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## PAPER

# The indications, efficacy and adverse events of rituximab in a large cohort of patients with juvenile-onset SLE

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**Background:** B cells drive antibody formation and T cell activation. This study aimed to describe the clinical indications, efficacy and adverse events (AEs) for the B-cell depleting agent, rituximab, in a large cohort of children with lupus. **Methods:** Prescribing records and the UK JSLE Cohort Study database identified rituximab use. **Results:** Sixty-three patients received 104 courses of intravenous rituximab over a 10-year period. Patients were aged 12.2 (IQR 9.0–13.9) years at diagnosis and 50 (79%) were female. They had disease for 1.4 (0.2–3.0) years at the time of rituximab. Lupus nephritis was the most common indication (36% of first courses). Clinical biomarkers, 2.5 (1.6–4.3) months after treatment, demonstrated a statistically significant improvement in ESR, C3, C4, creatinine, albumin, haemoglobin, anti-dsDNA titres and urine albumin:creatinine ratio. IgG, IgA and IgM levels decreased ( $p < 0.01$ ). Oral corticosteroid dose significantly reduced after rituximab (dose before 0.26 (0.09–0.44) mg/kg, after 0.17 (0.09–0.30) mg/kg;  $p = 0.01$ ). AEs occurred in 19 (18%) of all courses including; delayed second dose (8%), Ig replacement (2%) and infusion reactions (6%; anaphylaxis 2%). The global BILAG score showed a trend toward improvement (before 4.5 (2.0–9.0), after 3.0 (2.0–5.0);  $p = 0.16$ ). **Conclusion:** Rituximab improves disease activity in children with lupus and serious AEs are infrequent. Controlled studies are required. *Lupus* (2014) 0, 1–8.

**Key words:** Rituximab; B-cell depletion; lupus; child; SLE

## Introduction

Rituximab is a chimeric monoclonal antibody against the B cell protein CD20. It acts as a depleting agent of naïve and memory B cells and it is increasingly being used as an additional therapy in childhood immune-mediated diseases, including rheumatic diseases.<sup>1</sup> The optimal dosing schedule, timing and indications of treatment remain uncertain.

In systemic lupus erythematosus (SLE), B cells are key immune mediators as they drive antibody formation and promote T cell activation.<sup>2</sup> Children with SLE (termed childhood or juvenile-onset SLE, JSLE) have a more severe and active disease course

than those patients with adult-onset disease,<sup>3</sup> together with a greater requirement for corticosteroids.<sup>4,5</sup> Additional or alternative therapies aimed at reducing disease activity, with more tolerable side effects, are therefore warranted. Recently, a large cohort study involving 86 adult SLE patients demonstrated that rituximab is effective in reducing disease activity with a good safety profile,<sup>6</sup> confirming data published from previous smaller studies.<sup>7,8</sup> However, large clinical trials using rituximab in renal and non-renal lupus, the so-called Lupus Nephritis Assessment with Rituximab (LUNAR) and Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trials, respectively, failed to reach their primary outcomes or demonstrate a significant response in improving disease activity.<sup>9,10</sup> Subsequent consideration of why these large randomized controlled trials might not have demonstrated significant differences, other than the potential lack of clinical efficacy, includes concerns regarding the trial design, sample size,

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corticosteroid regimens and appropriateness of outcome measures employed.<sup>11</sup> Robust data on the efficacy and safety of rituximab in JSLE are, however, still lacking and to date are dependent on case reports and very small cohort studies, despite increasing clinical use.

The aim of this study therefore is to describe the clinical indications, efficacy and adverse events (AEs) of rituximab in a large cohort of patients with JSLE.

## Methods

### *Patient cohort*

All patients attending Great Ormond Street and Alder Hey Children's NHS Foundation Trusts (United Kingdom (UK)) with a clinician's diagnosis, based on the SLE American College of Rheumatology (ACR) classification criteria,<sup>12</sup> of JSLE before the age of 17 years old, were eligible for this study. Those who had received rituximab between August 2003 (the date of first clinical use in either centre) and March 2013, were identified using local prescribing records and the UK JSLE Cohort Study database.<sup>13</sup>

### *Data collection*

Case notes were reviewed retrospectively. Data were recorded using an electronic proforma documenting demographic data (date of birth, gender, ethnicity), date of diagnosis, date and dose of rituximab administration, weight, previous use of rituximab, clinical disease indications, immunosuppressive medications at the time and the measurements of routine clinical biomarkers of disease activity before and after treatment.

Disease activity markers assessed included: haemoglobin concentration, white cell count (WCC), neutrophils, lymphocyte count, erythrocyte sedimentation rate (ESR), complements C3 and C4, immunoglobulin (Ig)G, IgA, IgM, creatinine, and albumin concentrations, early morning urine albumin:creatinine ratio (UACR) and double-stranded DNA titres (dsDNA). In patients who had prospective measurement of JSLE disease activity, the British Isles Lupus Assessment Group (BILAG) global score was recorded.<sup>14</sup> Any associated short-term AEs (between rituximab administration to the time of follow-up bloods) were recorded using previously published definitions and classification systems.<sup>15</sup> Infectious complications were recorded using the medical case notes

where documentation relating to a recent illness was present or where there was evidence of an acute admission within that hospital.

### *Statistical analysis and ethics approval*

Statistics package for social sciences (SPSS) version 20.0 and GraphPad Prism version 5.0 were used for all data analysis and graphical illustrations. The demographic data were descriptive and comparison was made between demographic data and the need for single or multiple courses of rituximab using Mann-Whitney *U* analysis. Biomarkers of disease activity before and after rituximab treatment were assessed for normality using the Shapiro-Wilk test and were non-parametric. Comparisons between paired samples were made using the Wilcoxon signed rank test. The data are presented as median values with interquartile ranges (IQR) using the data for the patients' first course of rituximab and for all courses of rituximab. Statistical probability (*p*) values of <0.05 were considered significant.

The study was a retrospective evaluation of the clinical use of rituximab in JSLE and therefore did not require ethics approval.

## Results

### *Demographic data*

Sixty-three JSLE patients were identified who had received a total of 104 courses of rituximab. Patients were aged 12.2 (IQR 9.0–13.9) years at the time of JSLE diagnosis and 50 (79%) patients were female. The ethnic origin of patients was: 36% White, 32% Asian, 30% Black African/Caribbean and 2% mixed race. At the time of rituximab administration the patients were aged 14.4 (12.0–15.5) years and had been diagnosed with JSLE for 1.4 (0.2–3.0) years. Those patients with the shortest lead-time between JSLE diagnosis to rituximab use tended to have renal impairment. Nineteen patients (30% of the cohort) received more than one course of rituximab during the study period with the average being a total of 3.2 courses (ranging from two to six courses) in this subgroup. Those patients who required only one course of rituximab during the study period were presumably in clinical remission and therefore did not warrant further courses; however, this was not specifically assessed in this study. There was an increase in rituximab use over the decade in these two centres, as shown in Figure 1.

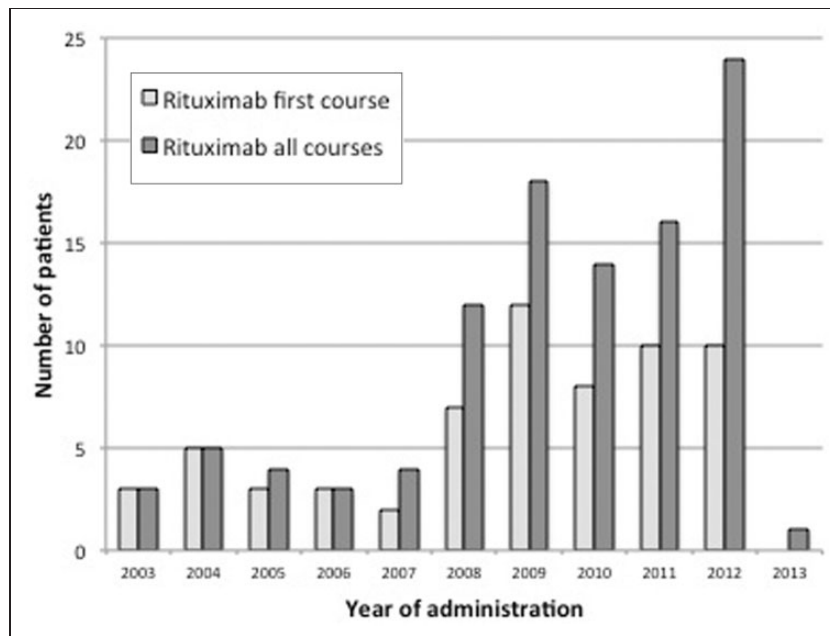


**Figure 1** Year of rituximab use in patients' first course and in all courses, showing an increase in use over time (data from August 2003–March 2013).

#### *Rituximab administration*

All patients within this study received a dose of rituximab at 750 mg/m<sup>2</sup> given on two separate occasions approximately 14 days apart; for the majority of patients (first course: 46 patients (73%); all courses: 70 courses (67%)) this included a dose of cyclophosphamide at 375 mg/m<sup>2</sup> prior to each dose (in accordance with standard UK British Society for Paediatric and Adolescent Rheumatology (BSPAR) protocol<sup>16</sup>) and a quarter of patients (first course: 16 patients, 25%; all courses: 27 courses (26%)) received rituximab without any prior cyclophosphamide.

Two patients received additional treatment at the time of their first dose of rituximab: One patient received plasma exchange therapy and another patient had intravenous immunoglobulin (IVIg). When assessing all courses of rituximab there were a total of 11 courses (11/104; 11%) that received additional treatment at the time of rituximab administration. This included: five courses treated additionally with plasma exchange, two courses with pulsed IV corticosteroids, two courses with IVIg, one course with tocilizumab and one course with thalidomide. Three of the five plasma-exchange courses also had treatment with haemodialysis, IVIg and IV corticosteroids, respectively. One patient received three doses of rituximab each two weeks apart during a subsequent course of treatment.

#### *Medication use and disease indications for rituximab treatment*

Fifty-seven patients (90%) had complete medication details available. All of these patients had been treated with immunosuppression prior to receiving rituximab. At the time of initial treatment 26 patients (41%) had received a combination of two or more immunosuppressive treatments (any two of: azathioprine, mycophenolate mofetil (MMF), pulsed monthly cyclophosphamide, ciclosporin, IVIg, infliximab, methotrexate, etanercept, tacrolimus, plasma exchange or thalidomide). Six (10%) patients had consecutively received azathioprine, MMF and then cyclophosphamide and still had ongoing disease activity at the time of first rituximab administration. Fifty-three of the 57 patients with medication data available (93%) were on oral corticosteroids at the time of rituximab administration. The median dose of oral corticosteroids at the time of rituximab administration was 0.26 (0.09–0.44) mg/kg. Sixteen patients (25%) had been receiving MMF and corticosteroids alone, nine (14%) after azathioprine and corticosteroids, two (3%) after ciclosporin and corticosteroids, one (2%) patient after cyclophosphamide and corticosteroids, one (2%) after treatment with plasma exchange, one (2%) corticosteroids alone and one (2%) treated with methotrexate.

Table 1 shows that the most common indication for patients requiring rituximab was refractory

**Table 1** The clinical disease indications for administering rituximab to patients with juvenile systemic lupus erythematosus (SLE) during the first course and all courses

| <i>Disease activity indications for rituximab</i>  | <i>Number of patients<br/>(first course, n = 63, %)</i> | <i>Number of patients<br/>(all courses, n = 104, %)</i> |
|----------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|
| Multisystem disease plus general symptoms          | 0 (0%)                                                  | 1 (1%)                                                  |
| Pancreatitis, pleural effusion                     | 0 (0%)                                                  | 1 (1%)                                                  |
| Pleural effusion                                   | 0 (0%)                                                  | 1 (1%)                                                  |
| Poor growth                                        | 1 (2%)                                                  | 1 (1%)                                                  |
| Refractory disease                                 | 1 (2%)                                                  | 1 (1%)                                                  |
| Skin involvement plus general symptoms             | 1 (2%)                                                  | 1 (1%)                                                  |
| Maintenance dosing                                 | 0 (0%)                                                  | 2 (2%)                                                  |
| Gastrointestinal disease                           | 4 (6%)                                                  | 5 (5%)                                                  |
| Bone pains/arthritis/arthralgia                    | 3 (5%)                                                  | 7 (7%)                                                  |
| Cardiac involvement                                | 3 (5%)                                                  | 4 (4%)                                                  |
| Thrombocytopenia                                   | 3 (5%)                                                  | 4 (4%)                                                  |
| Cerebral disease                                   | 4 (6%)                                                  | 5 (5%)                                                  |
| Vasculitis                                         | 1 (2%)                                                  | 8 (7%)                                                  |
| Not clearly documented                             | 3 (5%)                                                  | 4 (4%)                                                  |
| General symptoms: fever, lethargy, malaise, rashes | 14 (21%)                                                | 20 (19%)                                                |
| Renal disease                                      | 25 (39%)                                                | 38 (36%)                                                |
| Poor compliance                                    | 0 (0%)                                                  | 1 (1%)                                                  |

lupus nephritis (36% of all first courses). The clinical features of lupus nephritis included: microscopic proteinuria in 10 patients (16%), nephrotic syndrome in seven patients (11%; including two patients who had mixed nephrotic/nephritic features), one patient was nephritic (2%) and seven patients had acute kidney injury (11%). The cohort included patients with histologically defined lupus nephritis, including class IV disease; however, the histological classification was not routinely recorded as part of this study.

#### *Biomarkers of disease activity*

Table 2 presents the clinical biomarkers measured before and after rituximab treatment taken 2.5 (IQR 1.6–4.3) months after treatment. These demonstrated a statistically significant improvement in ESR, C3, C4, creatinine, and albumin concentrations and anti-dsDNA titres following rituximab treatment (Figure 2). Haemoglobin concentration improved but WCC and platelet counts did not differ significantly after treatment (Table 2). UACR levels did improve statistically significantly in those with initially abnormal levels (defined as a UACR >30 mg/mmol). As shown in Table 2, the post-rituximab IgG, IgA and IgM concentrations were all statistically significantly reduced, as typically seen after treatment; however, only a few patients required replacement because of clinical concerns about infection. Improvement of disease activity after rituximab tended to occur regardless

of the patients' ethnicity; however, it was noted that patients of Black ethnic origin had statistically significantly increased disease activity prior to starting rituximab (increased ESR and anti-dsDNA) when compared to patients of other ethnicity.

The dose of oral corticosteroids statistically significantly reduced after rituximab use in the patients' first course and also in all courses of rituximab included in this study (first course: corticosteroid dose before 0.26 (0.09–0.44) mg/kg, after 0.17 (0.09–0.30) mg/kg;  $p = 0.01$ , all courses: before 0.24 (0.09–0.40) mg/kg, after 0.19 (0.09–0.32) mg/kg;  $p = 0.01$ ).

#### *AEs*

AEs were experienced in 19 of the 104 total courses of rituximab treatment (18%). The most common AE experienced in patients receiving rituximab was a need to delay the second dose of treatment during the course of rituximab. This occurred in 8% of all courses. The reason for delaying treatment was due to the following ( $n$  = number of courses): neutropenia ( $n = 1$ ), fever ( $n = 3$ ), surgery for oesophageal stricture ( $n = 1$ ), drug not available ( $n = 1$ ), no hospital beds ( $n = 1$ ) or due to an upper respiratory tract infection ( $n = 1$ ). Patients also developed reduced Ig levels requiring replacement (2% of courses) and allergic reactions (6% of all courses), four of which were mild/moderate and 2% were anaphylactic. Only 1% of patients had poor B-cell depletion (although B cell numbers were not routinely measured post treatment) and 2% had a documented infection within

**Table 2** Laboratory markers measured before and after rituximab treatment demonstrating the median values (interquartile ranges (IQR)) and statistical probability (*p*) values. The results were measured 2.5 (IQR 1.6–4.3) months after treatment

| Laboratory marker               | First course of rituximab (n = 63) |                                  | p value             | All courses of rituximab (n = 104) |                                  | p value             |
|---------------------------------|------------------------------------|----------------------------------|---------------------|------------------------------------|----------------------------------|---------------------|
|                                 | Before rituximab,<br>median (IQR)  | After rituximab,<br>median (IQR) |                     | Before rituximab,<br>median (IQR)  | After rituximab,<br>median (IQR) |                     |
| Haemoglobin (g/l)               | 10.9 (9.6–12.2)                    | 11.7 (10.5–12.5)                 | <0.001 <sup>a</sup> | 10.8 (9.7–12.3)                    | 11.7 (9.9–12.9)                  | 0.002 <sup>a</sup>  |
| WCC (× 10 <sup>9</sup> /l)      | 5.8 (3.7–8.5)                      | 5.1 (3.8–8.4)                    | 0.819               | 5.1 (3.7–8.0)                      | 4.9 (3.6–8.0)                    | 0.944               |
| Neut (× 10 <sup>9</sup> /l)     | 3.9 (2.3–6.3)                      | 3.5 (2.5–5.8)                    | 0.433               | 3.33 (2.45–5.28)                   | 3.2 (2.2–5.0)                    | 0.31                |
| Lymph (× 10 <sup>9</sup> /l)    | 1.1 (0.8–1.5)                      | 0.9 (0.6–1.3)                    | 0.023 <sup>a</sup>  | 1.1 (0.8–1.6)                      | 1.0 (0.6–1.3)                    | 0.08                |
| Platelet (× 10 <sup>9</sup> /l) | 243 (161–328)                      | 277 (209–351)                    | 0.084               | 242 (157–334)                      | 274 (219–343)                    | 0.117               |
| ESR (mm/hour)                   | 60 (26–101)                        | 37 (12–56)                       | <0.001 <sup>a</sup> | 58 (23–91)                         | 40 (14–70)                       | <0.001 <sup>a</sup> |
| C3 (g/l)                        | 0.88 (0.52–1.03)                   | 0.94 (0.70–1.20)                 | <0.001 <sup>a</sup> | 0.70 (0.54–0.99)                   | 0.89 (0.67–1.10)                 | <0.001 <sup>a</sup> |
| C4 (g/l)                        | 0.11 (0.07–0.17)                   | 0.17 (0.03–0.50)                 | 0.001 <sup>a</sup>  | 0.09 (0.06–0.23)                   | 0.15 (0.07–0.23)                 | 0.001 <sup>a</sup>  |
| Albumin (g/l)                   | 35 (25–41)                         | 38 (33–43)                       | <0.001 <sup>a</sup> | 37 (28–42)                         | 40 (32–42)                       | 0.026 <sup>a</sup>  |
| Creatinine (mmol/l)             | 58 (48–70)                         | 53 (48–66)                       | 0.004 <sup>a</sup>  | 58 (45–71)                         | 55 (45–68)                       | <0.001 <sup>a</sup> |
| IgG (g/l)                       | 11.9 (6.0–17.1)                    | 9.7 (4.7–13.1)                   | <0.001 <sup>a</sup> | 12.0 (7.6–16.7)                    | 10.9 (5.6–13.8)                  | <0.001 <sup>a</sup> |
| IgA (g/l)                       | 1.7 (1.1–2.5)                      | 1.3 (0.8–2.5)                    | 0.001 <sup>a</sup>  | 1.7 (1.2–2.5)                      | 1.7 (1.0–2.5)                    | <0.001 <sup>a</sup> |
| IgM (g/l)                       | 1.0 (0.5–1.3)                      | 0.6 (0.3–0.8)                    | <0.001 <sup>a</sup> | 0.7 (0.6–1.3)                      | 0.6 (1.0–2.5)                    | <0.001 <sup>a</sup> |
| UACR (mg/mmol)                  | 37 (2–351)                         | 40 (2–142)                       | 0.081               | 57 (2–212)                         | 40 (1–152)                       | 0.101               |
| UACR (mg/mmol) <sup>b</sup>     | 284 (165–631)                      | 145 (70–441)                     | 0.057               | 229 (112–575)                      | 140 (48–485)                     | 0.04 <sup>a</sup>   |
| Anti-dsDNA (IU/l)               | 95 (13–283)                        | 30 (5–91)                        | <0.001 <sup>a</sup> | 61 (7–178)                         | 28 (5–73)                        | <0.001 <sup>a</sup> |

WCC: white cell count; Neut: neutrophil count; Lymph: lymphocyte count; ESR: erythrocyte sedimentation rate; C: complement C; Ig: immunoglobulin; UACR: urine albumin:creatinine ratio; anti-dsDNA: anti-double-stranded DNA titres.

<sup>a</sup>Statistically significant.

<sup>b</sup>Using cases with a baseline UACR >30 mg/mmol (*n* = 31 and 54 cases, respectively).

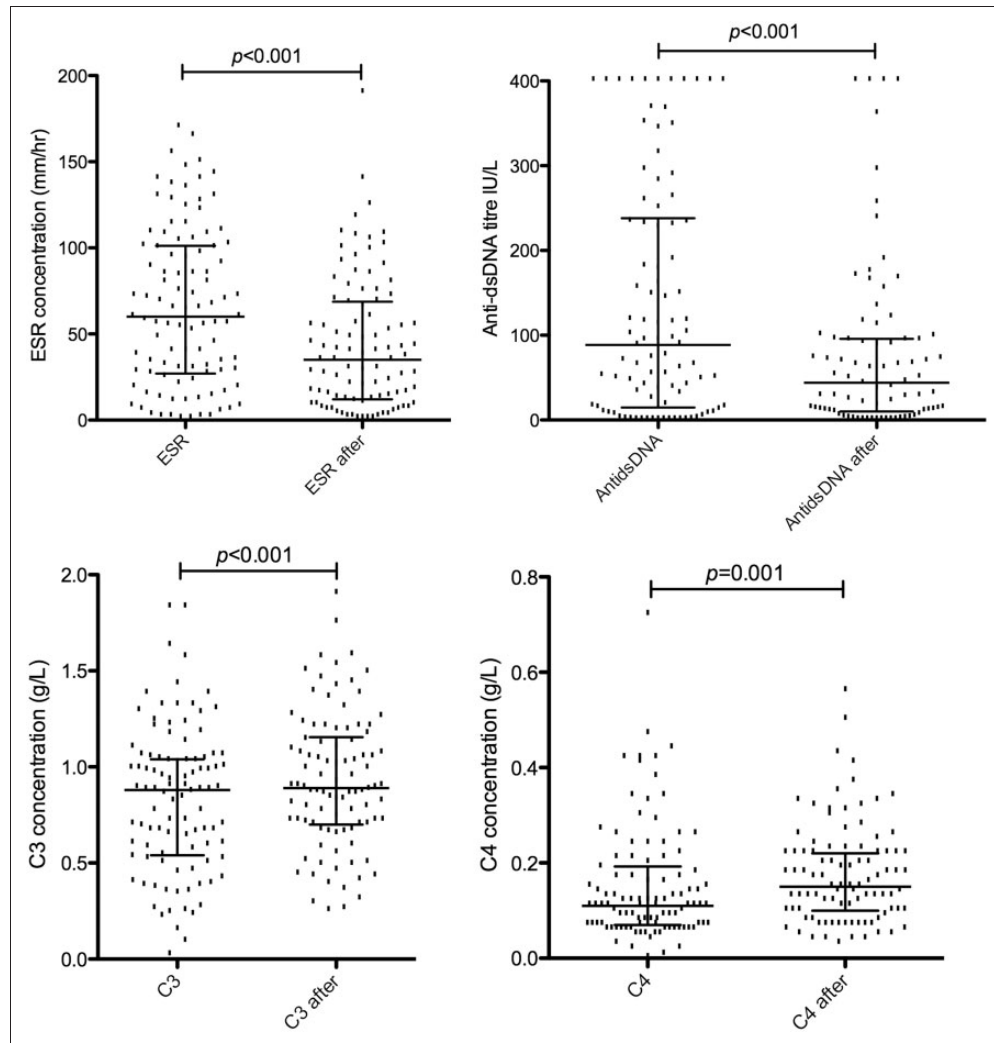


**Figure 2** Clinical disease activity markers, erythrocyte sedimentation rate (ESR), anti-double-stranded DNA (anti-dsDNA), complement C3, C4 before and after rituximab administration in patients with juvenile-onset systemic lupus erythematosus (SLE) showing decrease in the ESR and anti-dsDNA levels and improvement in C3 and C4.

three months of treatment (one patient had cytomegalovirus (CMV) and adenovirus; one patient had herpes zoster infection).

#### *Patients with multiple courses of rituximab*

Nineteen patients (30%) received more than one course of rituximab accounting for a total of 60 of the 104 courses (58%). Patients who received more than one course of rituximab were statistically significantly younger at the time of their first rituximab course when compared to those who received only a single course of rituximab (>1 course median age 12.7 (4.5–15.0) years, one course median age 14.6 (12.7–16.2) years;  $p = 0.02$ ). There was no difference in the disease duration between the groups ( $p = 0.15$ ) or the gender between the groups ( $p = 0.47$ ). There was no

difference between the groups with regards to the clinical indications for using rituximab.

BILAG disease activity data were available for 46 of the courses of rituximab (46/104; 44%) in 25 patients. The global BILAG score before rituximab was 4.5 (2.0–9.0, range 0–28) that reduced to 3.0 (2.0–5.5, range 0–15;  $p = 0.16$ ) after rituximab, although this did not reach statistical significance.

#### **Discussion**

This study, using patients from two leading UK paediatric lupus centres, is by far the largest cohort describing the use of rituximab in patients with JSLE to date. It builds upon (and includes) the seven patients originally described from one of

our centres.<sup>17</sup> In SLE, B cells contribute to disease pathology by facilitating antigen presentation and autoantibody production together with permitting the secretion of cytokines and the co-stimulation of T cells.<sup>18</sup> Rituximab, as a B-cell depleting agent, offers an alternative or adjunctive therapeutic option for patients with JSLE who have suboptimal disease response to first-line treatment or in whom the side effects of toxic immunosuppression are no longer tolerable.<sup>18,19</sup> This study aimed to assess the clinical indications, efficacy and AEs of rituximab use in children with lupus.

We have demonstrated that the use of rituximab has increased over the past decade, emphasizing the importance both of this study and the urgent need for prospective collection of detailed efficacy and safety data. Notably, the most common clinical indication for its use was refractory lupus nephritis. An Australian study also described lupus nephritis as one of the leading indications for using off-label rituximab.<sup>20</sup> Since the first report of rituximab use in childhood lupus published by our group in 2005,<sup>17</sup> other reports have continued to report its efficacy using small case series.<sup>21</sup> We have confirmed the efficacy of rituximab, in terms of a reduction in laboratory marker concentrations, a reduction in corticosteroid dose and an improving trend in the global BILAG score, using 63 children and over 100 courses of rituximab. Balancing disease activity against corticosteroid avoidance is a challenge in SLE, especially in childhood disease for which up to 97% of patients will require corticosteroids during their disease.<sup>22</sup> We have shown that rituximab appears to reduce the amount of corticosteroid required in a short follow-up period and may have an important role in patients experiencing steroid-associated side effects.

This is now the largest series to date to describe the AEs of rituximab using a non-selected cohort. It aims to reduce positive reporting bias that may occur in case reports or small series. We have shown that rituximab does have associated AEs, occurring in 17% of patients, albeit relatively infrequently severe. The most common AE encountered was the requirement to delay the treatment followed by infusion reactions, seen in 11% and 5% of our patients, respectively. Delay in treatment has not been previously reported and occurred for a variety of reasons. Infusion reactions have been described previously with adult cohort studies reporting a frequency of 0%–16% of cases,<sup>6,23,24</sup> similar to our data. Our infection rate was low (up to 2%) when compared to other studies and this may represent underreporting due to bias introduced with either our retrospective data

collection methods or the short follow-up period. A Spanish study assessing adults with SLE demonstrated infection to be the leading AE from rituximab use, with 12.6 infections per 100-patient years.<sup>25</sup> In our study Ig levels (IgG, -A and -M) significantly reduced after rituximab, a recognized finding; however, only 2% of cases in this study required IVIg replacement that was administered on clinical grounds.

Limitations of this study include its retrospective nature and data restricted to two centres. Our retrospective methods may have produced reporting bias with regards to the AEs experienced by our patients and the uncontrolled nature of this cohort means that there is no comparable control group to corroborate our findings. Additionally our numbers were too small to fully evaluate the effect of interventions such as plasma exchange or haemodialysis on disease activity or rituximab efficacy. It would be essential to study the longer-term effects of rituximab and in particular whether the effects of treatment are sustained as the B cells repopulate. This was not possible within this study as many of the patients within our cohort had medication changes after the study period, meaning that it would be impossible to determine the independent effect of rituximab. Further prospective studies, preferably well designed, randomized, controlled trials, are required to obtain more accurate data on the efficacy of rituximab in JSLE; additionally reliable pharmacokinetic data on dosing and administration of this drug in children is urgently needed. Long-term studies are required to further assess the safety of rituximab, for example its future carcinogenic risk and any potential fertility or teratogenic consequences. Despite these limitations, our data provide essential information for clinicians who are considering using rituximab to manage children with SLE and have broader implications for clinicians using it for other immune-mediated diseases.

## Conclusion

The use of rituximab in JSLE is increasing over time. Using data from the largest JSLE cohort treated with rituximab, it can be concluded that it effectively reduces disease activity biomarkers and steroid burden in patients failing standard therapy. AEs do occur, although in less than one in five patients. These are generally mild but include a 2% risk of anaphylactic infusion reactions and therefore it should be administered within an

appropriate setting. Further studies are urgently needed.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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