**The Effectiveness and Safety of Biological Therapeutics in Juvenile-Onset Systemic Lupus Erythematosus (JSLE): A Systematic Review**

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# **Abstract**

**Objective:** To systematically review and summarise the available literature regarding the effectiveness and safety of biologics in the treatment of Juvenile-onset Systemic Lupus Erythematosus (JSLE).

**Methods:** PubMed was systematically searched for relevant literature (2012-17 inclusive) using the following criteria: (1) patients diagnosed with JSLE (≤18 years at diagnosis); (2) treatment with any biological agent; and (3) outcome measures assessing effectiveness and safety. Systematic literature reviews, meta-analyses, RCTs, cohort studies, case control studies, cross sectional surveys and case-series with ≥3 patients were included.

Independent extraction of articles by 2 authors using predefined criteria was performed. The quality of each study was assessed using CASP tools and Oxford CEBM Levels of Evidence.

**Results:** Nine articles met inclusion criteria: 6 cohort studies, 2 case series and 1 pilot study, totalling 230 patients. All but one article reported the effects of rituximab (RTX), the other those of belimumab (BMB). Overall, patients had active disease refractory to standard of care regimens using corticosteroids and immunosuppressants. Available evidence for RTX demonstrated improvements in disease activity, complement levels and anti-dsDNA titres accompanying a steroid-sparing effect.

**Conclusion:** RTX can be considered an effective treatment in JSLE patients with severe disease manifestations and/or refractory disease. Based on current evidence, use of BMB in JSLE patients cannot be recommended. The long-term safety of these biological agents remains uncertain. Further prospective studies, ideally robust randomised controlled trials (RCTs), are urgently needed to obtain more accurate data on the effectiveness and long-term safety of RTX, BMB and other biologics, in JSLE.

# **Key messages**

1. This review highlights the paucity of high-quality interventional drug trials investigating biologics in JSLE.
2. Available evidence indicates an improvement of disease activity indices following RTX therapy.
3. RCTs are needed to better evaluate the effectiveness and safety of biologics in JSLE.

**Key words**

JSLE, Biologics, Rituximab, Belimumab, Safety, Effectiveness, Paediatric Rheumatology

**Introduction**

Juvenile-onset systemic lupus erythematosus (JSLE) is a heterogenous autoimmune disease, resulting from complex dysregulation of the innate and adaptive immune systems 1, potentially affecting any organ and/or tissue. To be recognised as ‘juvenile-onset’ or ‘childhood-onset’, SLE is diagnosed at ≤18 years of age 2,3. The median age of onset is 11-12 years 4 with increased frequency in females (ranging from approximately 4:1 5 to 5:1 6). JSLE patients generally experience a more aggressive disease course than adult-onset SLE (ASLE) patients 7 with higher associated morbidity and mortality 1.

Current standard of care of JSLE involves the use of glucocorticoids, anti-malarials and immunosuppressant (ISS) drugs 1,8,9. However, some patients may have refractory disease or multiple simultaneous manifestations requiring additional treatment(s) to control disease activity 10.

Existing treatment regimens are associated with numerous debilitating side effects with younger patients at increased risk due to the duration of their disease 11. Systemic corticosteroids have causal associations with Cushingoid features, hyperglycaemia, hyperlipidaemia, premature atherosclerosis, secondary osteoporosis and growth delay 1,2,12. Cytotoxic ISS drugs1,8,9 including cyclophosphamide (CYC), mycophenolate motefil (MMF), azathioprine (AZA) and methotrexate (MTX) increase the risk of teratogenicity, infection, infertility and cancer 1,13,14.

In JSLE, the inflammatory response is driven by autoantibodies and pro-inflammatory cytokines such as: IL-6, TNFα, IL-1B and type 1 IFNs 15-18. There is ineffective clearance of apoptotic nuclear fragments 3,19; this triggers autoreactive B cells into autoantibody production against endogenous nuclear autoantigens 1,17. The resultant formation of antibody-antigen complexes leads to complement activation, thereby augmenting inflammation and tissue injury 17,20-22.

In recent years, there has been increased interest in the development and testing of targeted immunosuppression using biologic therapies 15,16. Biological agents may potentially improve JSLE disease activity by targeting specific components of the pathological cascade including B-lymphocytes and B stimulatory molecules, T lymphocytes and co-stimulatory molecules, interferons, and cytokines 15,22; thereby, preventing B and T cell activation, differentiation and survival 3,23.

Biologics are being increasingly used in the routine care of JSLE patients, especially those with refractory disease or severe organ-specific manifestations 1,8,24. However, none of these agents has been approved for use in paediatric patients. The paucity of robust evidence means that current regimens are guided by adapted adult-derived protocols along with limited retrospective cohort studies, case series and case reports 1.

The aim of this work was to systematically review and summarise the available literature regarding the effectiveness and safety of biologics in the treatment of JSLE.

# **Methodology**

*Search strategy*

Relevant articles/studies were identified in the PubMed bibliographic database, using a sensitive search strategy. Studies were eligible for inclusion if they were published between 1st January 2012 and 7th December 2016, written in English and involved humans only. Finally, a manual search was performed by reviewing the references of all the included studies. Ongoing assessment of the literature arising since the initial in-depth assessment using the same search strategy took place up until 31/12/2017; this identified 1 additional manuscript that described ASLE rather than JSLE, so was excluded.

*Selection criteria*

Studies retrieved were included if they met the following criteria:

* + 1. Patients diagnosed with JSLE (aged ≤18 years at diagnosis)
		2. Treatment with any biological agent
		3. Outcome measures assessing efficacy/effectiveness and safety were available

*Screening of studies*

The titles and abstracts of the retrieved articles were screened independently by 2 reviewers. Only systematic literature reviews, meta-analyses, RCTs, cohort studies, case control studies, cross sectional surveys and case-series with ≥3 patients were included. Papers were also excluded if they were: exclusively ASLE cases; if they were inaccessible through the University of Liverpool portal and the outcomes of biologics were not discussed separately from other standard of care therapies.

*Data collection*

Data extrapolation took place (EDP) using data extraction forms (Table 1 and supplemental 1) and were scrutinised for transcribing errors, inaccuracies or differences of opinion (MPK).

For each paper, systematic searches were performed for: number of patients included, patient demographics (age, gender, race), age at diagnosis/intervention, disease duration before biologic initiation, indication for treatment with biologic, regimen of biologic, follow-up period, concurrent immunosuppressive treatment, corticosteroid dosage, clinical and biological outcomes and adverse events. For manuscripts where outcomes were unclear or were presented alongside other populations (i.e. with ASLE patients, other autoimmune diseases), corresponding authors were contacted. Of four authors contacted, none met requests for further information, or clarification.

Due to the heterogeneity of the study designs, participants, interventions and reported outcomes, this review focused on qualitative synthesis. Formal meta-analysis was not performed.

The quality of the studies was assessed using the CASP tools 25 and Oxford CEBM Levels of Evidence 26. Risk of bias was assessed using the ROBINS-I tool 27 and each paper was assigned a risk of bias described as low, moderate, serious or critical (supplemental 4).

# **Results**

The literature search produced 482 articles, of which 30 underwent full review and 16 further studies were identified manually. Of these 46 studies, 9 met the inclusion criteria (Figure 1). The final studies included 6 cohort studies 24,28-32 (1 prospective 32 , 5 retrospective 24,28-31, 2 case series 21,33 and 1 pilot study 34, which analysed a total of 230 JSLE patients (summarised in Table 1, supplementals 1, 2 and 3). Three of the studies 28,30,33 included paediatric patients with other rheumatological diseases as well as JSLE patients. Wherever possible, data pertaining only to JSLE patients was extracted; whenever this was not possible, this is explicitly stated.

In 8 of the studies, ≥75% of patients were female; one case series 21 had exclusively male participants. The most common indication for initiation of biologics was active disease refractory to corticosteroids and/or immunosuppressant drugs, with 5 studies 21,24,31,33,34 including ≥50% patients with lupus nephritis (LN).

Regarding therapies, 8 studies 21,24,28-31,33,34 presented patients receiving RTX and one 32 presented patients receiving BMB. Other biologics were included in the search strategy ,owever, no relevant articles were identified - these were subsequently excluded from further analyses.

In 4 of the studies using RTX 24,28,33,34, a dose of 750 mg/m2 was administered on 2 separate occasions, 14 days apart. In the remaining 4 studies, the RTX dose varied between 375–500 mg/m2 given either weekly for 4 weeks, or on 2 separate occasions, 14 days apart. In all studies, almost all patients were receiving concomitant corticosteroids and/or ISS drugs. Two studies 31,34 included CYC as part of the treatment regimen, given on 2 separate occasions, 1 day after the administration of RTX. The prospective cohort study 32 using BMB did not report the dosing regimen used.

Follow-up in the retrospective cohort studies and case series ranged from 0.1–13 years and in the prospective cohort study 32 and pilot study 34 follow-up was 0.5 years and 5 years, respectively. Adverse events and outcomes relevant to safety were reported in all studies.

The main outcomes regarding effectiveness and safety are summarised in Table 1.

*Global Disease Activity*

All but 3 studies 31,33,34 reported disease activity outcomes with different scores or indices. One pilot study 34, one cohort study 31 and one case series 33 used the SLE Disease Activity Index (SLEDAI) score 35. All reported a long-term (≥12 months) improvement in disease activity after RTX initiation; with statistical significance being assessed and achieved in 2 of these studies 31,34. Notably, the pilot study 34 had a follow-up period of 5 years during which the reduced SLEDAI score was sustained. Tambralli 28, Trachana 21 and Watson 24 used the Physician’s Global Assessment (PGA) 36, European Consensus Lupus Activity Measurement (ECLAM) 37 and British Isles Lupus Assessment Group (BILAG) 38 scores respectively. All studies reported a reduction in these scores following RTX therapy after short-term 24 (3-9 months) and long-term 21,28 (≥12 months) follow-up; however, the reporting and achievement of statistical significance was inconsistent.

The 2 remaining cohort studies 29,32, reported short-term 32 (3-9 months) and long-term 29 (≥12 months) significant improvement in disease activity (64-96% complete response (CR) or clinical improvement); however, statistical significance was not reported. In the final cohort study 30, the long-term (≥12 months) modified Rankin Scale (mRS) for children 39 had decreased after RTX intervention and the clinicians’ impressions were that 94% patients had had a possible, probable or definite response. Statistical significance was not reported.

Available evidence suggests it is acceptable to support the use of RTX for disease activity in JSLE patients with refractory disease. There is very little evidence for use of BMB, but this single prospective cohort study 32 suggests that BMB might be useful. The primary phase of the PLUTO trial (NCT01649765) evaluating the use of BMB in JSLE was expected to finish in January 2018 and results are pending.

*Corticosteroid-sparing effect*

Seven studies 21,24,28,31-34 demonstrated a significant steroid-sparing effect by addition of RTX or BMB. Lehman’s 34 pilot study found a 76% reduction by 60 months, similarly the cohort studies investigating RTX 21,24,28,29,31,33 found a reduction ranging from 22% to 100% at a range of 2.5 to 21.5 months. The cohort study investigating BMB demonstrated a corticosteroid dose reduced by 35% at 6 months 32. Current evidence suggests RTX is effective to reduce corticosteroid doses in JSLE patients.

*Hypocomplementaemia*

In all 6 cohort studies 21,24,28,31-33 and 1 pilot study 34 where hypocomplementaemia was identified, mean or median complement levels increased significantly with RTX therapy. In the prospective cohort study 32, improved C3 levels were observed within 3 months of treatment and were sustained at 6 months. In the pilot study 34, C3 level improvement was sustained at 60 months following 3 cycles of RTX at 0, 6 and 18 months. Available evidence indicates RTX is effective in improving hypocomplementaemia.

*Anti-dsDNA titres*

Anti-double-stranded DNA (anti-dsDNA) titres were reported in 4 cohort studies 24,28,31,32 and 1 case series 33. In most studies, the anti-dsDNA titres decreased with use of RTB or BMB but statistical significance was only achieved in 2/4 studies 24,32. Available evidence indicates moderate effectiveness of RTX and/or BMB in reducing anti-dsDNA titres in JSLE patients.

*Specific disease manifestations*

One cohort study 29 explicitly assessed the effect of RTX on persistent autoimmune thrombocytopaenia (AITP) and autoimmune haemolytic anaemia (AIHA). In this cohort, 96% patients had a complete response within 48 (IQR 14 – 103) days, defined as a platelet count >100 x109/l for pts with AITP; or haemoglobin (Hb) ≥ 120 g/l for pts with AIHA. Hb and platelet levels were not measured in all of the remaining studies. However, in those that measured platelets 24,31,33 and Hb 24,28,33,34, there was a positive response to RTX with an improvement in these parameters. These findings suggest RTX is effective in the treatment of haematological manifestations of JSLE.

Lupus nephritis has significant morbidity and is a poor prognostic indicator in JSLE patients 40. One pilot study 34, two cohort studies 24,31 and two case series 21,33 included patients with renal manifestations of SLE and were treated with RTX. Laboratory measures (serum albumin, serum creatinine, proteinuria, urinary protein:creatinine ratio) demonstrated improved renal function in almost all of these patients. In one case series 21, all patients achieved renal remission within a median interval of 3.5 (range 2-4) months. However, in the pilot study 34 and one cohort study 31, all patients were concomitantly treated with CYC infusion 24 hours after each RTX infusion. Similarly, 73% patients in Watson et al’s study 24 also received CYC prior to each RTX dose. Evidence suggests that RTX may be effective in the treatment of severe, refractory LN.

One cohort study 30 study assessed JSLE patients with neuropsychiatric involvement: 94% patients demonstrated clinical improvement after RTX initiation. This was evidenced by reduced modified Rankin Scale (mRS) scores and subjective clinical assessment. However, specific data on manifestation improvement (e.g. psychosis, confusion) in JSLE patients could not be extrapolated from the general cohort which included other neurological autoimmune diseases. Current evidence is limited to suggest the effectiveness of RTX in NPSLE.

*Relapses and repeat cycles*

Relapses and/or flares (definitions of which varied widely) were reported in all but 2 studies 28,30. Repeat cycles of RTX or BMB were required in 8-50% patients; however, clinical and laboratory improvement was reported in almost all cases. In one cohort study 29, survival analysis reported that the probability of flare at up to 8 years after complete response in patients with AITP or AIHA is <40%. There is little evidence on relapse rates following RTX or BMB therapy. However, in the 7 studies in which this was explored, it seemed that relapse was appreciable.

*B cell depletion*

Four studies 21,24,29,34 refer to the effect of treatment on B cell depletion. In two cohort studies 24,29 and one case series 21, **~**99% patients who had immunophenotyping achieved B cell depletion within 14-30 days. Olfat et al. 29, also report that this was sustained at 3 months in patients who had repeat assays. Limited available evidence confirms RTX inhibits B cell proliferation and survival associated with treatment.

*Safety*

All studies reported adverse events. Severe (i.e. anaphylactic) infusion-related reactions were reported in 3 cohort studies 24,29,31 at a frequency of 2 - 13% with a median of 4%. Frequency of mild infusion reactions was 0% - 4%.

Infections after RTX administration were reported in the pilot study 34 and in 6 other studies 24,28-31,33**;** 2% to 25% patients required hospitalisation and/or intravenous antibiotics due to subsequent infection. Tambralli et al. 28, reported the rate of severe infection as 90.8/100 000. Trachana et al. 21, reported no serious infections. Hui-Yuen et al. 32, reported that 4% patients developed infections requiring hospitalisation but the frequency amongst JSLE patients specifically was not reported.

In studies that evaluated immunoglobulin (Ig) levels 21,24,29,33,34, hypogammaglobulinaemia occurred transiently in the majority of patients although this was not persistent in most cases. Intravenous immunoglobulin (IVIG) therapy was indicated for 2%- 50% patients in 3 24,29,33 of the 5 studies. Olfat et al. 29, reported that 4% patients required IVIG to correct hypogammaglobulinaemia that was directly attributable to RTX therapy. In the remaining studies it is unclear whether hypogammaglobulinaemia was pre-existing or attributable to co-interventions and/or infections.

Withdrawals were reported in 2 cohort studies 31,32 due to: anaphylactic infusion reaction 31, worsening NPSLE, or lack of clinical improvement 32.Watson et al. 24, reported that in 8% courses of RTX, the second dose was delayed for reasons including: neutropenia, an unavailable drug or hospital bed. No complete withdrawals were reported 24.

Overall, infusion reactions and infection were the most common adverse events and in most instances, these were mild. However, there were several patients who required hospitalisation for anaphylactic reactions, IV antibiotics or IVIG therapy. Therefore, available evidence indicates that RTX and BMB are well-tolerated but caution is advised with their use in JSLE patients.

**Table 1 – Results table summarising safety and effectiveness measures of evaluated biological regimens**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Number of Patients (n)** | **Outcome Measures** | **Safety Outcomes** | **Level of Evidence** |
| **AIE'ed (2014)** | *n=16* | Treatment (s) | Rituximab + cyclophosphamide | bESRAnti-dsDNA | ESR not reported**↓** anti-dsDNA by 41% | ***Infusion reactions**** 13% pts developed infusion-related anaphylactic reactions reported

***Infections**** 13% pts developed infections requiring hospital admission and IV antibiotics/antifungals

***Ig levels**** Not reported

***Withdrawals**** 6% pts withdrew due to an anaphylactic infusion reaction

***Other**** 6% pts developed pancreatitis
 | IV |
| Study type | Single-centre retrospective cohort | Hb levelsPlatelets | Not reported |
| Clinicalresponse | **↓** cSLEDAI by 57%  | Renal outcomes | * 3 pts with class V nephritis had significant improvement in proteinuria (exact figures not reported)
* 4 pts with class IV nephritis showed improvement of renal function (exact figures not reported)
 |
| aCS dose | **↓** dose by 53% | B cell depletion | Not reported |
| C3 levelsC4 levels | **↑** C3 by 49%**↑** C4 by 55% | Relapses | 25% patients required repeat cycles |
| **Dale (2014)** | *n=18* | Treatment(s) | Rituximab | bESRAnti-dsDNA | Not reported | ***Infusion reactions**** 2% pts developed hgrade 4 infusion reactions (anaphylaxis) **in entire cohort** (NPSLE pts + other CNS autoimmune disease)
* 10% pts developed hgrade ≤3 infusion reactions **in entire cohort** (NPSLE pts + other CNS autoimmune disease)

***Infections**** 1 hgrade 4 infectious complication in NPSLE population
* 7 (5%) hgrade 3 infectious complications **in entire cohort** (NPSLE pts + other CNS autoimmune disease) requiring hospitalisation/IV antibiotics

***Ig levels**** Out of 124 pts with available data **in entire cohort** (NPSLE pts + other CNS autoimmune disease), hypogammaglobulinaemia was reported in 22% pts

***Withdrawals**** Not reported
 | IV/V |
| Study type | Multi-centre retrospective cohort | Hb levelsPlatelets | Not reported |
| Clinicalresponse | **↓** dmRS by 67%  | Renal outcomes | Not reported |
| aCS dose | Not reported | B cell depletion | Not reported |
| C3 levels C4 levels | Not reported | Relapses | Not reported |
| **Hui-Yuen****(2015)** | *n=39* | Treatment(s) | Belimumab | bESRAnti-dsDNA | ESR not reported**↓** anti-dsDNA: 44% pts had at least 25% decrease | ***Infusion reactions*** * 2% pts developed infusion reactions **in entire cohort** (adult- and juvenile-onset SLE pts)

***Infections**** 4% pts developed infectious complications **in entire cohort** (adult- and juvenile-onset SLE pts)

***Ig levels**** Not reported

***Withdrawals (management NR)**** 3% pts discontinued due to development/worsening of NPSLE **in entire cohort** (adult- and juvenile-onset SLE pts)
* 3% pts discontinued due to a lack of clinical improvement
 | IV/V |
| Study type | Prospective cohort | Hb levelsPlatelets | Not reported |
| Clinicalresponse | **↑** \*clinical improvement in 64% | Renal outcomes | Not reported |
| aCS dose | **↓** dose by 35%CS discontinued in 36% | B cell depletion | Not reported |
| C3 levels C4 levels | **↑** C3: 18% pts had at least 25% \*improvement C4 not reported | Relapses | 8% patients reported flares of LN |
| **Lehman (2014)** | *n=12* | Treatment(s) | Rituximab + cyclophosphamide | bESRAnti-dsDNA | **↓** ESR by 72%Anti-ds DNA not reported | ***Infusion reactions**** None reported

***Infections**** 17% pts were hospitalised for febrile neutropaenia

***Ig levels**** Serum Ig levels were transiently decreased but were within normal range at 60 months

***Withdrawals**** None reported
 | IV |
| Study type | Pilot study | Hb levelsPlatelets | **↑** Hb by 17%Platelets not reported |
| Clinicalresponse | **↓** cSLEDAI by 100%  | Renal outcomes | **↑** serum albumin by 26%Serum creatinine remained stable |
| aCS dose | **↓** dose by 76% | B cell depletion | CD19 levels returned to normal by 12 months (exact levels not reported) |
| C3 levelsC4 levels | **↑** C3 by 95%C4 not reported | Relapses | 17% pts required repeat cycles |
| **Olfat (2015)** | *n=24* | Treatment(s) | Rituximab | bESRAnti-dsDNA | Not reported | ***Infusion reactions*** * 8% pts developed infusion

***Infections**** 8% pts developed infections (note that 1 pt had hypogammaglobulinaemia that preceded RTX treatment) therapy

***Ig levels**** 17% of pts (of those who had normal/elevated IgG at initiation) developed transient hypogammaglobulinaemia
* 75% pts who had hypogammaglobulinaemia before RTX initiation developed persistent hypogamamaglobulinaemia

***Withdrawals**** None reported
 | IV |
| Study type | Single-centre retrospective cohort | Hb levelsPlatelets | **↑** Hb by 636% in AIHA pts**↑** platelets by 68% in AITP pts |
| Clinicalresponse | 96% pts had $clinical response | Renal outcomes | Not reported |
| aCS dose | Pts using steroids (71%) were able to discontinue | B cell depletion | **↓** CD20 count to <1% in all pts who had immunophenotyping |
| C3 levelsC4 levels | Not reported | Relapses | 21% patients required repeat cyclesSurvival analysis indicates that probability of flare at up to 8 years post $clinical response is < 40% |
| **Reis (2016)** | *n=4* | Treatment(s) | Rituximab | bESRAnti-dsDNA | **↓** ESR by 61% (in 3/4 pts)**↓** anti-dsDNA by 25% (in 2/4 pts) | ***Infusion reactions**** None reported

***Infections**** 50% pts developed infection; both successfully treated with antibiotics

***Ig levels**** 25% pts was treated with IVIG for hypogammaglobulinaemia (note pre-treatment Ig levels not reported)

***Withdrawals**** None reported
 | IV/V |
| Study type | Case series | Hb levelsPlatelets | **↑** Hb by 39% (in 3/4 pts)**↑** platelets by 7% (in 3/4 pts) |
| Clinicalresponse | **↓** cSLEDAI by 81%  | Renal outcomes | **↑** serum creatinine by 7% (in 3/4 pts) |
| aCS dose | **↓** dose by 39% | B cell depletion | Not reported |
| C3 levelsC4 levels | **↑** C3 by 29% (in 3/4 pts)**↑** C4 by 59% (in 3/4 pts) | Relapses | 50% patients required repeat cycles |
| **Tambralli (2015)** | *n=50* | Treatment(s) | Rituximab | bESRAnti-dsDNA | **↓** ESR by 35%**↓** anti-dsDNA by 90%  | ***Infusion reactions**** 5.6% of infusions caused reactions **in entire cohort** (JSLE pts and other rheumatic diseases)

***Infections**** 12 infections occurred requiring hospitalisation out of 132.2 patient-years (rate of 90.8/100 000)

***Ig levels**** 13% pts developed hypogammaglobulinaemia requiring IVIG, **in entire cohort** (JSLE pts and other rheumatic diseases)

***Withdrawals**** None reported
 | IV |
| Study type | Single-centre retrospective cohort | Hb levelsPlatelets | **↑** Hb by 10%Platelets not reported |
| Clinicalresponse | **↓** ePGA by 66%  | Renal outcomes | **↑** serum albumin by 14% |
| aCS dose | **↓** dose by 65% | B cell depletion | **↓** CD19 count by 99% |
| C3 levels C4 levels | **↑** C3 by 63%**↑** C4 by 121% | Relapses | Not reported |
| **Trachana (2013)** | *n=4* | Treatment(s) | Rituximab | bESRAnti-dsDNA | Not reported | ***Infusion reactions**** No serious infusion reactions reported (no qualification of ‘serious’)

***Infections**** No serious infections reported (no qualification of ‘serious’)

***Ig levels**** 47% decrease in IgM levels before and after RTX infusion but there no indication that IVIG was needed

***Withdrawals**** None reported
 | IV |
| Study type | Case series | Hb levelsPlatelets | Not reported |
| Clinicalresponse | **↓** fECLAM by 77% | Renal outcomes | **↓** 24h urinary protein excretion by 90% |
| aCS dose | **↓** dose by 76% | B cell depletion | B cell depletion achieved in 100% pts (exact data not reported) |
| C3 levels C4 levels | **↑** C3 by 61%**↑** C4 by 108% | Relapses | 25% pts required repeat cycles |
| **Watson** **(2015)** | *n=63* | Treatment(s) | Rituximab + cyclophosphamide | bESRAnti-dsDNA | **↓** ESR by 31%**↓** anti-dsDNA by 54% | ***Infusion reactions**** 6% courses associated with an infusion reaction – 2% anaphylactic; 4% mild/moderate

***Infections**** 2% courses developed infection within 3 months of treatment

***Ig levels**** 2% courses developed Ig levels that required IVIG replacement

***Withdrawals**** In 8% courses, second dose (i.e. on day 14) was delayed due to neutropaenia, fever, surgery for oesophageal stricture, drug unavailable, no hospital bed available, URTI

***Overall**** AEs were reported in 18% courses
 | IV |
| Study type | Multi-centre retrospective cohort | Hb levelsPlatelets | **↑** Hb by 8%**↑** platelets by 13% |
| Clinicalresponse | **↓** gBILAG by 33% | Renal outcomes | **↓** serum creatinine by 5%**↑** serum albumin by 8%**↓** urinary albumin:creatinine ratio by 39% |
| aCS dose | **↓** dose by 21% | B cell depletion | B cell levels not routinely measured |
| C3 levelsC4 levels | **↑** C3 by 27%**↑** C4 by 67% | Relapses | Not reported, however 30% pts received >1 course of *g*RTX |
| aCS dose: corticosteroid dose; bESR: erythrocyte sedimentation rate; cSLEDAI: SLE Disease Activity Index; dmRS: modified Rankin Scale score; ePGA: physician’s global assessment; fECLAM: European Consensus Lupus Activity Measurement; gBILAG: British Isles Lupus Assessment Group global score; hAdverse effects classified using Common Terminology Criteria for Adverse Events (CTCAE v4.0) \*Clinical improvement in Hui-Yuen, 2015: defined as the treating physician’s impression of a ≥50% improvement in the initial manifestation(s) being treated and the ability to taper existing steroids by at least 25% of the initial dose; laboratory response was defined as a ≥25% improvement in the levels of C3, C4, and/or a 25% decrease in anti-dsDNA$CR in Olfat, 2015 defined as a platelet count >100 x109/l for pts with AITP; or Hb >/= 120 g/l for pts with AIHA**Values shown in bold and underlined are extracted from the entire cohort and are not specific to JSLE participants** |

# **Discussion**

The aim of this review was to systematically evaluate the reported effectiveness and safety of biologics in patients with JSLE. No biologic therapies have yet had regulatory approval for JSLE. They are however being increasingly incorporated into treatment regimens for patients with severe disease manifestations or refractory disease. The most notable finding from our search, is the significant paucity of interventional drug trials using biologics in JSLE patients, and large, prospectively collected, robust observational cohort studies to inform practice in the meantime. Ongoing assessment of the literature throughout 2017 identified just one further study. This reported the use of BMB in SLE patients, concluding that BMB in addition to standard therapy was a safe and effective treatment for active lupus patients 41. However, the results from this retrospective open-labelled study could not be authentically extrapolated to the JSLE population as it was not evident how many (if any) patients had been diagnosed with JSLE rather than ASLE.

The use of RTX in SLE, a chimeric monoclonal antibody against CD20+ B-cells, has increased dramatically over the past decade 24. Two randomised control trials: phase II/III EXPLORER 42 and LUNAR 43 (exclusively ASLE patients) did not find any difference between RTX and placebo 42. However, Cobo-Ibanez et al’s systematic review of ASLE reported that RTX was found to be safe and effective in the treatment of non-renal SLE 10. This discrepancy might be explained by methodological bias in the EXPLORER 42 and LUNAR 43 trials. Perhaps the clinical and serological measurements lacked sensitivity and were unable to detect the potential benefits of RTX 10.

This review supports Cobo-Ibanez et al’s findings 10. In JSLE patients there was a significant improvement in disease activity, serum and urine markers of disease activity and reduced oral corticosteroid dose after RTX treatment. Conversely, up to 30% of patients required more than one course, several patients required treatment for severe infection and up to 13% developed hypogammaglobulinameia. Therefore, it is paramount to monitor IgG levels before RTX therapy and RTX should be used cautiously in patients with pre-existing hypogammaglobulinaemia.

BMB is a fully humanised monoclonal antibody that binds to and inhibits BLyS, attenuating B-cell survival and differentiation into plasma and memory cells 44. Although there is scant literature on the use of BMB in JSLE, improved clinical and serological outcomes were observed after BMB therapy 32, corresponding with earlier adult studies 45-48. For example, the phase III RCTs BLISS-52 and BLISS-76, found that BMB plus standard-of-care therapy significantly reduced the rate of disease flares, permitted lower corticosteroid doses, and decreased serologic SLE activity when compared to placebo 45-48.

The use of BMB for JSLE in only one study 32 suggests that there is much more to be done for JSLE patients. The relative rarity of JSLE and the sensitivity of studies (i.e. difficulty in obtaining ethical clearance) involving children might steer drug companies and clinicians away from embarking on costly clinical trials.

*Limitations*

We evaluated one study 32 that included both ASLE with JSLE patients. Similarly, 3 studies also reported on patients with non-SLE autoimmune disease 28,30,33. These diseases manifest themselves via similar pathological processes - B cells play a central role in the pathogenesis of several paediatric rheumatological diseases 49. This provides a sound basis for the inclusion of these non-SLE studies in the present review and that B-cell targeted therapies remain a promising option for JSLE.

The inclusion of studies using non-validated measures may lead to over- or under-reporting of a positive effect. For example, defining an outcome response as “complete” or “partial” may be too reductionist to detect any positive effect. Equally, using an experienced clinician’s impression is highly subjective and could also lead to over- or under-reporting. It has also been suggested that the SLEDAI and BILAG scores lack sensitivity to some disease activity change 42. Similarly, the retrospective nature of most of the studies - plus the widely variable duration of follow-up times **-** likely resulted in the under-reporting of adverse effects and the over-reporting of positive effects.

One of the most significant confounders in this review is the substantial variability in concomitant medications used. It is therefore difficult to attribute any effect directly to the biological intervention alone when several other medications were used either as co-intervention or as background medications. It is also worth noting, that compliance to background medication(s) was neither measured nor reported in any of the included studies and therefore acts as a confounding variable. Similarly, JSLE is known for its chronic and fluctuating course; it may be that a percentage of the positive responses to biological therapy were in fact spontaneous remissions.

Conducting trials in the JSLE population can be challenging due to the rarity of JSLE 1, thus leaving a relatively small group of patients (i.e. reflected by the number of patients included in this review) for clinical trials. Other challenges encountered in our evaluations included: the lack of a comparable control group, the large range of follow-up times, the open-label study design, and that most of the studies were single-centre, hence not being truly representative of the whole JSLE population. It must also be mentioned that due to the complexity and sensitivity of biologics, these drugs are at increased risk of quality issues compared with traditional agents, which may affect the effectiveness and safety of these treatments 50.

The lack of any RCTs or case-control studies is significant (i.e. study evidence grades were IV or below) and highlights the importance of conducting appropriately designed trials for patients with JSLE. It is paramount to perform sufficient RCTs so that meta-analysis scrutinising the efficacy and safety of these drugs can be performed. Meta-analysis would facilitate high-quality data to obtain the best scientific evidence to guide the responsible inclusion of these drugs into standard of care treatment for JSLE patients.

# **Conclusion**

Further prospective studies, including RCTs are urgently needed to obtain more accurate data on the efficacy of rituximab and belimumab in JSLE, especially pharmacokinetic data to guide dosing and administration. Other emerging biologics also require RCTs including children, plus quality control for the biologics themselves. Novel trial design and/or including children in adult-focused trials, are options to overcome these challenges. The apposite use of disease activity indices validated in JSLE (i.e. BILAG or SLEDAI scores) to measure clinical response as well as immunological response need to be appropriately utilised. Similarly, the dearth of data on long-term safety and efficacy must be addressed. There are currently 3 ongoing trials investigating the use of biologics in JSLE patients (supplemental 5) that will help expand the evidence-base for management of this debilitating disease.

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**Figure 1 – Identification of studies evaluating the use of biologics in JSLE patients**

