



Full Length Article

Real world treatment of juvenile-onset systemic lupus erythematosus: Data from the UK JSLE cohort study



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ABSTRACT

Background: In the absence of clinical trials evidence, Juvenile-onset Systemic Lupus Erythematosus (JSLE) treatment plans vary.

Aim: To explore 'real world' treatment utilising longitudinal UK JSLE Cohort Study data.

Methods: Data collected between 07/2009–05/2020 was used to explore the choice/sequence of immunomodulating drugs from diagnosis. Multivariate logistic regression determined how organ-domain involvement (pBILAG-2004) impacted treatment choice.

Result: 349 patients met inclusion criteria, median follow-up 4-years (IQR:2.6). Mycophenolate mofetil (MMF) was most commonly used for the majority of organ-domains, and significantly associated with renal involvement (OR:1.99, 95% CI:1.65–2.41, $p_c < 0.01$). Analyses assessing the sequence of immunomodulators focused on 197/349 patients (meeting relevant inclusion/exclusion criteria). 10/197 (5%) solely received hydroxychloroquine/

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prednisolone, 62/197 (31%) received a single-immunomodulator, 69/197 (36%) received two, and 36/197 patients (28%) received \geq three immunomodulators. The most common first and second line immunomodulator was MMF. Rituximab was the most common third-line immunomodulator.

Conclusions: Most UK JSLE patients required \geq two immunomodulators, with MMF used most commonly.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-system autoimmune/inflammatory disorder [1–4]. Patients diagnosed with SLE during childhood and adolescence account for 15–20% of all SLE patients [1,5]. The incidence of juvenile-onset SLE (JSLE) ranges between 0.4 and 0.9 per 100,000 children per year, and as such it is classified as a rare disease [6,7]. JSLE patients exhibit more aggressive clinical phenotypes with increased organ damage when compared to patients with disease-onset in adulthood [8]. In the absence of evidence from prospective trials, the treatment of JSLE is based on data from adult-onset SLE cohorts. However, JSLE patients often require more intensive treatment than adults [9,10].

JSLE is associated with significant morbidity, including cerebrovascular accidents, cognitive impairment, and end-stage renal disease [11,12]. Though mortality in SLE has declined over recent decades, standardized mortality rates continue to be substantially higher as compared to either the general population (18.3 in JSLE) or adult-onset SLE patients (3.1) [13]. The unpredictable nature of JSLE poses great challenges in the management of patients [1], and it is vitally important to minimise disease activity to prevent the accumulation of organ damage [12].

Notably, there is no standardized approach to the clinical management of JSLE. Clinical practice differs around the world and even within the same country, region, and/or individual centre [14–16]. Collaborative efforts have resulted in consensus treatment plans by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) [17], and diagnostic and therapeutic recommendations from the Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) initiative [15,16].

In adult-onset SLE patients, achievement of a low disease activity is associated with reduced organ damage, and has been used as a clinical target in disease management [18,19]. However, treat-to-target strategies have yet to be determined and prospectively evaluated in JSLE. The TARGET LUPUS[®] research program ‘Targeting disease, Agreeing Recommendations and reducing Glucocorticoids through Effective Treatment, in LUPUS’ aims to deliver a JSLE treat-to-target (T2T) trial [20].

The aim of this study was to explore ‘real world’ treatment approaches in JSLE utilising longitudinal data from the UK JSLE Cohort Study. This will help to facilitate development of T2T treatment regimens that are underpinned by the albeit limited evidence available in JSLE [15,17,21,22], and data on real world treatment practices from the UK JSLE Cohort Study.

2. Materials and methods

2.1. Patients

This study included UK JSLE Cohort Study participants from 21 paediatric rheumatology centres. Written informed assent and/or consent was obtained from patients/parents to participate in the study. This study received ethical approval from the National Research Ethics Service North West, Liverpool East, UK (reference 06/Q1502/77), and was conducted in accordance to the declaration of Helsinki.

Inclusion criteria:

1. UK JSLE Cohort patients fulfilling \geq 4 American College of Rheumatology (ACR-1997) criteria for SLE [23,24]
2. Diagnosed with JSLE before their 18th birthday.

Exclusion criteria (separate exclusion criteria applied for the three different sub-analyses included in the manuscript):

Exclusion criteria for analysis looking at *corticosteroid treatment at baseline* (*‘baseline’ refers to the first visit at the time of or within 6 months of initial diagnosis*):

1. Patients with missing corticosteroids data at baseline
2. Patients with no body weight recorded at baseline (as it would not be possible to determine the dosage in mg/kg)

Exclusion criteria for analysis looking at the *sequence of immunosuppressant use from baseline onwards*:

1. Patients diagnosed with JSLE before July 2009 (to facilitate assessment of relatively recent treatment practices)
2. Those where the diagnosis date was not available (as it would be impossible to determine which treatment was used first-line treatment)
3. Patients where data on the medications used at baseline are missing (as it would be impossible to determine the first-line treatment)
4. Patients with only a single baseline visit and no follow up (as it would be impossible to determine second- or third-line treatments)
5. Patients where there was no visit within 6 months of their diagnosis (unable to accurately determine first-, second- and third-line treatments)

Exclusion criteria for analysis looking at how *different clinical manifestations may guide immunosuppressant choice during follow-up*:

1. Data collected from visits before July 2009 (excluded to facilitate assessment of relatively recent treatment practice)

2.2. Data collected

The following clinical and laboratory data were collected:

- Demographics at baseline including age at symptoms onset, age at diagnosis, gender and ethnicity. For the purposes of the analysis, data of patients who were of mixed race were grouped with those of the associated ethnic minority group (e.g. Asian if mixed Asian and White Caucasian).
- Clinical and laboratory results required to calculate a paediatric British Isles Lupus Assessment Grade 2004 (pBILAG) score [25,26], weight, antinuclear antibodies (ANA) titres.
- Medications at baseline and longitudinally, including corticosteroids, immunosuppression (mycophenolate mofetil (MMF), cyclophosphamide, azathioprine, methotrexate, cyclosporin, IV immunoglobulins (IVIg), rituximab, and ‘other’ medications e.g. angiotensin converting enzyme (ACE) inhibitors. Data on Belimumab, Ofatumumab and Obinutuzumab were not collected by the Cohort Study during the study period.

At each visit, pBILAG scores were calculated, assessing disease activity across nine organ domains, including: neuropsychiatric, renal, cardiorespiratory, gastrointestinal, haematological, ophthalmic, musculoskeletal (MSK), mucocutaneous and constitutional. A pBILAG score of A or B indicates severe or moderate disease, pBILAG C indicates mild disease, pBILAG D indicates previous organ involvement but no active disease and finally pBILAG E indicates that there has been no

previous activity in a particular organ domain [27,28]. In terms of exploring the sequence of immunomodulators used, simultaneous treatment was determined by treatment recorded on the same pBILAG form/visit. Sequential treatment was determined by treatment recorded on different pBILAG forms/visits.

2.3. Data analysis

Corticosteroid treatment at baseline investigated, including the prednisolone dosage in mg/kg, and whether IV methylprednisolone was used. The study then explored the sequence of immunosuppressants used in the clinical management of JSLE (first-, second- and third-line treatments) from diagnosis onwards. Hydroxychloroquine was considered standard care for all patients [21]. Therefore, the first-, second- and third-line treatments were those that were given in addition to hydroxychloroquine. For patients who were commenced on two immunosuppressants simultaneously, both immunosuppressants were accounted for simultaneously in the sequence of immunosuppressants used. In patients who received repeated courses of rituximab or cyclophosphamide, these treatments were only considered once in the first-, second- and third-line treatment sequence. They were not classed as a new treatment each time a new course of was given. For example, in a patient where rituximab was given second-line, if the treatment was repeated 6 months later it would not be classed as a third line treatment.

To investigate which treatments were used for different types of organ domain involvement, binary coding was used to indicate if particular organ domains were involved, and which treatment was used at each visit. A pBILAG score of A or B was taken to indicate that an organ domain was involved (receiving a "1") and pBILAG C-E were taken to indicate that a patient had no or mild involvement in a given organ domain (receiving a "0"). At each visit, for each immunosuppressive treatment (MMF, azathioprine, cyclophosphamide, methotrexate, cyclosporin, rituximab and IVIg), patients were allocated a "1" if they were receiving a particular treatment and "0" if they were not receiving that treatment. A multivariate binary logistic regression model was fitted to assess for an association between the different pBILAG defined organ domains involved (model covariates) and whether the patient was on a certain treatment or not (model outcome). The final multivariate model was derived after stepwise selection of covariates with a p -value of <0.1 within univariate models. The multivariate model was adjusted for those with simultaneous multiple organ domains of involvement. Within each logistic regression model, a Bonferroni correction was applied for nine tests (as nine pBILAG organ domains were tested for), and a corrected p -value (p_c) stated.

When exploring how different clinical manifestations may guide immunosuppressant choice, in patients where >1 pBILAG defined organ domain was involved the treatments were presented as being used for each organ domain (e.g. if a patient were to have neuropsychiatric and MSK involvement and was treated with cyclophosphamide, cyclophosphamide treatment is the reported treatment for both the neuropsychiatric and MSK involvement). A pBILAG score of A or B was taken to indicate that an organ domain was involved [29].

Descriptive statistics were included (confidence intervals (CI), median, interquartile range (IQR)). p values of <0.05 were considered statistically significant. All statistical analysis was undertaken using SPSS version 26 (IBM Corporation).

3. Results

3.1. Demographics and baseline data

A total of 349 UK JSLE Cohort Study patients met the study's inclusion criteria; 290 females (83%) and 59 males (17%). Patients were followed for a median of 4.0 years (IQR: 2,6), with a median of 9 visits per patient (IQR: 4,13) and 3266 follow-up visits overall. The median age at diagnosis was 13 (IQR: 11,15) years. A substantial proportion of

patients were from non-Caucasian backgrounds (194/349, 56%). Patients fulfilled a median of 5 (IQR: 4,6) ACR-1997 criteria at baseline. At diagnosis, the majority of patients were antinuclear antibody (ANA) positive (334/349, 96%) with 178/349 (51%) also testing positive for anti-double stranded deoxyribose nucleic acid antibodies (anti-dsDNA). Demographic information of patients meeting inclusion criteria for analyses looking at the sequence of immunomodulating treatments use ($n = 197$) are displayed in Table 1.

3.2. Corticosteroid treatment at baseline

For 18/349 patients, data on medications at baseline were incomplete, and so these patients were excluded from these specific analyses, leaving 331 patients. 179/331 (54%) patients received oral prednisolone only at baseline, 13/331 (4%) received IV methylprednisolone only and 76/331 (23%) received both oral prednisolone and IV methylprednisolone. 63/331 (19%) did not receive corticosteroids at baseline (Fig. 1A). Of the patients receiving oral prednisolone (179 patients received oral prednisolone alone, 76 patients had oral prednisolone in combination with IV methylprednisolone, total $n = 255$), 46/255 (18%) patients did not have their body weight recorded at diagnosis, therefore weight-adjusted dosage (mg/kg) could not be determined. In the

Table 1

Clinicodemographic features of UK JSLE Cohort Study participants at baseline.

Demographic and clinical information	Full cohort (included in the analyses assessing how different clinical manifestations may guide immunosuppressant choice, $n = 349$)	Sub-cohort (included in the analyses assessing the sequence of immunosuppressants used from diagnosis onwards, $n = 197$)
Gender		
Female	290 (83%)	162 (82%)
Male	59 (17%)	35 (18%)
Age at diagnosis (years)	13 [11,15]	13 [11,15]
Ethnicity		
White	155 (44%)	87 (44%)
Caucasian		
South Asian	84 (24%)	56 (28%)
African/Caribbean	61 (17%)	29 (15%)
Other White ^a	6 (2%)	3 (2%)
Other Asian ^a	39 (11%)	21 (11%)
Other Black ^a	1 (0)	0 (0)
Other mixed background ^a	2 (1%)	1 (0)
Unknown	1 (0)	0 (0)
Length of follow up (years)	4 [2,6]	3 [2,5]
Total number of visits	3266	2062
Number of visits per patient	8 [4,13]	10 [6,14]
ANA positive at baseline ^b	336 (96%)	191 (97%)
Number of ACR criteria fulfilled	5 [4,6]	5 [4,6]
Anti-dsDNA positive at baseline ^c	178 (51%)	106 (54%)

^a Other Asian included patients of Chinese, Malaysian, Phillipino, Vietnamese, Arab or unspecified Asian descent. Other mixed background included those from unspecified mixed backgrounds. Other black included those from unspecified black backgrounds.

^b ANA positivity was defined as a titre of $\geq 1:80$.

^c Anti-dsDNA positivity was defined as a titre of ≥ 20 IU/L. Anti-dsDNA data missing for 102 patients. ANA - anti-nuclear antibodies. ACR - American College of Rheumatology, dsDNA - anti-double-stranded deoxyribose nucleic acid antibody (anti-dsDNA). Data shown are either number of patients and percentage, or median values and interquartile ranges. Total $n = 349$.

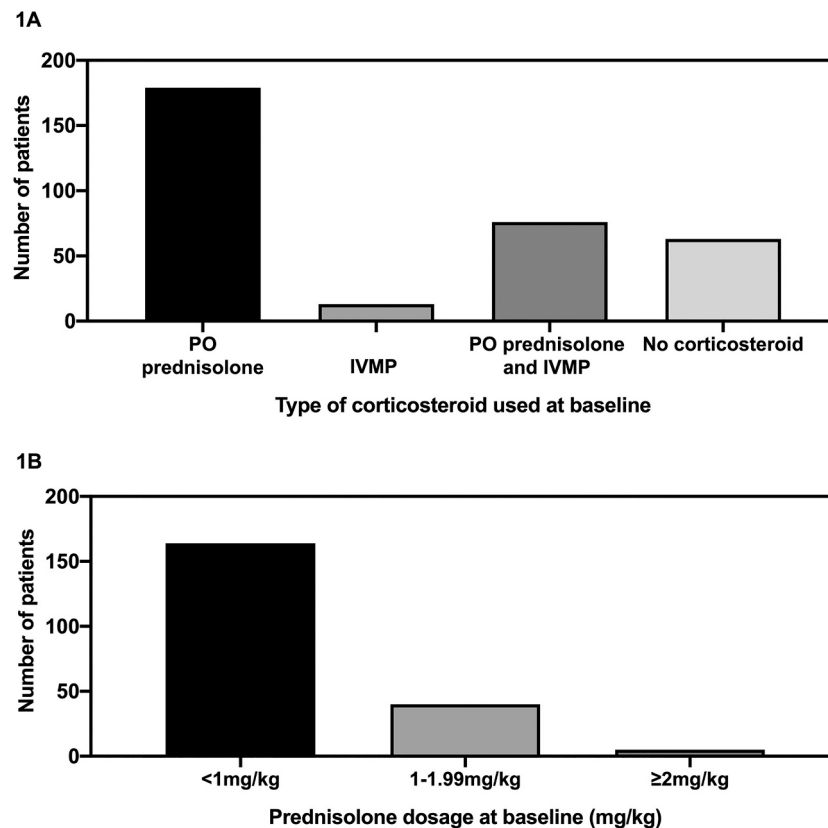


Fig. 1. Use of intravenous and oral corticosteroids at baseline. A) Type of corticosteroid used at baseline ($n = 331$ as 18 patients had incomplete data on corticosteroid use at baseline). B) Corticosteroid dose at baseline (mg/kg) ($n = 285$, as 46 patients did not have their body weight recorded at baseline). PO - oral. IVMP - intravenous methylprednisolone.

remaining 209 patients, the oral prednisolone starting dose was <1 mg/kg in 164/209 (78%), 1–1.99 mg/kg in 40/209 (19%) and ≥ 2 mg/kg in 5/209 (3%) (Fig. 1B).

3.3. Sequence of immunomodulating treatments used

A sub-cohort of 197/349 patients (56%) met the aforementioned inclusion/exclusion criteria for the following analyses (152 patients excluded due to the following reasons: 120 diagnosed before July 2009, 19 patients did not have a visit recorded within 6 months of diagnosis, 11 only had a single visit, and 2 patients did not have a diagnosis date recorded). The median time between visits was 13 weeks (IQR 9, 18).

174/197 (88%) patients received hydroxychloroquine at baseline, with the remaining patients (23/197, 12%) receiving hydroxychloroquine at a later stage during follow-up. For those that started hydroxychloroquine later, this was commenced a median of 5 weeks post diagnosis (IQR 3, 11). Over a median of 3 years (IQR: 2,7) follow-up, 10/197 (5%) patients were exclusively treated with hydroxychloroquine and prednisolone, with no (additional) immunomodulating treatments used. 62/197 (31%) patients were treated with a single (additional) immunomodulator, 69/197 (36%) had treatment with two, 36/197 (18%) patients received three, and 20/197 (10%) patients were treated with four or more (additional) immunomodulating drugs during follow-up (Fig. 2A).

The most commonly used first-line treatment was MMF (72/197, 37%) followed by azathioprine (56/197, 28%) and methotrexate (43/197, 22%). Cyclophosphamide (20/197, 10%), IVIg (12/197, 6%) and rituximab (8/197, 4%) were used as first-line immunomodulating treatments in a small number of patients (Fig. 2B). MMF was also the most commonly used second-line treatment (40/197, 20%), followed by rituximab (23/197, 12%), hydroxychloroquine (20/197, 10%), and

azathioprine (17/197, 9%). Cyclophosphamide (14/197, 7%), methotrexate (9/197, 5%), IVIg (6/197, 3%) and cyclosporin (1/197, 1%) were used as second-line treatment in a small number of patients. Rituximab was the most commonly chosen third-line treatment (15/197, 8%), followed by MMF (11/197, 6%). A relatively small proportion of patients received azathioprine (3/197, 2%), methotrexate (3/197, 2%), IVIg (4/197, 2%), hydroxychloroquine (2/197, 1%) and cyclophosphamide (4/197, 2%) as third-line treatments (Fig. 2B). In patients who received repeated courses of rituximab or cyclophosphamide, these treatments were only considered once in the first-, second- and third-line treatment sequence (not classed as a new treatment each time a new course of was given).

3.4. Treatment in relation to active organ domain involvement

Fig. 3 provides a graphical representation of treatments used across pBILAG-defined organ system domains (based on data from 349 JSLE patients fulfilling inclusion criteria mentioned above, across 3266 visits). Of note, treatments are presented as being used for every pBILAG-defined organ domain that was active at a given visit. MMF was the most common treatment for most types of organ system involvement, except for gastrointestinal and ophthalmic pBILAG domains. Statistically, however, the logistic regression analyses (Table 2) demonstrated that MMF use was significantly associated with renal involvement (OR: 1.99, 95%, confidence interval (CI): 1.65–2.41, $p_c < 0.01$). Conversely, patients with mucocutaneous involvement were less likely to be treated with MMF (OR: 0.75, CI: 0.61–0.92, $p_c < 0.01$).

Azathioprine was the most commonly used immunomodulator for gastrointestinal involvement (Fig. 3), with the logistical regression analyses supporting this observation (OR: 3.1, 95% CI: 1.59–6.04, $p_c = 0.004$, Table 2), and also demonstrating haematological involvement to

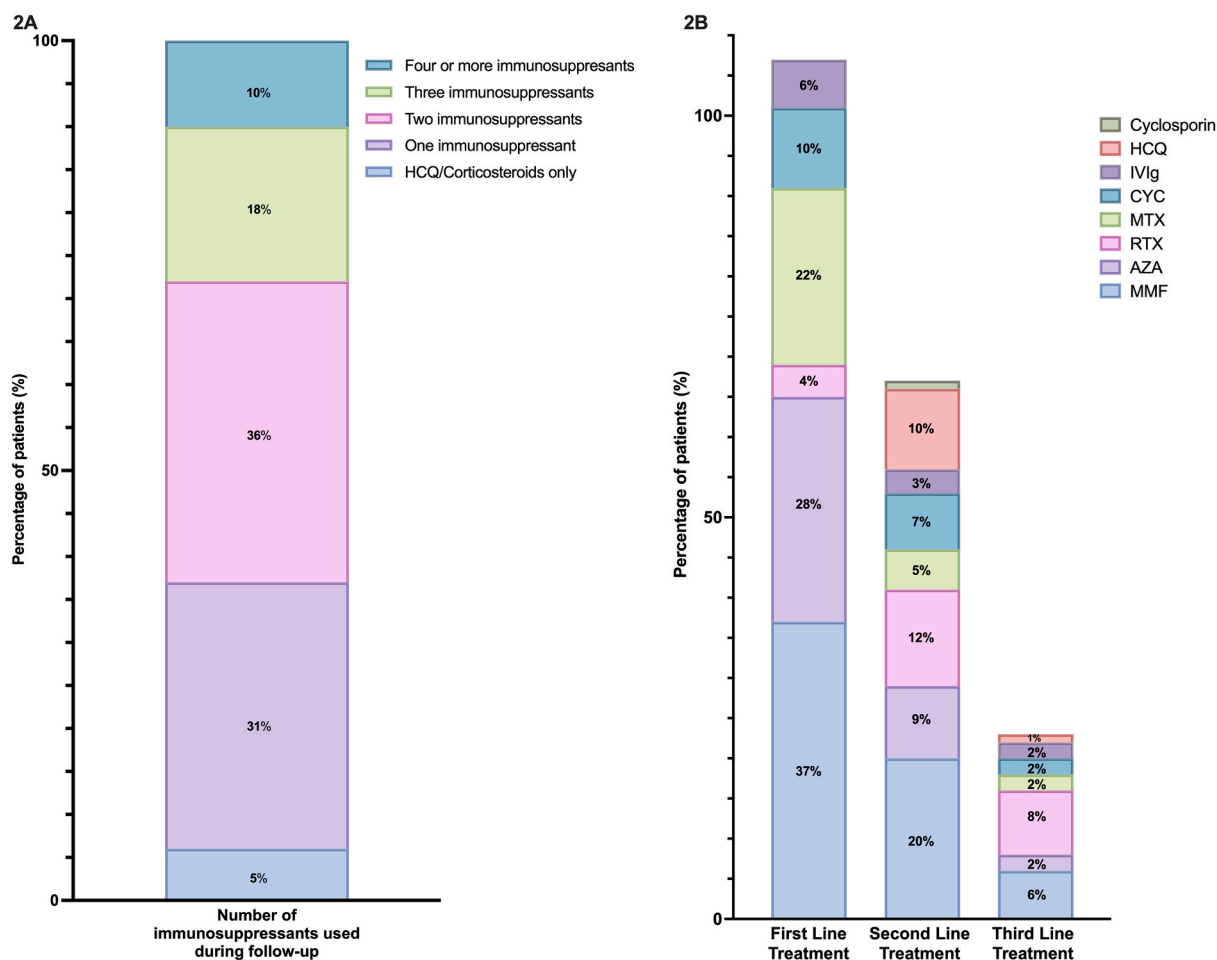


Fig. 2. First, second- and third-line treatment used in UK JSLE Cohort Study patients. 197 JSLE patients met inclusion criteria, diagnosed with JSLE between July 2009 to May 2020. A) Stacked bar chart showing the number of treatments received during the follow up period. B) Stacked bar chart showing the first, second- or third-line immunosuppressants used in addition to baseline HCQ and corticosteroids. For patients who were commenced on two immunosuppressants simultaneously; both immunosuppressants were accounted for simultaneously in the sequence of immunosuppressants used. HCQ: hydroxychloroquine, IVIg: intravenous immunoglobulin, CYC: cyclophosphamide, MTX: methotrexate, RTX: rituximab, AZA: azathioprine, MMF: mycophenolate mofetil.

be associated with azathioprine use (OR: 1.55, 95% CI: 1.15–2.09, $p_c = 0.04$, Table 2). Patients with renal involvement were significantly less likely to be treated with azathioprine (OR: 0.66, 95% CI: 0.52–0.85, $p_c < 0.01$), as compared to the other treatments assessed.

Fig. 3 suggests that cyclophosphamide was the second commonest treatment for cardiorespiratory and neuropsychiatric involvement, with logistic regression analysis supporting the association between cyclophosphamide use and both of these organ domains (cardiorespiratory involvement OR: 5.05, 95% CI: 2.82–9.04, $p_c < 0.01$, and neuropsychiatric involvement OR: 3.10, 95% CI: 1.80–5.33, $p_c < 0.01$), but also demonstrating cyclophosphamide use to be associated with haematological (OR: 2.82, 95% CI: 1.92–4.16, $p_c < 0.01$), renal (OR: 1.61, 95% CI: 1.16–2.23, $p_c = 0.04$), and mucocutaneous domain involvement (OR: 1.95, 95% CI: 1.39–2.74, $p_c < 0.01$, Table 2).

Rituximab was the third most preferred treatment for neuropsychiatric, renal, gastrointestinal, mucocutaneous and cardiorespiratory involvement (Fig. 3), with the logistic regression analysis supporting an association with cardiorespiratory involvement (OR: 2.57, 95% CI: 1.40–4.74, $p_c = 0.02$) in particular.

Methotrexate was the second most frequently used treatment for MSK domain involvement (Fig. 3), with the logistic regression analysis supporting this observation (OR: 2.55, 95% CI: 1.87–3.48, $p_c < 0.01$). Patients with renal involvement (OR: 0.44, 95% CI: 0.31–0.62, $p_c < 0.01$) were less likely to receive methotrexate.

Use of IVIg and cyclosporin and was infrequent within the UK JSLE

Cohort (Fig. 3), therefore the associated logistic regression models must be interpreted with caution (Table 2).

4. Discussion

The study presented here provides insights into the ‘real world’ clinical management of JSLE in the UK. MMF was the most commonly used first-line immunomodulating agent, and the most frequently used treatment across the majority of pBILAG organ domains. During follow up, the majority of JSLE patients required at least two immunomodulators, in addition to hydroxychloroquine and prednisolone. A small proportion of patients were solely treated with hydroxychloroquine and prednisolone. Rituximab was the commonest third-line treatment. Observations from this study will be considered (along with additional evidence from the literature) when developing a clinical decision support tool that will be used within a future T2T study.

European SHARE recommendations [15,21,22] and CARRA consensus treatment plans [17] both consider classical DMARD treatment options in JSLE patients who fail to respond to hydroxychloroquine and/or corticosteroids alone. Over recent years, MMF has been increasingly favoured over the cytotoxic agent cyclophosphamide as the first-line induction therapy for adult-onset lupus nephritis [30,31]. A Cochrane review including 74 studies reported little or no difference between MMF and cyclophosphamide in terms of achievement of remission of at 6 months (risk ratio, RR: 1.17, 95% CI:

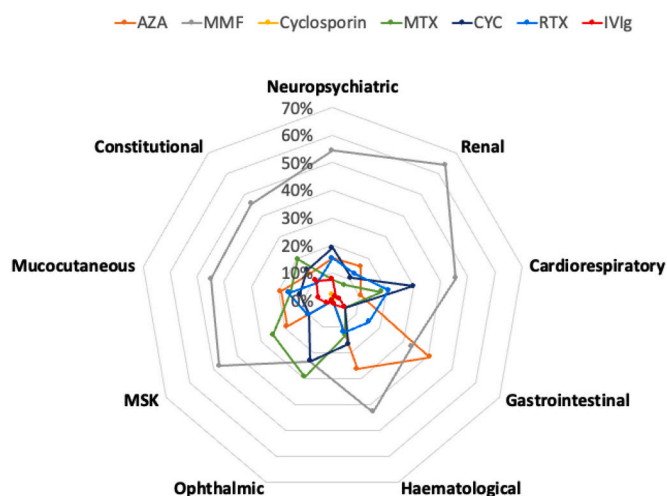


Fig. 3. Radar diagrams showing the treatments used for different pBILAG defined areas of organ involvement on a per visit basis. Radar diagram shows the particular treatments prescribed as percentage of all visits where a particular pBILAG defined area of organ involvement was present. Organ domains of involvement were defined using the pBILAG score, with those scoring an A or B in a given organ domain described as having involvement of that area. In patients where >1 pBILAG defined organ domain was involved, the treatments are presented as being used for each individual organ domain. The diagram is based on 3266 recorded visits from January 2010 to 2020 from 349 JSLE patients. HCQ: hydroxychloroquine, IVIg: intravenous immunoglobulin, CYC: cyclophosphamide, MTX: methotrexate, RTX: rituximab, AZA: azathioprine, MMF: mycophenolate mofetil.

0.97–1.42). In terms of adverse events, evidence was limited, but authors concluded that MMF was likely to be associated with reduced alopecia risk (RR: 0.29, 95% CI: 0.19 to 0.46) and more diarrhoea (RR: 2.42, 95% CI: 1.64 to 3.58). Notably, little or no differences were determined in relation to infection rates (RR: 1.02, 95% CI: 0.67 to 1.54) [31]. In-keeping with these data, a recent study from the UK JSLE Cohort Study suggested that MMF is also favoured over cyclophosphamide in JSLE patients with lupus nephritis, whilst delivering comparable renal outcomes [32]. Individual studies have suggested that MMF exhibits a better safety profile than cyclophosphamide. For example, Ginzler et al showed a 54% risk reduction in relation to adverse events with MMF [33]. However, this present study highlights that MMF is also frequently used for extra-renal areas of involvement. There are some evidence supporting MMF use in SLE for pulmonary arterial hypertension and interstitial pneumonia [34], haematological and dermatological manifestations [35,36], lupus hepatitis [37] and transverse myelitis [38].

Here, azathioprine was the second most commonly chosen first-line immunomodulating agent (after MMF), and the preferred treatment for patients with gastrointestinal involvement during follow-up. This treatment choice may in part be influenced by the gastroenterology colleagues involved in the management of such patients, as they tend to have vast experience with azathioprine (compared to MMF or methotrexate). Gastrointestinal involvement has been demonstrated in a relatively small number of UK JSLE Cohort patients at the time of the initial presentation (<10%) [26], with other studies describing gastrointestinal involvement in up to 30% of patient with JSLE during follow-up [39]. Other factors which may impact on the choice of azathioprine could be the teratogenic potential of MMF, leading to a potential preference for azathioprine in older teenage girls who are planning to / more likely to become pregnant [40]. The need for pre-treatment screening of thiopurine methyltransferase (TPMT) enzyme metabolites, and concern about potential myelosuppression may, however, deter some clinicians from using azathioprine.

Methotrexate was the third most commonly used first-line immunomodulating drug in this study. It has a well-established role in the

management of musculoskeletal and mucocutaneous manifestations, particularly in adult-onset SLE [40,41]. However, reports on its efficacy in JSLE are limited [42]. Logistic regression analyses included within the current study are in-keeping with the patterns of use in adult SLE, with the strongest association seen between methotrexate use and MSK involvement. Use of alternative DMARDs (within the UK JSLE Cohort Study) was limited to cyclosporin, which was used rarely. Cyclosporin use was associated with neuropsychiatric, renal and haematological organ domain involvement. Consensus opinion outlines cyclosporin use for haematological disease in the 2019 EULAR update [40]. This limited use of cyclosporin within the UK JSLE Cohort Study is unsurprising, given the potential for cyclosporin related adverse events (nephrotoxicity, hypertension and neurotoxicity) [43,44].

Biologic agents are a relatively recent addition to the arsenal of treatment used in SLE [45]. Due to the absence of regulatory approval and/or their relative novelty, biologic drugs can only be accessed for treatment resistant cases and (frequently) as “off label” options [46]. In the UK, the National Institute for Health and Care Excellent (NICE) regulations stipulate that Rituximab can be used for refractory SLE patients (adults/post-pubescent children) with active moderate/severe refractory SLE (BILAG A and/or two B scores or a SLEDAI-2 K score > 6, or requiring unacceptably high levels of oral glucocorticoids e.g. >7.5 mg prednisolone per day in an adult, to maintain a lower disease activity state). These patients must also have failed to respond to two or more immunosuppressive therapies (including MMF or cyclophosphamide) [46]. The European SHARE initiative recommended that rituximab may be used in JSLE in otherwise treatment refractory cases, including lupus nephritis [15]. Indeed, in the present study, rituximab was the most commonly used third-line treatment (and the second most commonly chosen second-line treatment). As mentioned above, this is in line with consensus opinion [15,21,40], despite both the EXPLORER and LUNAR adult SLE trials (investigating rituximab use in SLE in general, and lupus nephritis respectively) both having failed to meet their primary endpoints [47,48]. A study involving the UK JSLE Cohort has previously shown lupus nephritis to be the most common indication for rituximab in the UK, associated with improvement in blood and urine biomarkers of active JSLE, and a significant reduction of corticosteroid dosage [49]. Although Belimumab has been approved by NICE for use in children, uptake in clinical practice has been slow [50]. Data on Belimumab will be collected by the UK JSLE Cohort Study over the coming years.

There are significant concerns regarding use of the cytotoxic agent cyclophosphamide especially in children and young people with JSLE [33,42]. Based on data from this study, cyclophosphamide is predominantly used in JSLE patients with the more severe types of organ involvement. Indeed, cyclophosphamide was the second most commonly used immunomodulator in patients with neuropsychiatric involvement. In this study, cyclophosphamide was demonstrated to be used less frequently than azathioprine for patients with renal involvement. Renal involvement is defined by the BILAG score (A or B) rather than the histological class, in-keeping with how other organ domains of involvement are defined. The high use of azathioprine in patients with LN in this study therefore largely reflects patients who are on maintenance treatment and develop further episodes of lupus nephritis after their initial induction treatment. It is important also to note that, whilst our cohort of patients is ethnically diverse and minority ethnic background are disproportionately affected, the largest single ethnic group of patients are white Caucasians (42%). By contrast, in North America, higher proportions of patients from Black/African American and East Asian backgrounds are observed [51]. Black/African American and East Asian SLE patients tends to have more acute and severe organ/life-threatening disease presentations when compared to white Caucasians [52]. Therefore, use of cyclophosphamide may be more prevalent in these demographic groups when compared to Europeans [53].

In the absence of clinical trials in JSLE, a T2T approach is being formulated as part of the TARGET LUPUS® research program, as a means of structuring patient assessments, harmonizing therapeutic

Table 2
Logistic regression exploring the association between different organ domains and the treatments used at follow-up visits.

	MMF		AZA		CYC		RTX		MTX		IVIg*		Cyclosporin*	
	OR (95% CI)	p _c	OR (95% CI)	p _c	OR (95% CI)	p _c	OR (95% CI)	p _c	OR (95% CI)	p _c	OR (95% CI)	p _c	OR (95% CI)	p _c
Neuropsychiatric (n = 105)	1.23 (0.82–1.83) n = 57	1.0	0.71 (0.41–1.23) n = 16	1.0	3.10 (1.8–5.33) n = 20	<0.01	1.84 (1.05–3.22) n = 16	0.30	0.44 (0.21–0.94) n = 8	0.31	3.48 (1.55–7.85) n = 8	0.03	6.88 (1.28–37.01) n = 2	0.23
Renal (n = 575)	1.99 (1.65–2.41) n = 369	<0.01	0.66 (0.52–0.85) n = 94	<0.01	1.61 (1.16–2.23) n = 62	0.04	1.50 (1.12–2.00) n = 74	0.05	0.44 (0.31–0.62) n = 41	<0.01	0.78 (0.39–1.57) n = 10	1.0	6.10 (1.66–22.43) n = 6	0.06
Cardiorespiratory (n = 77)	0.83 (0.51–1.35) n = 36	1.0	0.48 (0.23–1.03) n = 8	0.54	5.05 (2.82–9.04) n = 24	<0.01	2.57 (1.40–4.74) n = 17	0.02	1.19 (0.63–2.27) n = 14	1.0	0.78 (0.17–3.59) n = 2	1.0	NA n = 0	–
Haematological (n = 260)	0.69 (0.53–0.89) n = 113	0.05	1.55 (1.15–2.09) n = 69	0.04	2.82 (1.92–4.16) n = 45	<0.01	1.39 (0.92–2.09) n = 34	1.0	0.98 (0.66–1.44) n = 35	1.0	0.45 (0.15–1.35) n = 4	1.0	7.59 (2.02–28.48) n = 4	0.03
Gastrointestinal (n = 39)	0.49 (0.25–0.96) n = 13	0.36	3.10 (1.59–6.05) n = 16	<0.01	0.37 (0.08–1.77) n = 2	1.0	1.64 (0.67–4.05) n = 6	1.0	0.26 (0.06–1.12) n = 2	0.63	2.58 (0.58–11.50) n = 2	1.0	NA n = 0	–
MSK (n = 274)	0.92 (0.71–1.20) n = 129	1.0	0.91 (0.66–1.26) n = 52	1.0	0.96 (0.59–1.57) n = 28	1.0	0.99 (0.64–1.54) n = 28	1.0	2.55 (1.87–3.48) n = 68	<0.01	0.63 (0.24–1.64) n = 6	1.0	NA n = 0	–
Ophthalmic (n = 17)	0.33 (0.11–1.03) n = 4	0.54	NA n = 0	–	3.00 (0.8–10.64) n = 4	0.81	NA n = 0	–	2.47 (0.84–7.27) n = 5	0.90	NA n = 0	–	NA n = 0	–
Mucocutaneous (n = 464)	0.75 (0.61–0.92) n = 208	<0.01	0.88 (0.69–1.14) n = 89	1.0	1.95 (1.39–2.74) n = 58	<0.01	2.27 (1.70–3.03) n = 76	0.17	1.24 (0.93–1.66) n = 72	1.0	3.14 (1.82–5.44) n = 24	<0.01	0.71 (0.09–5.74) n = 1	1.0
Constitutional (n = 118)	0.91 (0.61–1.37) n = 54	1.0	0.58 (0.32–1.03) n = 15	0.54	0.66 (0.34–1.30) n = 18	1.0	0.42 (0.20–0.87) n = 10	<0.01	1.54 (0.91–2.62) n = 23	0.99	4.85 (2.20–10.70) n = 11	<0.01	NA n = 0	–

These analyses include 349 UK JSLE Cohort patients. Organ domain involvement defined using the pBILAG score, with those scoring a A or B in a given organ domain described as having active disease in that area. The logistic regression was adjusted for those with multiple organ involvements. *p* values <0.05 were considered as statistically significant. CI - 95% confidence interval; OR - odds ratio. P_c - given that 9 domains were tested for association with each treatment, a Bonferroni-correction was applied with each *p*-value corrected for 9 tests. Significant association are shown in bold text. *n* = the absolute number of visits with affected organ domain involvement(s) and/or number of visits treated with a specific immunomodulator. *The models for IVIg and Cyclosporin should be interpreted with caution given the low number of visits where these treatments were used. NA - not available due to insufficient sample size for logistical analysis.

approaches, and targeting disease and unwanted treatment side-effects [54]. Results from the present study will be considered alongside the literature during the development of a clinical decision support tool, to be used within a future T2T study [54,55]. Overall, only a very small proportion of patients do not require immunomodulating therapy (in addition to hydroxychloroquine and/or corticosteroids), with the majority JSLE patients receiving MMF. Indeed, early use of MMF and, in individual cases with severe organ involvement and/or high disease activity, timely adjunctive introduction of biologic DMARDs (rituximab, belimumab) is supported by observations from the here presented study. However, criteria for timely introduction of biologic DMARD use remain to be defined, and may include clinical data including e.g. inability to wean corticosteroids, ongoing disease activity or flares under current DMARD treatment, or failure to meet a pre-specified targets, and serum and/or urine protein signatures [56–59]. Such an approach would align JSLE management more closely with approaches taken in Juvenile Idiopathic Arthritis (JIA), where biologic DMARDs are added when there is inadequate improvement after 3 months of treatment [60], and/or in patients with axial involvement [61].

This study however has important limitations. Data are derived from a national ‘real world’ cohort which collects information alongside routine clinical care, leading in some instances to missing or incomplete data points. It is reliant of data inputted on each BILAG form. Therefore, if a patient changes medication after a clinic visit or during discharge (i. e. between visits), it will be captured on the next BILAG form. Wherever possible, contact was made with the appropriate centres to obtain further information as necessary. Renal biopsy data was not available for all patients, in order to comment on histological class and how this affects the choice of immunomodulator used.

There were patients who were lost to follow-up, with limited data on the reasons for dropping out, which may have caused susceptibility to exclusion bias. To some extent, treatment choices may have been affected by accessibility to treatment (e.g. for IVIg and rituximab), with different rules governing the accessibility of treatments across the UK. Treatments may also have been changed due to treatment failure, side effects or compliance. However, these data are not collected by the Cohort and therefore we cannot comment on whether treatment changes were due to the treatment being in-effective, poorly tolerance, unavailable, or dure to patient/carer preference. Within the multivariate logistic regression (Table 2) an association was seen with both cyclophosphamide/rituximab and mucocutaneous involvement. This should be interpreted with caution and may relate to the high prevalence of this manifestation relative to other organ domains of involvement.

4.1. Conclusions

Treatment of JSLE is complex and varies between individual patients and centres. The majority of patients require at least two immunomodulatory agents over time, with MMF being the most commonly used first- and second-line treatment option. Rituximab was the most commonly chosen third-line treatment. Observations from this study on ‘real world treatment practices’ will be considered alongside the literature during the development of T2T study treatment algorithms as part of the TARGET LUPUS© research programme.

Authors contributions

EMDS, NE, CMH and MWB led on the conception and design of the study. NE and EMDS performed the statistical analysis. All authors participated in the acquisition of and interpretation of the data. MWB is Chief Investigator of the UK JSLE Cohort Study. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. They have also all read and given final approval of the version to be published.

Data availability

Data available on reasonable request.

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Declaration of interest

None of the authors has any potential financial conflict of interest related to this manuscript.

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