=261; 178 assessed at 6 months	Rituximab + immunosuppressant agents Observational study therefore no comparator	Primary Clinical effectiveness	Major clinical response[p]	**At 6 months** MCR achieved in 33/178(18.4%) **No p values reported**	7/10	Direct	No comparative overall results were reported; without a comparator it is not possible to know the relative effectiveness of adjuvant RTX. Complete data were not available for every patient and the unblinded nature of any registry has the potential to confound interpretation of results as does the potential for inter-physician variability in assessing disease activity and reporting adverse events. It is not clear what the optimum dose of RTX should be as the dose of RTX administered was not explicitly reported in the analysis. Effect of RTX on quality of life not reported in the studies so it is unclear what the results mean in terms of activities of daily living or quality of life. No long-term outcomes were reported.
				Primary Clinical effectiveness	Change in BILAG-2004 score[q]	Primary response[r] achieved in 91/178 (51%) patients at 3 months & 88/178 (49%) patients at 6 months. Median (IQR) BILAG-2004 global score Baseline (n=109): 15 (10 to 23) At 3 months **(n=70)**: 4 (2 to 13), p<0.001 At 6 months **(n=56):** 3 (2 to12), p<0.001			
				Primary Clinical effectiveness	Change in SLEDAI-2K score[s]	Patients who had a reduction in SLEDAI-2K of>1 point: At 3 months: 129/178 (72.5%) At 6 months: 128/178 (71.9%). Median SLEDAI-2K score (IQR) Baseline: 8 (5 to 12)			

[o] persistent active SLE (defined as at least one BILAG A score and/or two B scores, or a SLEDAI-2K score >6) and failure to respond or documented adverse events to two or more standard immunosuppressive therapies

[p] A major clinical response, defined as BILAG-2004 C/D/Es only with SLEDAI-2K ≤4 and daily oral glucocorticoid (prednisolone)dose ≤7.5 mg

[q] Total BILAG score is obtained by adding the scores from all affected organs using the numerical scoring of the BILAG-2004 of A = 12, B = 8, C = 1, and D and E = 0

[r] Primary definition of response is loss of all A and B BILAG scores to ≤1; B score with no new A/B scores in other organ domains at 6 months

[s] The SLEDAI (SLEDAI-2K is the 2002 version) is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105.

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						At 3 months: 4 (2 to 8), p<0.001 At 6 months: 4 (0 to 7), p<0.001			
				Primary Clinical effectiveness	Reduction in prednisolone dose	Median (IQR) dose Baseline (n=149):11.25mg (8.375 to 20 mg) prednisolone/equivalent At 3 months **(n=not reported**:10mg (6.8 to 15 mg), p<0.001 At 6 months **(n=not reported:** 7.5mg (5 to 12 mg), p<0.001			
				Primary Clinical effectiveness	Adverse events	**At 9 months** Infections: 185 episodes in 82 patients Serious infections: 29 episodes in 26 patients. Multiple infections: 54 patients Most common infections: respiratory (n = 88) UTIs (n = 36) At 3 months: 111 (60%) infection episodes Between 3 & 6 months: 60 (32%) infection episodes Between 6 & 9 months: 14 (8%) infection episodes			
Shamliyan et al 2017 SR of three RCTs	S1-meta-analysis	Adult patients with refractory SLE with/without LN	Rituximab + immunosuppressant agents **VERSUS**	Primary Clinical effectiveness	Overall response rate	**SLE (1 RCT, n=257)** At 52 weeks RR 1.0 (95% CI 0.7 to 1.6) **ND**	7/10	Direct	Evidence was from low quality and very low quality studies because of high risk of bias mainly due to the fact that the studies were sponsored by the manufacturers and treatment effects reported were imprecise.

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Search date – Jan 2017		N=420	Immunosuppressant agents alone RTX dose (SLE) = 1g twice 14 days apart RTX dose (SLE + LN) = 1g, 4 injections, days 1, 15, 168, and 182			**LN (1 RCT, n=144)** At 52 weeks RR 1.2 (95% CI 0.9 to 1.7) **ND** At 78 weeks RR 1.3 (95% CI 0.9 to 1.7) **ND**			Results may not be generalisable as the immunosuppressant agents or doses as well as the RTX dose used in the studies may not be the same as those used in clinical practice in the UK. Effect of RTX on quality of life not reported in the studies so it is unclear what the results mean in term of daily life. No long-term results were reported.
				Primary Clinical effectiveness	Major clinical response[t] at 52 weeks	**SLE (1 RCT, n=257)** RR 0.8 (95% CI 0.4 to 1.5) **ND**			
				Primary Safety	Complete renal response at 52 weeks	**LN (1 RCT, n=144)** RR 0.9 (95% CI 0.5 to 1.5) **ND**			
				Primary Clinical effectiveness	Partial clinical response[u] at 52 weeks	**SLE (1 RCT, n=257)** RR 1.4 (95% CI 0.7 to 2.6) **ND**			
				Primary Safety	Partial renal response at 52 weeks	**LN (1 RCT, n=144)** RR 2.00 (95% CI 1.05 to 3.82) **NNT=7; favours RTX**			
				Primary Clinical effectiveness	Low disease activity at 52 weeks	**SLE (1 RCT, n=257)** RR 1.14 (95% CI 0.96 to 1.36)] **ND**			

[t] The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity. ******Major clinical response was defined as achieving British Isles Lupus Assessment Group (BILAG) C scores or better (score ≤1) in all organ systems at week 24 and maintaining this response without a flare to week 52.

[u] Partial response was defined as follows: (1) achieving total BILAG C scores or better (score ≤1) at week 24 and maintaining this response for 16 consecutive weeks; (2) achieving no more than 1 organ with a BILAG B score (score = 3) at week 24 without worsening remaining organs to week 52; or (3) achieving a maximum of 2 BILAG B scores (score = 3) at week 24 without developing BILAG A or B scores in new domains until week 52.

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
				Primary Clinical effectiveness	Low disease activity[v] without subsequent flare at 52 weeks	**SLE (1 RCT, n=257)** RR 1.41 (95% CI 1.02 to 1.95) **NNT=7; favours RTX**			
				Primary Clinical effectiveness	BILAG renal domain Improvement at 52 weeks	**LN (1 RCT, n=144)** RR 1.4 (95% CI 1.1 to 1.8) **NNT=5**; **favours RTX**			
				Primary Clinical effectiveness	UPC ratio, reduction by ≥50%,	**LN (1 RCT, n=144)** At 52 weeks RR 1.2 (95% CI 0.9 to 1.5) **ND** At 78 weeks RR 1.31 (95% CI 1.01 to 1.69**) NNT=6; favours RTX**			
				Primary Safety	Total adverse events leading to treatment discontinuation	**SLE (1 RCT, n=257)** At 52 weeks RR 0.8 (95% CI 0.4 to 1.5) **ND** **LN (RCT, n=144)** At 78 weeks RR 0.3 (95% CI 0.0 to 3.0) **ND**			
				Primary Safety	Serious infections at 52 weeks	**SLE (1 RCT, n=257)** RR 0.3 (95% CI 0.1 to 2.0) **ND**			
				Primary Safety	Any infection at 78 weeks	**LN (1 RCT, n=144)** RR 0.9 (95% CI 0.8 to 1.1) **ND**			
				Primary Safety	All-cause mortality	**SLE (1 RCT, n=257)** At 52 weeks RR 2.1 (95% CI 0.2 to 18.4)			

[v] Low disease activity was defined as achievement of BILAG C or better (score ≤1), without subsequent occurrence of ≥1 domain with BILAG A score (score = 9).

Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						ND **LN (2 RCTs, n=163)** At 52 to 78 weeks RR 4.9 (95% CI 0.2 to 99.6) **ND**			

BILAG - British Isles Lupus Assessment Group; CR – complete response; LN – lupus nephritis; MCR – major clinical response; MD - mean difference; ND – no difference; NNT – numbers needed to treat; NPSLE – neuropsychiatric systemic lupus erythematosus; PR – partial response; pSLE - Paediatric systemic lupus erythematosus; RCT - randomized controlled trial; RR – relative risk (the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group); RTX - rituximab; SI - serious infection; SLE - Systemic Lupus Erythematosus; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index; UPC ratio - urine protein : creatinine ratio; UTI – urinary tract infection.

8 Grade of Evidence Table

For abbreviations see list after the table

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Global/Overall response	Alshaiki et al 2018 Shamliyan et al 2017	7/10	Direct	A	Global or Overall response refers to any response to treatment. This was defined in the systematic review by Shamliyan et al (2017) as partial or complete response. Alshaiki et al (2018) reported global response rates based on three case series that enrolled 57 LN patients and four studies with 206 SLE patients. The pooled global response rates among LN and SLE patients were 70% (95% CI 55% to 81%) and 73% (95% CI 67% to 78%), respectively. No p values were reported and these were not comparative results. The two RCTs (n=401) assessed by Shamliyan et al (2017) that reported on overall response found no difference between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 1.0 (95% CI 0.7 to 1.6)] or with LN [RR 1.2 (95% CI 0.9 to 1.7)] at 52 weeks or those with LN at 78 weeks follow-up [RR 1.3 (95% CI 0.9 to 1.7)]. Global or overall response refers to any response to rituximab treatment; it is not an indication of mild disease or cure, just an improvement in disease activity. This is likely to be valuable to patients with refractory SLE. It is not entirely certain what these results mean for the patients with refractory SLE as Alshaiki et al (2018) suggest that about 70% of patients with refractory SLE will have some response (either complete or partial) when rituximab is added to standard treatment. On the contrary, Shamliyan et al (2017) suggests that adjunctive rituximab does not make a difference to overall response in patients with refractory SLE compared with standard treatment alone. These results however should be interpreted with caution as the meta-analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.
Complete response/remission	Alshaiki et al 2018	7/10	Direct	B	Complete response was not defined by Alshaiki et al (2018). However, Duxbury et al (2013) defined complete response as the absence of BILAG A or B scores. Alshaiki et al (2018) reported data on complete remission based on 28 studies - case series and one RCT. Of these, 17 studies (n=773 patients) were on refractory SLE, 10 (n=223 patients) on LN, and one study enrolled

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					10 patients with NPSLE. The pooled complete response rate was 46% (95% CI, 38% to 55%) in SLE patients, 51% (95% CI 34% to 68%) in LN patients and 90% (95% CI 53% to 99%) in NPSLE patients. No p values were provided. Complete response indicates a valuable effect of treatment however it does not indicate cure. The results suggest that adding rituximab to standard treatment increases the complete response rate in patients with refractory SLE with or without LN. However, it is unknown how the intervention compares to standard treatment alone. It is difficult to interpret these results because the outcome was not defined and may have been subject to inter-study and/or inter-assessor differences and individual interpretation. This is particularly noteworthy as the results were based on 28 studies (mostly non-comparative studies). These clinical benefits suggested by this systematic review may not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment.
Major clinical response	Shamliyan et al 2017 McCarthy et al 2017	7/10	Direct	A	Major clinical response refers to the presence of minimal disease activity, defined in the systematic review by Shamliyan et al (2017) as achieving BILAG C scores or better in all organ systems at week 24 and maintaining this response without a flare to week 52. A major clinical response, defined by McCarthy et al (2017) as BILAG-2004 C/D/Es only with SLEDAI-2K ≤4 and daily oral glucocorticoid (prednisolone)dose ≤7.5 mg Shamliyan et al (2017) reported that there was no reported difference in major clinical response at 52 weeks between immunosuppressive agents plus rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 0.8 (95% CI 0.4 to 1.5)]. This is based on one RCT (n=257) McCarthy et al (2017) reported that major clinical response was achieved in 33 (18.4%) of patients at six months follow-up. Major clinical response indicates a valuable effect of treatment although this does not indicate cure in patients with refractory SLE. The results reported by Shamliyan et al (2017) suggest that adjunctive rituximab is not beneficial in improving major clinical response while the analysis by McCarthy et al (2017) suggests that this outcome is achieved in less than a fifth of patients with refractory SLE. These results should be interpreted with caution as they were from an RCT deemed to be of low quality by the authors of the systematic review and non-comparative analysis.

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Partial response	Alshaiki et al 2018 Shamliyan et al 2017	7/10	Direct	A	Partial response is defined in the systematic review by Shamliyan et al (2017) as follows: 1. achieving total BILAG C scores or better at week 24 and maintaining this response for 16 consecutive weeks; 2. achieving no more than 1 organ with a BILAG B score at week 24 without worsening remaining organs to week 52; or 3. achieving a maximum of 2 BILAG B scores at week 24 without developing BILAG A or B scores in new domains until week 52. Alshaiki et al (2018) reported partial response to rituximab based on 25 case series; nine on LN and 16 on refractory SLE (N=928). The number of patients for the individual indications was not given. The pooled partial response rates were 27% (95% CI 18% to 39%) and 34% (95% CI, 28% to 40%) for LN and SLE respectively. No p values were reported and these were not comparative results as they were based mainly on non-comparable studies. Shamliyan et al (2017) on the other hand found that there was no difference at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE [RR 1.4 (95% CI 0.7 to 2.6)] based on one RCT (n=257). Partial response indicates an improvement in disease activity in refractory SLE patients. This could be maintaining minimal disease activity short term, moderate disease activity for slightly longer or a combination of these in different organs. Although this is not a cure it is likely to be of some value in patients with consistent active disease. The results reported by Alshaiki et al (2018) suggest that rituximab increases partial response rates in patients with refractory SLE with and without LN. Whereas the results by Shamliyan et al (2017) suggest that adjunctive rituximab is not beneficial in improving partial response in patients with refractory SLE compared with standard treatment alone. These results however should be interpreted with caution as the meta-analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in BILAG score	Alshaiki et al 2018	7/10	Direct	A	The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity. Total BILAG score is obtained by combining the scores from all affected organs using the numerical scoring of the BILAG-2004 of A = 12, B = 8, C = 1, and D and E = 0 Pooled results from four case series (number of patients was not reported) by Alshaiki et al (2018) showed that BILAG score was significantly reduced in both LN [mean difference -10 95% CI (-4.37 to -15.63), p<0.001] and SLE [mean difference -10.16 (95% CI -8.36 to -11.97), p<0.001] patients after rituximab therapy. The BILAG-BR analysis by McCarthy et al (2017) also reported that Primary response[w] in terms of BILAG score was achieved in 91 (51%) and 88 (49%) patients at 3 and 6 months respectively. The median (IQR) BILAG-2004 global score at baseline (n=109) was 15 (10 to 23), 4 (2 to 13); p<0.001 at 3 months (n=70) and 3 (2 to12); p<0.001 at 6 months (n=56). Primary response in terms of BILAG score indicates the loss of A (very active disease) scores and B (moderate disease activity) scores in one or no organs. The absence of active or moderate disease activity is likely to be a valuable treatment effect in patients with refractory SLE although it is not a cure. The results suggest that adding rituximab to standard treatment improves the BILAG scores in patients with refractory SLE with or without LN. However, it is unknown how the intervention compares to standard treatment alone. The clinical benefits reported by this systematic review need to be interpreted with caution as the meta-analysis only included non-comparative studies for this outcome which means that the comparative efficacy of adjunctive rituximab compared to standard treatment alone is unknown.
	McCarthy et al 2017	7/10	Direct		

[w] Primary definition of response is loss of all A and B BILAG scores to ≤1; B score with no new A/B scores in other organ domains at 6 months

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in SLEDAI score/low disease activity	Alshaiki et al 2018	7/10	Direct	A	SLEDAI scores are used to assess disease activity and response to treatment. It is a global index that evaluates disease activity over the previous 10 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and haematological. The maximum score is 105. Pooled results from four case series (number of patients was not reported) by Alshaiki et al (2018) showed that SLEDAI score significantly decreased from baseline in both LN [mean difference -10.59 (95% CI -9.40 to -11.78) p<0.001] and SLE [mean difference - 6.90 (95% CI -4.17 to -9.63), p<0.001] patients after rituximab therapy. The BILAG-BR analysis by McCarthy et al (2017) also reported that 129 (72.5%) and 128 (71.9%) patients had a reduction in SLEDAI-2K of greater than one point at three and six months follow-up respectively. The median (IQR) SLEDAI-2K reduced from 8 (5 to12) at baseline to 4 (2 to 8); p<0.001 at 3 months and 4 (0 to 7) p<0.001] at six months .Shamliyan et al (2017) found that there was no difference in low disease activity at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with SLE [RR 1.14 (95% CI 0.96 to1.36)] based on one RCT (n=257). However, they reported a significant difference in low disease activity without subsequent flares [RR 1.41 (95% CI 1.02 to 1.95), NNT=7]. SLEDAI is a measure of disease activity therefore a reduction in scores is likely to be valuable in patients with refractory SLE. The results reported by Alshaiki et al (2018) and McCarthy et al (2017) suggest that rituximab reduces diseases activity in patients with refractory SLE. Those reported by Shamliyan et al (2017) suggest that adding rituximab to standard treatment is not better than standard treatment alone in terms of reducing disease activity however it appears to be more effective in preventing subsequent flares. These results however should be interpreted with caution as the both the analysis by McCarthy et al (2017) and the meta-analysis by Alshaiki et al (2018) were based on non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors.
	Shamliyan et al 2017	7/10			
	McCarthy et al 2017	7/10			

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Change in steroid use post therapy	Alshaiki et al 2018 McCarthy et al 2017	7/10 7/10	Direct	A	Change in steroid use post therapy refers to any change in the dose of corticosteroids that occurred at study follow-up. Alshaiki et al (2018) reported that pooled mean difference from five case series (number of patients was not reported) showed that prednisolone dose (mg/d) was significantly decreased from baseline in both LN [mean difference -12.50 (95% CI -6.36 to -18.64), p<0.001] and SLE [mean difference -22.93 (95% CI -0.01 to -45.88), p<0.001] patients after rituximab therapy. The BILAG-BR analysis also reported a reduction from baseline in prednisolone dose at six months follow-up (n=149). The median dose reduced from 11.25mg (8.375 to 20 mg) to 7.5mg (5 to 12 mg) p<0.001 (McCarthy et al 2017). A reduction in the dose of steroids required is likely to be valuable to patients with refractory SLE particularly as long term steroid use is associated with organ damage. The results suggest that adding rituximab to standard treatment benefits patients with refractory SLE in terms of taking lower doses of steroids. However, it is unknown how this compares with standard treatment alone. The clinical benefits reported by this systematic review need to be interpreted with caution as the results were based on non-comparative studies for this outcome which means that the comparative efficacy of adjunctive rituximab compared to standard treatment only is unknown.
Change in proteinuria	Alshaiki et al 2018 Shamliyan et al 2017	7/10	Direct	B	Proteinuria identifies patients with renal damage and those at risk for worsening renal disease and increased cardiovascular morbidity. Proteinuria is the principal urinary biomarker for the screening of LN and for monitoring disease progression. Urine protein to creatinine ratio (UPC) assay is used typically to diagnose proteinuria and monitor patients with established proteinuria. Four case series (number of patients was not reported) included in the meta-analysis by Alshaiki et al (2018) reported on the change of proteinuria. Pooled results from these studies showed a significant decline in proteinuria from baseline was in SLE patients (mean difference -2.40 (95% CI -1.39 to -3.42) p<0.001]. However, these studies failed to show a significant decrease proteinuria from baseline in LN patients [mean difference -2.52 (95% CI 0.22 to -5.27) p=0.07]. On the contrary, based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant reduction in proteinuria demonstrated by a ≥50% reduction in UPC ratio at 78 weeks compared with standard treatment alone in patients with LN [RR 1.31 (95% CI 1.01 to 1.69), NNT=6)] although this was not the case at 52 weeks. Proteinuria indicates renal damage therefore a reduction is likely to be a

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					valuable treatment effect in patients with refractory SLE. The results reported by Alshaiki et al (2017) suggest that rituximab therapy reduces proteinuria in refractory SLE but not in LN. Those from one RCT included in the systematic review by Shamliyan et al (2017) suggest that adding rituximab to standard treatment may offers some benefit in reducing proteinuria compared to standard treatment in patients with refractory LN. These results however should be interpreted with caution as the meta-analysis by Alshaiki et al (2018) included non-comparative studies. The clinical benefits may therefore not be generalisable as the use of adjuvant rituximab was not compared to any conventional treatment. In addition, the findings by Shamliyan et al (2017) were from RCTs deemed to be of low quality by the authors
Complete renal response	Shamliyan et al 2017	7/10	Direct	B	Complete renal response was defined in the systematic review by Shamliyan et al (2017) as the presence of normal serum creatinine level, inactive urinary sediment, and UPC ratio <0.5. One RCT (n=144) included in the systematic review by Shamliyan et al (2017) reported no difference in complete renal response at 52 weeks between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with LN [RR 0.9 (95% CI 0.5 to1.5)] Change in renal BILAG scores gives an indication of disease activity in the kidneys. An improvement is likely to be a valuable treatment effect in patients with refractory SLE particularly those with LN The results suggest that adding rituximab to standard treatment makes no difference in increasing complete renal response compared to standard treatment in patients with refractory LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.
Partial renal response	Shamliyan et al 2017	7/10	Direct	B	Partial renal response was defined in the systematic review by Shamliyan et al (2017) as a reduction in serum creatinine level to ≤115% of baseline, the presence of inactive urinary sediment and at least a 50% decrease in the UPC ratio. Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in partial renal response at 52 weeks compared with standard treatment alone in patients with LN [RR 2.00 (95% CI 1.05 to 3.82) NNT=7]. Partial renal response indicates some improvement in renal function; this is likely to be of some value in patients with SLE particularly those with LN.

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					The results suggest that adding rituximab to standard treatment offers some benefit in improving renal response compared to standard treatment in patients with refractory SLE particularly those with LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.
BILAG renal domain Improvement	Shamliyan et al 2017	7/10	Direct	B	Renal BILAG scores are used to assess disease activity and response to treatment specifically in the kidneys. The BILAG-2004 index categorizes disease activity into five different levels from A to E. Grade A represents very active disease likely necessitating immunosuppressive drugs and/or a prednisolone (or equivalent) dose of more than 20 mg daily. Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressive drugs, anti-malarials, or non-steroidal anti-inflammatory drugs. Grade C indicates mild stable disease, and grade D implies no disease activity but suggests the system had previously been affected. Grade E indicates no current or previous disease activity. Based on one RCT (n=144), Shamliyan et al (2017) reported that adjuvant rituximab was associated with significant improvement in renal BILAG score at 52 weeks compared with standard treatment alone in patients with LN [RR 1.4 (95% CI 1.1 to 1.8) NNT=5]. Change in renal BILAG scores gives an indication of disease activity in the kidneys. An improvement is likely to be a valuable treatment effect in patients with refractory SLE particularly those with LN. The results suggest that adding rituximab to standard treatment offers some benefit in improving renal BILAG compared to standard treatment in patients with refractory LN. These results need to be interpreted with caution as they are from a low quality RCT and therefore may not be generalisable.
Adverse events	Alshaiki et al 2018	7/10	Direct	A	Adverse events (AE) were not specifically defined by Shamliyan et al (2017) or Alshaiki et al (2018). However, the WHO defines an AE as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention in this case standard treatment for SLE and rituximab. Alshaiki et al (2018) reported that in patients with refractory SLE, infections (four case series), acute or delayed infusion reactions (two case series), thrombocytopenia (one case series), sepsis-like syndrome (two case series) and serum sickness-like reactions (one case series) were reported. However, no other details provided.

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Shamliyan et al 2017				Shamliyan et al (2017) reported that there was no difference in adverse effects leading to treatment discontinuation between adjuvant rituximab and standard treatment alone in refractory SLE without LN (one RCT, n=257) at 52 weeks [RR 0.8 (95% CI 0.4 to 1.5)] and refractory SLE with LN (one RCT, n=144) at 78 weeks [RR 0.3 (95% CI 0.0 to 3.0)]. They found no difference in serious infections between the treatment arms in patients with refractory SLE at 52 weeks [RR 0.3 (95% CI 0.1 to 2.0)]. They also reported no difference in any infection or total adverse events at 78 weeks in patients with refractory LN based one RCT (n=144) [RR 0.9 (95% CI 0.8 to 1.1)] and [RR 1.03 (95% CI 0.97 to 1.09)] respectively. The BILAG-BR analysis by McCarthy et al (2017) reported 185 infectious episodes in 82 patients during a nine month period. Fifty-four patients suffered multiple infections and 29 (11%) serious infections occurred in 26 patients. The most common infections were respiratory (n = 88) and UTIs (n = 36). At three months, 111 (60%) infections occurred while 60 (32%) infections occurred between three and six months and14 (8%) occurred between six and nine months. Both Alshaiki et al (2018) and McCarthy et al (2017) reported that infections were the most common adverse events. Shamliyan et al (2017) reported no significant differences in the occurrence of adverse events between the study arms. The most common adverse events were infections which are transient however; details and/or p values were not reported. Prevention of adverse events is likely to be valued by patients, as they can be serious and/or require hospitalisation. The results suggest that the adverse effect profile in the two treatment arms is similar and that the most common adverse event s were transient infections. The results need to be interpreted with caution as no clear description of the numbers or p-values were reported. In addition, they are from a low quality RCT and therefore may not be generalisable. In addition the results reported by Alshaiki et al (2018) and McCarthy et al (2017) were not comparative, it is therefore unclear how this compares to standard treatment alone.
	McCarthy et al 2017	7/10			

Use of Intervention Rituximab plus immunosuppressant agents vs. immunosuppressant agents alone to treat refractory SLE					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
AII-cause mortality	Shamliyan et al 2017	7/10	Direct	B	All-cause mortality refers to any death that occurred during the trial. Based on three RCTs (n=420), Shamliyan et al (2017) reported that there was no difference in all-cause mortality between immunosuppressive agents plus adjunctive rituximab compared with immunosuppressive agents alone in adult patients with refractory SLE with or without LN: SLE (1 RCT, n=257) at 52 weeks: RR 2.1 (95% CI 0.2 to18.4) and LN (2 RCTs, n=163) at 52 to 78 weeks: RR 4.9 (95% CI 0.2 to 99.6) Survival is of high value to patients. However, it does not indicate a cure and is not a measure of disease activity or patients' symptoms. The results suggest that SLE patients treated with adjunctive rituximab are at no greater risk of mortality from any cause than those treated with standard therapy alone. These results need to be interpreted with caution as they are from a low quality RCT.

BILAG - British Isles Lupus Assessment Group; CR – complete response; LN – lupus nephritis; NNT – numbers needed to treat; PR – partial response; RCT - randomized controlled trial; RR – relative risk (the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group); RTX – rituximab; SLE - Systemic Lupus Erythematosus; SLEDAI - Systemic Lupus Erythematosus Disease Activity Index; UPC ratio - urine protein: creatinine ratio; UTI – urinary tract infection.

9 Literature Search Terms

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	*Patients (adults and children) diagnosed with SLE, who have refractory disease, defined as either* *1. ongoing moderate – severe active disease despite use of 2 or more conventional disease modifying anti-rheumatic drugs (DMARDs) or* *2. requiring excessive use of glucocorticoids (over 7.5mg) to maintain lower levels of disease activity despite use of 2 or more conventional disease modifying anti-rheumatic drugs (DMARDs)*
I – Intervention Which intervention, treatment or approach should be used?	Rituximab (MabThera, Biosimilars: Truxima, Rixathon) plus standard care (as described in studies)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Standard care alone (as described in studies)
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*<u>Critical to decision-making:</u>* *1. Steroid dose reduction* *2. Improved disease control i.e.,:* *a Reduced disease activity (measured using any validated disease activity score e.g. BILAG disease activity index score, any validated version of SLEDAI or the SRI)* *b Organ damage accrual (measured using any validated disease damage score e.g. SLICC/ACR damage index)* *3. Retreatment interval with rituximab* *4. Reduced hospitalisation* *<u>Important to decision-making:</u>* *5. Safety (serious adverse events, hospitalisation, infection)* *6. Quality of life (e.g., Lupus QoL, SF-36/EQ5D)* *7. Improved fertility/reproductive outcomes* *8. Cost effectiveness outcomes* *9. Reduced morbidity and mortality*

Assumptions / limits applied to search

Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.

Inclusions

- Study design: Systematic review, meta-analysis, randomised controlled trials, cohort study, well designed registry data with clear inclusion criteria and a significant study size expected for this population group.
- Language: English only.
- Patients: Human studies only.
- Age: Adults and children (from 0 onwards)
- Date limits: 2008 - 2018

Exclusions

- Publication Type: Conference abstracts, narrative reviews, commentaries, letters, editorials and case reports will be excluded

10 Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in England from **1st October 2008 to 18th October 2018**. We excluded conference abstracts, commentaries, letters, editorials and case reports.

Search date: 18th October 2018

Embase search:

1 *Rituximab/
2 (rituximab or mabthera or rituxan or truxima or rixathon).ti,ab.
3 1 or 2
4 exp *systemic lupus erythematosus/
5 (lupus or sle).ti.
6 (Systemic Lupus Erythematousus or Systemic Lupus Erythematosus or lupus nephritis).ti,ab.
7 ((refract* or resistant or sever* or serious*) adj5 (lupus or sle)).ti,ab.
8 4 or 5 or 6 or 7
9 3 and 8
10 (exp animals/ or nonhuman/) not human/
11 9 not 10
12 (editorial or letter or note or "review" or conference*).pt.
13 11 not 12
14 limit 9 to "reviews (maximizes specificity)"
15 13 or 14
16 limit 15 to (english language and yr="2008 -Current")

11 Evidence Selection

- Total number of publications reviewed: 117
- Total number of publications considered potentially relevant: 25
- Total number of publications selected for inclusion in this briefing: 3

References from the PWG supplied in the PPP		Paper selection decision and rationale if excluded
1	McCarthy E, Sutton E, Nesbit S, White J, Parker B, Jayne D, Griffiths B, Isenberg D, Rahman A, Gordon C, D'Cruz D, Rhodes B, Lanyon P, Vital E, Yee C, Edwards C, Teh L, Akil M, McHugh N, Zoma A. and Bruce I. 2017. Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register. Rheumatology, 57(3): 470-479	Included following discussion with NHS England. This study reports UK registry data analysis and is therefore observational and not comparative.
2	Gordon C, Amissah-Arthur M, Gayed M, Brown S, Bruce I, D'Cruz D, Empson B, Griffiths B, Jayne D, Khamashta M, Lightstone L, Norton P, Norton Y, Schreiber K. and Isenberg D. 2017. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology, 57(1): e1-e45.	Excluded These are evidence based guidelines for the management of SLE based on consensus agreement and not a systematic review of the clinical

		effectiveness of rituximab. However, it is useful for background of the condition and information on management pathway.
3	Duxbury B, Combescure C and Chizzolini C. 2013. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. Lupus, 22(14):1489-1503	Excluded This systematic review has been superseded by more recent ones; Shamliyan et al 2017 and Alshaiki et al 2018.They included all the studies in Duxbury et al.

12 References

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Gordon C, Amissah-Arthur M, Gayed M, Brown S, Bruce I, D'Cruz D, Empson B, Griffiths B, Jayne D, Khamashta M, Lightstone L, Norton P, Norton Y, Schreiber K. and Isenberg D. 2017. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology*, 57(1):e1-e45.

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Oon S, Huq M, Godfrey T and Nikpour M. 2018 Systematic review and meta-analysis of steroid-sparing effect, of biologic agents in randomized, placebo-controlled phase 3 trials for systemic lupus erythematosus. *Semin Arthritis Rheum,* 48(2):221-239

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