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Original article

Short-term efficacy and safety of rituximab therapy in refractory systemic lupus erythematosus: results from the British Isles Lupus Assessment Group Biologics Register

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Abstract

Objectives. To describe the baseline characteristics of SLE patients requiring biologic therapy in the UK and to explore short term efficacy and infection rates associated with rituximab (RTX) use.

Methods. Patients commencing biologic therapy for refractory SLE and who consented to join BILAG-BR were analysed. Baseline characteristics, disease activity (BILAG 2004/SLEDAI-2K) and rates of infection over follow-up were analysed. Response was defined as loss of all A and B BILAG scores to $\leqslant$ 1 B score with no new A/B scores in other organ systems at 6 months.

Results. Two hundred and seventy SLE patients commenced biologic therapy from September 2010 to September 2015, most commonly RTX ($n = 261$). Two hundred and fifty (93%) patients were taking glucocorticoids at baseline at a median [interquartile range (IQR)] oral dose of 10 mg (5–20 mg) daily. Response rates at 6 months were available for 68% of patients. The median (IQR) BILAG score was 15 (10–23) at baseline and 3 (2–12) at 6 months ($P < 0.0001$). The median (IQR) SLEDAI-2K reduced from 8 (5–12) to 4 (0–7) ($P < 0.001$). Response was achieved in 49% of patients. There was also a reduction in glucocorticoid use to a median (IQR) dose of 7.5 mg (5–12 mg) at 6 months ($P < 0.001$). Serious infections occurred in 26 (10%) patients, being more frequent in the first 3 months post-RTX therapy. A higher proportion of early infections were non-respiratory (odds ratio = 1.98, 95% CI: 0.99, 3.9; $P = 0.049$).

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Conclusion. RTX is safe and is associated with improvement in disease activity in refractory SLE patients with concomitant reductions in glucocorticoid use. Early vigilance for infection post-infusion is important to further improve treatment risks and benefits.

Key words: systemic lupus erythematosus, biologic therapy, rituximab, register

Rheumatology key messages

- Rituximab treatment is associated with improvement in disease activity in almost 50% of SLE patients.
- Infections occur most commonly in the first 3 months post-rituximab therapy in SLE patients.
- Access to biologic therapy is important to ensuring improved long term outcomes for SLE patients

Introduction

SLE is a complex autoimmune disease characterized by a diverse range of clinical features. Patients are treated with anti-malarial agents and glucocorticoids in conjunction with immunosuppressive agents including AZA, MTX, MMF and CYC, according to the extent of organ involvement [1]. Despite advances in therapy over the past 20 years, significant numbers of SLE patients remain either refractory to conventional immunosuppressive therapies or require unacceptably high glucocorticoid doses to control disease.

Biologic therapies have revolutionized the treatment of many inflammatory conditions [2, 3]. B cells play a crucial role in SLE pathogenesis and therapies that specifically target B cells have shown the most promise to date. Rituximab (RTX), a chimeric anti-CD20 mAb that transiently depletes B cells, has been used for a number of years with several case series, open-label trials and a more recent meta-analysis reporting efficacy in refractory SLE [4–7]. However two randomized placebo-controlled trials (RCTs) of RTX in active SLE patients, Lupus Nephritis Assessment With Rituximab Study (LUNAR) and Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER), failed to reach their primary endpoints.

More recently the anti-BLyS antibody (belimumab), which also targets B cells, has been licensed by the Food and Drug Administration and European Medicines Agency for the treatment of SLE based on two pivotal trials [8, 9]. Additional biologic agents such as tocilizumab and abatacept have failed to show efficacy for SLE in controlled trials although *post hoc* trial analyses and case reports suggest they may be useful in select patients [10–12]. Thus the role of biologic agents in the management of SLE remains to be defined, with their long term safety and efficacy remaining an ongoing area of debate.

Exploratory RCTs, by their nature, involve select patient populations and focus on short term efficacy. Patients with comorbid illnesses are frequently excluded and therefore RCTs represent only a limited spectrum of patients. In clinical practice, treatment is likely to be prolonged and the patient population more heterogeneous. Therefore, there is uncertainty as to whether the tolerance and safety data obtained in RCTs can be extrapolated to patients in routine practice.

Registry data are complementary to those of RCTs for evaluation of safety and efficacy of biologic agents in real world practice as exemplified by registry data on biologics in RA [13–18]. Registries capture information on patient comorbidities and provide additional information on treatment efficacy as they may analyse different populations and the safety/efficacy of different treatment strategies that have not been evaluated in RCTs. For example, patients with CNS involvement or severe LN have been excluded from previous RCTs of biologics in SLE [8, 19]. Furthermore the use of prior immunosuppressive agents such as CYC may exclude patients from clinical trials [20]. Thus registry data are reflective of the real-life condition of patients requiring biologic therapy.

In response to the need to capture real world data on the safety and efficacy of biologics in SLE, the BILAG established the BILAG Biologics Register (BILAG-BR) in 2010. Modelled on the British Society of Rheumatology's RA Biologics Register, the primary aim of BILAG-BR is to investigate whether biologic treatment in SLE is associated with an increased rate of hospitalization for infection compared with standard therapy. Secondary end-points include treatment efficacy.

In this paper our primary objective was to describe the baseline characteristics of patients commencing their first biologic for refractory SLE in the UK who were enrolled in BILAG-BR in the first 5 years of the register. We also aimed to describe early efficacy of RTX over the first 6 months in the cohort as well as infections in the early phase of follow-up post-RTX.

Methods

Inclusion criteria

Patients with SLE (1997 ACR or 2012 SLICC criteria [21, 22]) who were $\geqslant$5 years old, capable of providing informed consent (parent/guardian for children) and had commenced a new biologic therapy for treatment within the last 12 months were included. Therapeutic decisions are at the discretion of the treating rheumatologist and since September 2013, in England has been informed by the NHS England interim commissioning policy for the use of RTX [23]. The commissioning criteria are as follows: persistent active SLE (defined as at least one BILAG A score and/or two B scores, or a SLEDAI-2K score $>$6) and failure to respond or documented adverse events to two or more standard immunosuppressive therapies

(including one of MMF or CYC, unless contraindicated) in combination with glucocorticoids. Failed response is defined as being unable to achieve sustained disease control and still having evidence of at least one BILAG A or at least two BILAG B scores (or requiring unacceptably high levels of long term oral glucocorticoids to maintain a lower disease activity state).

We also enrolled a comparison cohort of patients with a diagnosis of SLE, $\geqslant$5 years old, who are within a month of starting treatment with a non-biologic immunosuppressive therapy (namely MMF, CYC, AZA or a calcineurin inhibitor).

Patient recruitment and baseline assessment

Patients were recruited by their treating clinician as part of their scheduled care from 34 recruiting centres in the UK. Patients consented to be flagged with the Health and Social Care Information Centre for malignancies and deaths. Disease activity (BILAG 2004 index [24] and SLEDAI 2K [25]) and the SLICC Damage Index (SDI) [26] were recorded pre-treatment and a baseline standardized questionnaire was used to record demographic data including age, gender and treatment group. Additional information was recorded including ACR/SLICC 2012 criteria [21], organ involvement, disease duration, SLE family history, presence of comorbidities, risk factors for infections including vaccination history and current serology. Registration treatment (biologic/conventional immunosuppressant), the planned treatment schedule and previous immunosuppressive/glucocorticoid treatment (with reasons for discontinuation) were detailed as were other current medications for lupus.

Patients were asked to provide blood and urine samples for future analysis at baseline pre-treatment as well as at 3, 6 and 12 months post-biologic. The clinical data were supplemented by a participant questionnaire regarding quality of life and lifestyle factors.

Patient follow-up assessments

Patients were followed up at 3, 6 and 12 months for the first year post-treatment and then annually for a minimum of 2 years, with all recording occurring at the time of scheduled clinic appointments. Patients requiring retreatment or a switch in therapy (including from standard of care to biologic) were followed for a minimum of 3 years from the last change in treatment. Disease activity scores were recorded at each review and the SDI was recorded annually. Changes in biologic and standard lupus treatment, glucocorticoid dose and concomitant medications between visits were documented. New medical diagnoses and adverse events were recorded, regardless of whether causation was ascribed to treatment. We specifically enquired as to the following adverse events of special interest: infections, malignancy, hospitalization (for any reason), pregnancy, operations (for any reason) and antibiotic courses (out-patient or in-patient).

Efficacy analysis

For the purpose of this analysis we adopted a response definition informed by the NHS England interim policy for RTX use [23] at 3 and 6 months using the BILAG-2004 Index as follows: improvement was defined as loss of all A scores and loss of B scores to $\leqslant$ 1 B score with no new A/B scores in other organ systems. Persistent disease activity was defined as an ongoing A score and/or $\geqslant$2 B scores with no new A/B scores in other organ systems. Deterioration was defined as development of a new A score in an organ system with baseline B or a new A or B score in an organ system previously rated C/D/E.

The numeric BILAG-2004 global score was calculated at each time point using the values: A = 12, B = 8, C = 1 and D/E = 0 [27].

Infection analysis

Infection-related events were coded using MedDRA software (www.meddra.org). Serious infections (SIs) were defined as any infection resulting in treatment with i.v. antibiotics, hospitalization, disability or death. Infections occurring within 9 months of RTX use were deemed to be therapy-related, as used in the BSR RA biologics registry [28].

Data analysis

Data were entered into a secure database at the University of Manchester. Baseline demographic data are presented using descriptive statistics performed using Stata v13 (StataCorp, College Station, TX, USA). The total number of responses available for each analysis performed are shown throughout the text. Differences between groups was analysed using the non-parametric Mann–Whitney test and results are presented as median [interquartile range (IQR)]. Statistical significance was defined as a $P < 0.05$ (two sided).

Ethics approval

Ethics approval was granted by the NRES Committee North West–Greater Manchester West (REC: 09/H1014/64) and the local Research and Development departments at participant sites. All patients provided written informed consent at the time of study registration.

Results

Baseline demographic data of patients commencing biologic therapy

Between September 2010 and September 2015, 270 patients started biologic therapy for SLE. RTX was the commonest biologic agent prescribed (n = 261) followed by belimumab (n = 7), abatacept (n = 1) and tocilizumab (n = 1). Of these, 248 (92%) were female and the mean (S.D.) disease duration was 8.4 (8.7) years (Table 1). One hundred and twenty-four (60%) were Caucasian. The most common ACR classification criteria recorded as ever present up to and including the registration visit were arthritis (233/266, 87%), ANA postive (231/266, 87%) and immunological involvement (176/266, 66%) (Table 1). More patients were not working due to permanent disability or were on sick leave due to their SLE than were in permanent full time employment (29% *vs* 23%).

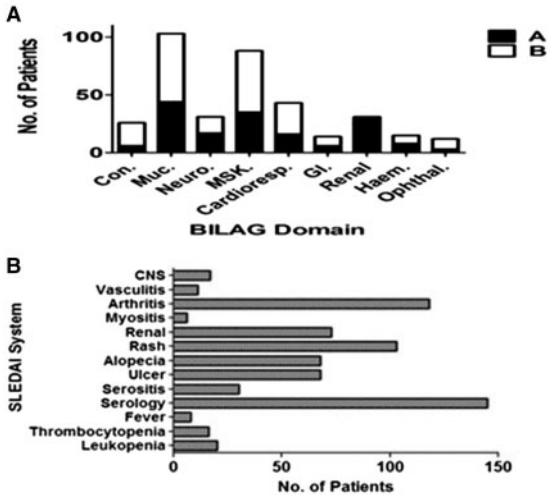
Table 1 Baseline demographic and clinical characteristics of SLE patients commencing biologic therapy in BILAG-BR

Demographic characteristic (no. of respondents)	*n* (%)
Gender (*n* = 270)	
Female	248 (92)
Male	22 (8)
Age, mean (S.D.), years	40.1 (14.6)
Duration from first criteria to diagnosis, median (IQR), years	0 (0–2)
Disease duration, median (IQR), years	6 (2–13)
Ethnicity (*n* = 208)	
Caucasian	124 (60)
Asian	35 (17)
Caribbean	15 (7)
African	13 (6)
Mixed	12 (6)
Other	9 (4)
Family history of SLE (*n* = 256)	
Yes	24 (9)
No	186 (73)
Do not know	46 (18)
Smoker (*n* = 210)	
Current	32 (15)
Ever	82 (39)
Never	128 (61)
Education completed (*n* = 192)	
Age ⩽18 years	117 (61)
Employment (*n* = 211)	
Disability/sick leave	62 (29)
Full-time employment	48 (23)
Part-time employment	42 (20)
Unemployed	9 (4)
Other (student/retired)	50 (24)
ACR criteria (*n* = 266)	
Malar rash	148 (56)
Photosensitivity	146 (55)
Discoid rash	41 (15)
Mucosal ulcers	159 (59)
Arthritis	233 (87)
Serositis	90 (34)
CNS	29 (11)
Renal	111 (42)
Haematological	140 (53)
Immunological	176 (66)
ANA	231 (87)

Baseline disease activity

Two hundred and fifty (93%) completed BILAG-2004 and 247 (91%) SLEDAI-2K forms were analysed. With regard to BILAG-2004, 164 A scores in 119 patients and 199 B scores in 140 patients were recorded. Mucocutaneous disease followed by musculoskeletal and renal involvement were the systems most frequently recorded as having a BILAG-2004 A score (Fig. 1A). Similarly mucocutaneous and musculoskeletal systems were the most frequently scored 'B' items. Of note the renal and neuropsychiatric systems were the only systems in which a higher proportion of A scores were observed in comparison with B scores (renal A : B = 29 : 2; neuropsychiatric A : B = 17 : 14).

Fig. 1 Baseline disease activity scores for SLE patients upon entry into register



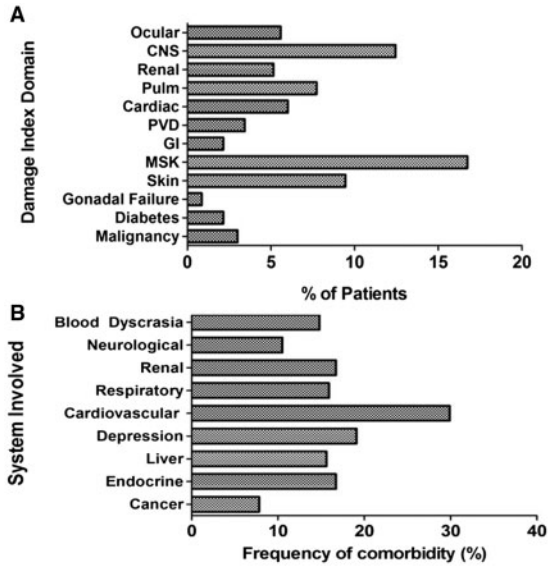
(**A**) Number of individual patients scoring either an A or B on BILAG-2004 scoring system across the systems assessed. (**B**) Number of individual patients scoring one or more points across the systems assessed by SLEDAI-2K. CNS includes seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache and stroke. Renal includes proteinuria, haematuria, urinary casts and pyuria. Serositis includes both pleurisy and pericarditis. Serology included low complement and/or elevated dsDNA either alone or in combination. Cardioresp.: Cardiorespiratory; Con.: Constitutional; GI: gastrointestinal; Haem.: haematological; Muc.: mucocutaneous; MSK: musculoskeletal; Neuro.:Neurological; Ophthal.: Ophthalmic.

The median (IQR) SLEDAI-2K score was 8 (5–12). The systems distribution on the SLEDAI-2K is demonstrated in Fig. 1B (complete data are available in supplementary Table S1, available at Rheumatology Online). Serological activity was the feature scored most often in patients with 59% (146/247) having either a low complement and/or elevated dsDNA titre. Thirty per cent (73/247) had active renal disease on the SLEDAI-2K at time of enrolment to the register, the vast majority of which was attributable to proteinuria (70/73). CNS activity was recorded in 18 patients.

Damage and co-morbidities

Baseline SDI scores were available in 233 (86%) patients, the median (IQR) SDI score was 0 (0–1) and 41% (*n* = 96/233) had one or more damage items. Damage was most frequently observed in the musculoskeletal domain [*n* = 39 (17%); Fig. 2A] with deforming arthropathy [*n* = 17 (7%)] and osteoporotic fracture [*n* = 12 (5%)] the most frequently recorded items. Neuropsychiatric damage was recorded in 29/233 (12%) patients.

Fig. 2 Rates of damage and comorbidity in SLE patients requiring rituximab therapy



(**A**) Frequency of SLE patients scoring one or more points across the individual domains assessed by SLICC-SDI. (**B**) Frequency of comorbid conditions in SLE patients at time of rituximab therapy. GI: gastrointestinal; MSK: musculoskeletal; Pulm: pulmonary; PVD: peripheal vascular disease.

Two hundred (74%) patients had one or more other comorbidities and the median (IQR) number of comorbidities was 1 (0–2). Cardiovascular comorbidities ($n = 77$, 29%) were most common followed by depression ($n = 49$, 18%) and chronic kidney disease ($n = 33$, 12%) (Fig. 2B). Hypertension ($n = 62$, 23%) was the most frequent cardiovascular co-morbidity. Baseline malignancy history was confirmed with the UK Health and Social Care Information Centre database; 19 cancers were recorded in 18 (6.7%) patients. The commonest were cervical (including CIN-III) ($n = 7$), lymphoma ($n = 3$) and non-melanoma skin cancer ($n = 3$).

Baseline medication use

In total 243 (91%) patients were on antimalarial treatment. HCQ was the most commonly prescribed antimalarial (AM) amongst those patients on any AM (242/243, 99%). Ten per cent of patients (28/268) had dual AM therapy.

Two hundred and fifty (93%) patients were receiving glucocorticoid therapy (Table 2). The median (IQR) daily oral prednisolone dose at baseline was 10 mg (7.5–20 mg). Excluding i.v. methylprednisolone used as part of the RTX pre-medication regime, additional parenteral glucocorticoids had been received by 127 (48%) patients. Of the standard immunosuppressives used at baseline, MMF was most frequently used ($n = 183$, 68%) (Table 2).

Table 2 Prior/current medication use in refractory SLE patients requiring biologic therapy

Medication type	*n* (%)
Glucocorticoids ($n = 268$)	
p.o.	233 (87)
i.v.	117 (44)
i.m.	10 (4)
Antimalarial ($n = 268$)	
Any AM	243 (91)
HCQ	242 (90)
Dual AM therapy	28 (10)
Immunosuppressive agent ($n = 268$)	
MMF	183 (68)
AZA	175 (65)
MTX	99 (37)
CYC	
i.v.	65 (24)
p.o.	7 (3)
Ciclosporin	24 (9)

AM: antimalarial.

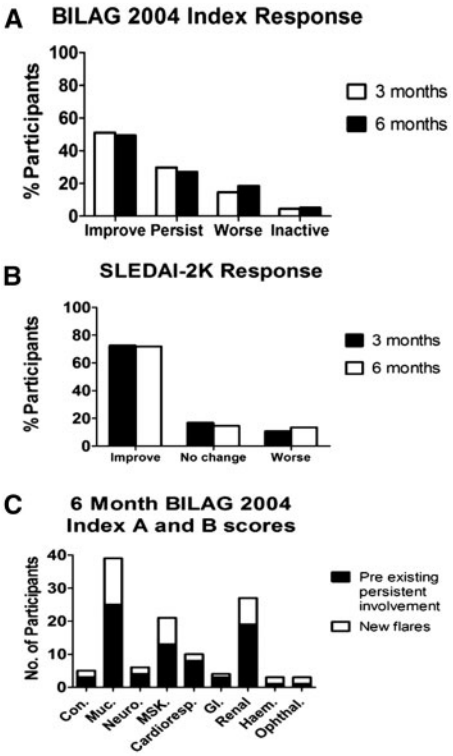
Efficacy of RTX

One hundred and seventy-eight RTX-treated patients had complete baseline and 6-month assessments. Our primary definition of response (loss of all A and B BILAG scores to $\leqslant 1$ B score with no new A/B scores in other organ domains at 6 months) was achieved in 91 (51%) and 88 (49%) patients at 3 and 6 months, respectively (Fig. 3A). A further nine (5%) patients, eligible for RTX due to requiring an unacceptably high dose of steroid to maintain inactive disease, experienced no worsening in disease control over the 6-month period post-RTX treatment facilitating steroid reduction in these patients [baseline prednisolone dose median (IQR) 10 mg (9.25–17.5 mg), 6-month dose 7.5 mg (5–10 mg)]. The median (IQR) BILAG-2004 global score fell from 15 (10–23) at baseline to 4 (2–13) at 3 months and 3 (2–12) at 6 months ($P < 0.0001$). In total, 120 BILAG A scores were recorded in 92 patients at baseline which fell to 30 and 34 A scores in 28 and 29 patients, respectively, at 3 and 6 months ($P < 0.001$). Similarly there was a significant reduction in B scores over the 6-month follow-up [total (no. of patients)]: baseline: 150 ($n = 109$); 3 months: 92 ($n = 70$); 6 months: 70 ($n = 56$) ($P < 0.001$).

One hundred and twenty-nine (72.5%) and 128 (71.9%) patients had a reduction in SLEDAI-2K of > 1 point at the 3 and 6 months, respectively (Fig. 3B). The median (IQR) SLEDAI-2K reduced from 8 (5–12) at baseline to 4 (2–8) and 4 (0–7) at 3 and 6 months, respectively ($P < 0.001$).

Complete glucocorticoid dose data at each follow-up time point were available for 149 patients. The median (IQR) glucocorticoid dose across the cohort reduced from 11.25 mg (8.375–20 mg) prednisolone or equivalent to 10 mg (6.8–15 mg) and 7.5 mg (5–12 mg) at 3 and 6 months post-RTX, respectively ($P < 0.001$ for both *vs* baseline and 3 *vs* 6 months visit). One hundred and ten

Fig. 3 Rates of response to rituximab therapy in refractory SLE



The percentage of patients (n = 178) with improvement, persistent disease activity and deterioration in disease activity following rituximab therapy at 3 and 6 months as assessed by (**A**) BILAG 2004 Index *vs* baseline assessment and (**B**) SLEDAI-2K. (**C**) The number of patients with persistent disease or new organ involvement at 6-month assessment as per BILAG organ domain. GI: gastrointestinal; MSK: musculoskeletal.

(77%) patients were taking >7.5 mg of prednisolone at baseline of whom 47 (43%) reduced to ⩽ 7.5 mg at 6 months.

A major clinical response, defined as BILAG-2004 C/D/Es only with SLEDAI-2K ⩽4 and daily oral glucocorticoid dose ⩽7.5 mg, at 6 months was achieved in 33 (18.4%) of patients. We also observed an increase in disease activity post-RTX in 26 (15%) and 33 (19%) patients at 3 and 6 months, respectively. The mucocutaneous and renal systems were the most likely to have persistent disease activity or manifest new organ involvement (Fig. 3C).

Infections following RTX exposure

One hundred and eighty-five infectious episodes were reported in 82 (30%) patients during the 9-month period of interest. Fifty-four (20%) patients suffered multiple infections. Twenty-nine (11%) SIs occurred in 26 patients. The frequency of all infections and SIs is shown in Fig. 4A and B. Respiratory (n = 88) and urinary tract infections (n = 36) were the commonest infections observed. Within the first 3 months, 111 (60%) infections occurred while 60 (32%) infections occurred between 3 and 6 months and 14 (8%) between 6 and 9 months. A similar trend was noted for SIs with 17 (59%) occurring within 3 months, 9 (31%) at 3–6 months and 3 (10%) at 6–9 months (Fig. 4C). The excess infections observed in the first 3 months post-RTX were related to a relative increase in non-respiratory infections (respiratory *vs* non-respiratory infection: odds ratio = 1.98, 95% CI: 0.99, 3.9; P = 0.049).

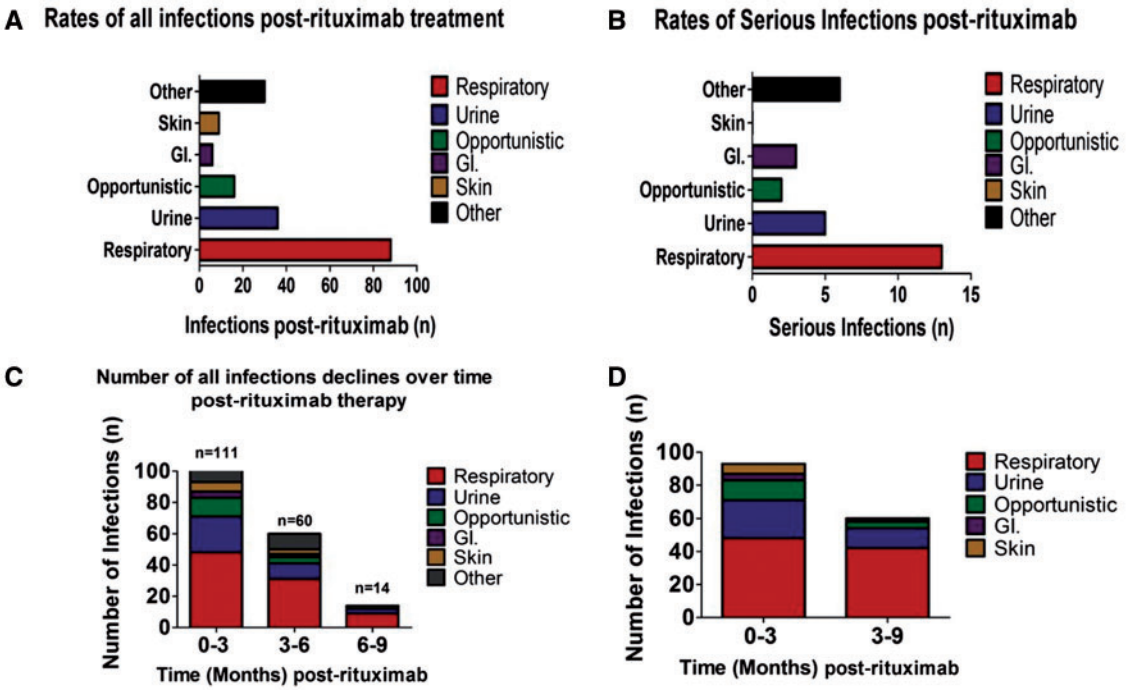
Discussion

SLE remains refractory to conventional therapy for many patients for whom biologic therapies offer the potential of disease control and improved long term outcomes. Long term real world data on patterns of use, response rates and adverse events for such therapies is, however, lacking. The BILAG-BR seeks to address these issues by studying patients in a UK setting where the NHS and expert groups have provided guidance for starting biologic treatment.

Our data show that patients of non-Caucasian origin are over-represented within the registry. Previous studies from UK lupus centres show that ~70% of the cohorts are White Caucasian patients compared with 60% in the BILAG-BR [29]. Given the equity of access to healthcare in the UK we are likely to have included patients from less advantaged populations who may have been excluded from RCTs and cohort studies in different healthcare environments. It is also recognized that there is a higher incidence and prevalence of SLE in Asian and Afro-Caribbean populations in the UK [30]. These ethnicities experience more severe manifestations of disease such as lupus nephritis and an overall poorer prognosis [31–33]. Thus in this setting of equal access to healthcare, our register suggests that non-Caucasian patients are more likely to have refractory disease that will require biologic therapy.

The pattern of refractory disease is also of note. The only organ systems with a higher proportion of BILAG A scores than B scores were the neurological and renal domains. Such severe organ involvement is routinely excluded from non-lupus nephritis SLE trials [8, 9]. In addition we observed a large proportion of patients with moderate disease (represented by multiple BILAG B scores) across two or more organ domains. Including such cases of refractory disease across the whole disease spectrum provides evidence that is not readily available from conventional clinical trials. A significant number of BILAG-BR patients commencing biologics already had co-morbidities including renal impairment or history of malignancy that again are usually exclusions in formal RCTs. The high rates of baseline damage and glucocorticoid use confirm these agents are being used in a population with a high burden of disease sequelae where greater potential benefits may be expected in long term follow-up. Baseline damage and glucocorticoids have both been associated with accumulation of further damage and mortality [29]. Taken together, such a real world sample of SLE patients improves the generalizability of our findings to inform the

FIG. 4 Rituximab treatment is associated with an increased risk of infection



Rates of (**A**) all and (**B**) serious infections post-rituximab treatment in SLE patients. (**C**) The rate of all infections declined over time with (**D**) the excess infection burden in the first 3 months being attributed to non-respiratory infections. GI: gastrointestinal.

management of severe refractory disease in routine practice.

Previous case series as well as a detailed systematic review have suggested efficacy of RTX in SLE [34], a result not replicated in large RCTs [5, 19]. While the modest inclusion criteria in some case series may lead to an overestimation of the efficacy of RTX, design limitations with a number of the clinical trials may in turn have led to an underestimation of the effectiveness of the drug in refractory patients. Here we report that in a large cohort of patients with refractory SLE, ~50% of patients will experience early objective improvement in their disease in the first 6 months following RTX. Although endpoints varied, this rate is similar to the efficacy results observed in trials of alternative biologic agents in SLE and substantially greater than the ~30% response in a RCT of RTX [19, 20, 9, 35]. This emphasizes that use of RTX is an important treatment option for a large proportion of SLE patients with refractory disease. Access to such biologic therapy is vital to ensure optimal long term outcomes for patients, by enabling better disease control while facilitating steroid reduction. While improvement in disease activity indices remained stable between the 3- and 6-month assessments a further significant reduction in glucocorticoid dose was observed between these two time points. Given the role that glucocorticoids play in potentiating damage in SLE, this observation supports previous case series highlighting the potential benefits of glucocorticoid-sparing regimes based on RTX in SLE [36–38]. Furthermore these data will assist in informing expectations with regard to expected efficacy of RTX (and other biologics) in SLE and help to provide reliable outcome estimates to power future SLE trials.

Future work identifying predictors of response to RTX is ongoing. In this regard it is notable that almost one in five patients achieved a major clinical response at 6 months. In contrast, 19% of our cohort were noted to have a significant deterioration in disease by this same time point. While the extent and degree of peripheral B cell depletion may be an important factor in predicting the response to RTX, B cell depletion is associated with a corresponding increase in BLyS levels that may play a role in propagating disease [39]. Continued recruitment of patients as they commence treatment will allow for a better understanding of how we can predict treatment outcomes towards developing stratified medicine approaches for the use of RTX (and other biologics) in SLE.

Regarding adverse events, no unexpected infection-related events were observed. Seventy per cent of those studied did not develop any infectious complications following RTX therapy with SIs observed in ~10% of patients. These proportions are equivalent to those seen in the studies of RTX in RA [40] as well as the EXPLORER study (9.5%) [8], despite patients having greater rates of co-morbidity and more severe organ involvement, in particular renal and CNS disease. The majority of infections

(including severe infections) occurred in the first 3 months post-RTX therapy, when patients were on the highest doses of glucocorticoids, with a higher proportion of these infections being non-respiratory in nature. Therefore, pre-treatment strategies to reduce infection such as vaccination, as well as extra vigilance for infection in the 3-month window post starting RTX is required by physicians and patients [41–44]. The infection risk at this time post-RTX may be explained by a number of factors including the period of maximum B cell depletion, disease activity itself, the effect of concomitant glucocorticoid and cytotoxic use as well as potential RTX-associated hypogammaglobulinaemia [45]. The timing of maximum impact of these various factors will vary and warrants further study. Ongoing recruitment of a control cohort of SLE patients starting conventional therapy will allow for future analysis of patterns of infection in SLE and assist us in identifying specific safety signals related to RTX.

Our study has a number of limitations inherent in any registry. Firstly, complete data were not available for every patient and the unblinded nature of any registry has the potential to confound interpretation of results as does the potential for inter-physician variability in assessing disease activity and reporting adverse events. Nonetheless, given the large number of recruiting centres across the UK, we feel that our results are both robust and generalizable in the real-world setting. We have only reported short term outcomes in this current study. However longer term safety and efficacy data are being collected as well as re-treatment use. The early changes in glucocorticoid doses will also be followed longer term to assess if they are sustained.

In summary, SLE is refractory to conventional therapy in a significant number of patients for whom biologic therapies offer the potential of disease control and improved outcomes. The BILAG-BR provides real-world data on such patients recruited from multiple centres across the UK. RTX use appears safe and efficacious in a subset of SLE patients with 50% already having a good clinical response at 6 months. Our results are comparable to the response rates observed in other biologic trials in SLE. As additional biologic agents become available for the treatment of SLE, inclusion of these agents in the register will allow for real-world comparison of their safety and efficacy and may assist physicians in identifying patients in their clinics who will benefit from the addition of a particular biologic therapy in an effort to improve their long term outcome.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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