

# Off-label use of rituximab in systemic lupus erythematosus: a systematic review

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**Abstract** Considerable interest in the efficacy of rituximab (a monoclonal CD20 antibody) in patients with systemic lupus erythematosus (SLE) has been generated due to its unique mode of action, culminating in a series of randomized and open trials, and case reports. However, this use is off-license and two significant RCTs have reported negative findings, reopening the debate on clinical benefit. This review of the available data suggests that rituximab induces B-cell depletion in 95% of patients, and a significant reduction in disease activity is achieved with a relatively good safety profile in patients with SLE.

**Keywords** B-cell depletion · Rituximab · Systemic lupus erythematosus

## Introduction

Systemic lupus erythematosus (SLE) is a multisystem inflammatory disorder with a myriad of underlying immune system aberrations and patho-physiological changes, leading

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Dr. Perry received funding to travel to the ARC meeting from Roche, and an honorarium for speaking (proceeds to the charity Lupus UK).

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to heterogeneous symptoms. Immunologically, B lymphocytes generate auto-reactive antibodies to nuclear antigens, and modulate the T-cell repertoire through cytokine production and antigen presentation [1]. Pathologically, inflammation and immune complex deposition results in end-organ damage. Thus, targeting aberrant B cells is a promising approach in a disease where new treatments are long-awaited (none have been validated in the last 30–40 years); current therapeutic options can carry serious adverse effects (e.g. ovarian failure and opportunistic infections with cyclophosphamide), and significant numbers of patients fail to respond [2].

Worldwide prevalence of SLE is estimated at 5 to 50 per 100,000 (varying with methodology and ethnic group) [3]; incidence is highest in young women and 90% of those diagnosed are female. Despite treatment the course of the disease is remitting-relapsing, highly variable between individuals, and 20-year survival rate remains less than 80%, largely due to cardiovascular disease [4]. Inducing and maintaining remission is often an unattainable goal, and we compromise with alleviating symptoms and limiting end-organ damage.

B cells express CD20, a surface molecule involved in regulating cell cycle initiation and differentiation; it is neither shed from the cell surface nor internalized, making it a reliable target. Rituximab is a chimera of murine variable regions against CD20 and human IgG constant region. Initially introduced in the 1990s as a treatment of non-Hodgkin's lymphoma, it has more recently been licensed in the treatment of rheumatoid arthritis (RA).

Both lymphoma and SLE have aberrant B lymphocyte activity, which rituximab targets via the CD20 ligand. B cells express CD20 throughout their maturation, so depletion can be highly specific and sensitive—a more targeted

treatment option than traditional cyclophosphamide or steroid. However, autoantibody-producing plasma cells are CD20 negative, and therefore potentially resistant to rituximab. In addition, long-lived plasma cells can endure antiproliferative immunosuppressants and continue to produce autoantibodies [5].

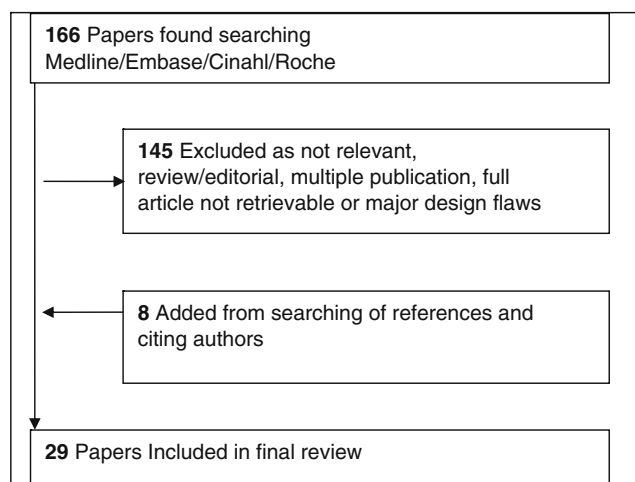
## Methodology

The search strategy included the terms “Systemic Lupus Erythematosus” and “Rituximab”, searching Medline, Embase, Cinahl, the Cochrane library and retrospective searching of citations. The manufacturer (Roche Products Ltd) was contacted regarding any trials currently awaiting publication. Where multiple publications under the same group of authors were found, the group was contacted to establish whether data for separate studies was derived from a common patient cohort; if this was the case only the most comprehensive and highest quality paper was included. The selection process is summarized in Fig. 1. Assessment of quality of the evidence was based on the Scottish Intercollegiate Guidelines Network (SIGN) Levels of Evidence and Grades of Recommendation [6]. Data was compiled onto a Windows XP Excel spreadsheet and analyzed with Minitab 15.

## Results

In vitro studies have confirmed that rituximab’s anti-CD20 action has diverse immunological effects:

- B-cell depletion (BCD) is achieved by preventing proliferation, inducing apoptosis, and stimulating complement- and antibody-mediated lysis [7, 8].



**Fig. 1** Process of selection of clinical trials in patients with SLE

- BCD is variable, influences including low-affinity FcγRIIIa alleles (involved in antibody-dependent cell-mediated cytotoxicity), B lymphocyte stimulator (BlyS) and bone marrow interferon response [8–10].

Murine models support the hypothesized benefit of transiently reducing B cell numbers, B cell-deficient mice being protected against lupus nephritis compared with littermates with normal lymphocyte repertoire [11]. Furthermore, B cells redundant at producing immunoglobulins nevertheless induce nephritis, supporting the earlier observation that production of auto-antibodies is not the only pathogenic mechanism which produces the SLE phenotype [12]. The in vivo clinical studies are outlined in Table 1.

## BCD

Of the studies included (see Table 1), 95% of patients achieved good B-cell depletion (257/271); those who failed to achieve depletion were largely from the same dose-escalation trial (R. Looney, 2004 [13]), although not in the low-dose group; this suggests that the real figure may be close to 100%. Peripheral blood B lymphocytes are depleted rapidly (within minutes), and the majority of splenic and lymph node cells by 24 h [14]. Maximal B-cell depletion occurs at around 3 months with mean duration of 6 months, although this remains highly variable, with a range of 2–17+ months, and generally shorter duration than observed in lymphoma patients.

SLE patients’ peripheral blood lymphocyte pool comprises of a higher proportion of naïve and pre-plasma cells than normal controls; B-cell depletion and reconstitution normalizes this aberrant lymphocyte state [15, 16]. However, patients are heterogeneous in their reconstitution of the B-cell population; with a subset demonstrating naïve B-cell predominance and delayed return of CD27+ memory B cells, correlating with prolonged clinical remission.

## Dosing

Rituximab dose was variable between studies, following either lymphoma schedule (375 mg/m<sup>2</sup> per week x 4 weeks) or rheumatoid arthritis guidelines (1 g 2 weeks apart). Percent change in SLEDAI and BILAG was significantly different between dosing schedules (P 0.02, one-way ANOVA) in favour of lymphoma doses; though validity is questionable given the diversity of trial methodology and consequent confounding variables.

Specific dose escalation trials found equivocal (though individually variable) B-cell depletion and rates of remission across the dosing schedules [13, 17–19]. There

**Table 1** Studies of Rituximab in SLE by author; same colour text denotes same patient cohort

Author	Study population	Dose	Other immunosuppression	Subjects	Median F/U months	SLEDAI change	% change	BILAG % change	Auto-antibodies	Proportion achieving BCD	Median BCD (months)
Albert [35]	Mild-moderate	375 mg/m <sup>2</sup> /week×4 weeks	100 mg MP with infusion only	18	12	4	50			17/18	7
Anolik [17]	Active SLE; 15 pts included in Looney 2004 data, but different outcome measures	Low dose (100 mg/m <sup>2</sup> ), high med (375 mg/m <sup>2</sup> ), high (375 mg/m <sup>2</sup> ) for 4 weeks	Current medications continued	15	41				Correlate with repopulation	11/15	10.5
Looney [13]	Active SLE	As above	Excluded CYC patients	17	12				No change ds-DNA		
Bolétis [54]	Lupus nephritis	375 mg/m <sup>2</sup> /week×4 weeks	MMF and prednisolone	10	38				dsDNS decreased		
Catapano [55]	Refractory SLE	375 mg/m <sup>2</sup> /week×4 weeks or 1 g days 1 and 15		31	30	Remission in 27/31					
Galarza [39]	SLEDAI >8, nephritis/cytopenia/NPSLE	375 mg/m <sup>2</sup> /week×4 weeks	MP with infusion; CYC stopped in all; MMF continued in 6 patients	43	12	8	64				
Gottenberg [53]	SLE and other autoimmune diseases	375 mg/m <sup>2</sup> /week×4 weeks	2 patients AZA, 1 HCQ, 2 MP, 1 CIC, 1 CYC	11	8.3	5.9	53		Variable	6/6	4–8
Gillis [18]	Refractory SLE	Varied	Steroids and existing Rx	6	12	7.7	57		No change		
Gunnarsson [37]	Lupus nephritis; 7 pts included in Jonsdottir paper, but some different outcome measures	375 mg/m <sup>2</sup> /week×4 weeks		7	12		80		dsDNA decreased (174 to 56)		
Jonsdottir [20]	Refractory SLE	375 mg/m <sup>2</sup> /week×4 weeks	CYC with 1st and last RTX; prednisolone (tapered)	16	27	7.4	61	11	dsDNA decreased	16/16	7 (2–12)
Hernandez [56]	Refractory SLE	375 mg/m <sup>2</sup> /week×4 weeks	CYC, steroids + others "as necessary"	7	12.8					18/19	5.5
Karpouzias [57]	Refractory SLE; 10 nephritis	375 mg/m <sup>2</sup> /week×4 weeks		30	9	7.1	82		223 to 34 at 6/12	30/30	
Li [46]	Lupus nephritis	375 mg/m <sup>2</sup> /week×2 weeks	9 RTX alone, 10 RTX +CYC	19	4					26/26	Repopulation: 17% by 3/12, 80% by 12/12
Lindholm [25]	Refractory nephritis (17) or cytopenia (14)	375 mg/m <sup>2</sup> /week×4 weeks	RTX added to regimen (CYC/MMF), maintained until remission	29	22				ds-DNA: 34.5 to 27.3 after 6/12, to 16.3 after 12/12	11/17	Variable (65% of baseline levels at 1 year)
Lu [24]	Refractory SLE	1 g IVI 2 weeks apart	CYC 750 mg, MP 250 mg	45	39.6			7	ds-DNA 106 to 42	45/46	6 (15pts >1 year)

Table 1 (continued)

Author	Study population	Dose	Other immunosuppression	Subjects F/U months	Median SLEDAI change	% change	BILAG % change	Auto-antibodies	Proportion achieving BCD	Median BCD (months)
LUNAR [29]	Placebo-controlled RCT, double blind, class III/IV lupus nephritis	375 mg/m <sup>2</sup> days 1 and 15	MMF and corticosteroids; retreated at 6/12 with same	144	Failed to meet outcomes					
Melander [58]	Lupus nephritis	375 mg/m <sup>2</sup> /week×4 weeks	3 also got CYC	20	Remission in 12/20					
Merrill [30]	Placebo-controlled (88 vs 169) RCT, moderate-severe active extrarenal SLE	1 g days 1, 15, 168 and 182	RTX added to existing regimen; steroids tapered down	257	Failed to meet outcomes					
Pepper [59]	Lupus nephritis	1 g days 1 and 15	MP during infusion; maintenance MMF (500 mg-1 g)	20	14/18 achieved remission					
Reynolds [21]	Refractory SLE, only 9/11 met ACR criteria	8 pts:750 mg or 1 g days 1 and 15; 2 pts: 375 mg/ m <sup>2</sup> ×2	7 had CYC 500-750 mg; 6 had MP	11			7.3	ds-DNA: no change	10/11	6, recovery predicts flare
Sangle [36]	Refractory; 12 with lupus nephritis	1 g days 1 and 15	500 mg CYC and 500 mg MP with RTX infusions	16	4-6		5			
Shahmir [40]	7 refractory, 1 emergency (4 nephritis, 3 AIHA, 2 thrombocytopenia, 1 hepatitis)	Mean total 2,812.5 ml	RTX and MP added to existing regimen	8	2-8					
Sfikakis [42]	Lupus nephritis	375 mg/m <sup>2</sup> /week×4 weeks	Prednisolone	10	12				10/10	1-7 months
Smith [31]	Active or refractory SLE	375 mg/m <sup>2</sup> /week×4 weeks	500 mg CYC with 1st RTX, added to existing regimen	11	24		11	ds-DNA 91 to 86 to 51.5 at 6 and 12 months (8/11pts)	11/11	9
Tamimoto [19]	3 NPSLE, 4 nephritis, 3 cytopenia; refractory to at least one treatment	4×weekly 100/250/375 mg/m <sup>2</sup>	All on prednisolone; 2 CIC; 1 CYC	8	10.3			dsDNA: 3/4 became -ve	8/9	>6
Tanaka [34]	Active (1+ A or 2+ B), renal and NPSLE	1 g×2.2 weeks apart (10pts) or 500 mg/week×4	Prednisolone only; others not allowed	14	7		5.4		15/15	>6
Tokunaga [49]	Refractory renal and NPSLE. Analysed 4 wks, F/U >1 year	375 mg/m <sup>2</sup> /week×2 weeks	Prednisolone	5	12+		58	dsDNA reduced 4/5		
Tokunaga [38]	Active NPSLE	Variable	Low-dose steroid only	10	7-45		69			Good BCD
Vignaperez [15]	Active renal (WHO III/IV)	0.5-1 g day 1 and 15	RTX added to regimen	22	3.85		36	Variable	0	0

is however consensus between studies that recovery of B-cell population precedes disease relapse [20, 21]. Collectively, the above features suggest that dose-response relations should be more clearly defined, after which individualized dosing may be appropriate, for example treating more intensively those with high B lymphocyte titers.

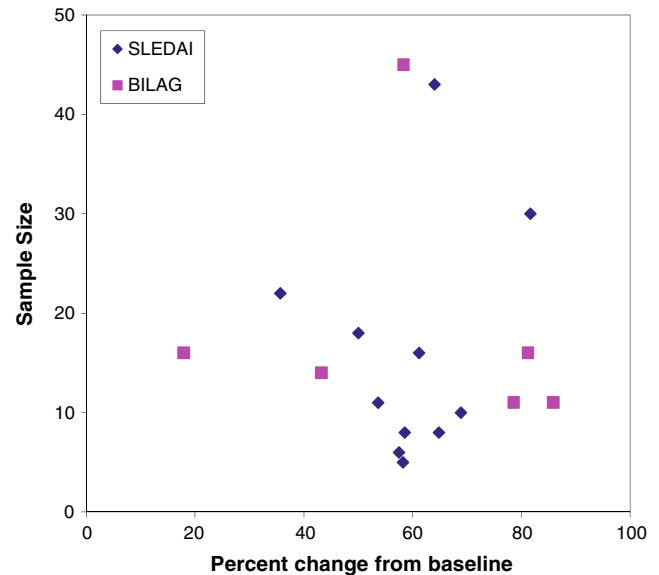
#### Antibody reduction

Rituximab induces B-cell depletion, increased T regulatory cell activity and decreased T-cell activation [7, 15], theoretically it should therefore be possible to clear auto-reactive antibodies and suppress disease activity [22]. ds-DNA antibodies correlate weakly with disease activity and also fall following steroid therapy for flares [23]. Regarding antibody levels following rituximab, studies are divided. For example, Looney et al found no change in double-stranded DNA antibodies, levels at baseline being  $2.40 \pm 0.74$  and at 3 months  $2.35 \pm 0.67$  (mean  $\pm$  SD log titre) [13]. In contrast, Lu et al found ds-DNA antibodies fell from a median of 106 to 42 IU/ml at 6 months ( $p < 0.001$ ) [24]. This might be explained by variable measurement techniques or the time-point at which levels are measured post-rituximab, with assessments at less than 6 months generally demonstrating no significant change. This is supported by papers with repeat measurements, Lindholm found ds-DNA antibodies at baseline of  $34.5 \pm 4.9$  U/ml, to  $27.3 \pm 5.3$  at 6 months ( $p = 0.038$ ), and  $16.3 \pm 3.9$  after 12 months ( $p = 0.0049$ ) [25].

#### Clinical efficacy

Twenty-seven uncontrolled studies totaling 456 patients support the efficacy of Rituximab in the treatment of a myriad of SLE-related disorders, including lupus nephritis and neuropsychiatric symptoms, these will be considered in more detail in due course. Clinical outcome measures quoted were the SLE Disease Activity Index (SLEDAI) [26], and the British Isles Lupus Assessment Group (BILAG) [27]; both reflect disease activity and have been cross-validated.

The mean SLEDAI baseline score was 14.8, falling to 5.4 following rituximab, a 59% reduction (8.8 points, 95% CI (6.58, 11.05)). Similarly, the mean baseline BILAG score was 14.7, with post-rituximab reduction of 61% to 7.0 (7.7 points, 95% CI (5.02, 10.5);  $p < 0.001$  and  $p = 0.001$  respectively (paired Student's *t* test), and supports the validity and reliability of these two different disease activity indices. Similar reductions in disease activity scores have been found with other therapeutic options including mycophenolate mofetil [28]. Figure 2 demonstrates visually the percent change from baseline by scoring system and sample size.



**Fig. 2** Percent change in disease activity scores following rituximab, by study sample size

However, the only two sizable randomized controlled trials (RCTs) on the subject, with a combined total of 401 patients and both running to a year, suggested no benefit of rituximab in SLE. Firstly, a randomized, double-blind study of mycophenolate mofetil (MMF) and corticosteroids with either rituximab or placebo in 144 patients with lupus nephritis failed to significantly reduce disease activity [29]. Secondly, “EXPLORER”, a double-blind, multi-centre study of rituximab, baseline immunosuppressives and high dose steroids compared to baseline immunosuppressives and high-dose steroids alone in 257 patients with SLE (excluding lupus nephritis), found no significant differences in its primary endpoint (clinical response defined by BILAG), or secondary endpoints at 52 weeks [30].

Given the considerable patient numbers, and randomized and placebo-controlled design, their results throw doubt over the potential role of rituximab in SLE. One possible explanation of the negative findings lies in the methodology, with considerable background immunosuppression clouding any measurable difference between the rituximab and placebo groups. Another potential design feature of the EXPLORER trial which may have negated the effects of rituximab was the timing of retreatment. As mentioned previously, there is evidence that B cell repopulation contributes to the immune system changes; removing the reconstituted B cell pool with a 6-month re-treatment may diminish the benefit.

#### HACA

The overall incidence of developing of human anti-chimeric antibodies (HACAs) was 25%, although not all authors

measured them and there was high variability between studies, reasons for which are not clear. Frequency was predictably higher in studies with repeated use of rituximab following relapse [31]. Two issues transpire with the development of HACA; firstly, they are a potential barrier to continued drug effectiveness, although successful B cell depletion and induction of remission occur despite HACA; secondly, they increase the risk of infusion reactions or serum-sickness, which occur more commonly with both repeat rituximab dosing and HACA development [31, 32]. HACAs and the associated concerns should be avoidable with the fully humanized anti-CD20 MAbs.

Smith et al analyzed time to BCD and repopulation, time to remission, and to relapse; although small numbers are considered, some interesting trends are suggested. Firstly, HACA positive patients may have shorter time to B-cell repopulation and to clinical relapse. Secondly, with repeat rituximab dosing following relapse, patient's time to remission was shorter (mean 1.6 vs 4.1 months), but the duration of said remission was also curtailed (mean 10.5 vs >23 months), irrespective of HACA status [31, 33].

#### Ig levels

Most studies have found that IgM and IgG levels are maintained within normal range following rituximab, consistent with the low rates of infection observed and the CD20-negative status of plasma cells [31, 34]. More specifically, antibodies to tetanus toxoid and other previously vaccinated diseases are preserved [13]. Paradoxically, the response to new vaccines does appear sub-optimal [35], and immunization with live vaccines is not recommended, many study protocols therefore recommend completion of vaccination schedules four weeks prior to rituximab.

#### Lupus nephritis

Lupus nephritis has significant associated morbidity and many trials have focused on achieving renal remission. However, the LUNAR RCT of 144 patients mentioned previously failed to meet its primary endpoint (proportion achieving normalization of renal function) [29], and other smaller reports of non-responders have dampened enthusiasm [36]. In contrast, collating the results from smaller open trials gives a complete renal response rate of 27% (26/96), and partial response of 39% (37/96). See Table 2.

A possible explanation for this is concomitant immunosuppressive agents, the open trials favouring cyclophosphamide but the LUNAR group using mycophenolate mofetil, although both agents are used in SLE and no theoretical difference of combination with rituximab has been proposed.

In addition to clinical and laboratory improvement, post-rituximab renal biopsies have demonstrated histological

**Table 2** Cumulative data from the following trials: Boletis, 2009; Gunnarsson, 2007; Li, 2009; Lindholm, 2008; Melander, 2009; Sangle, 2007; Sfikakis 2005; Vigna-Perez, 2006

Response	Number	Percent	Parameters
Complete	26	27	Normal serum creatinine/albumin, inactive urine sediment and 24-h urinary protein <0.5 g
Partial	37	39	>50% improvement all abnormal parameters
None	29	30	
Worse	4	4	
Total	92	100	

restitution according to WHO classification, although the results were based on small numbers and only 6 months of follow-up [37].

#### Neuropsychiatric SLE

Lack of consensus regarding diagnostic testing makes interpretation of this domain difficult. For this reason, and with this caveat in mind, the dearth of studies looking specifically at neuropsychiatric SLE is unsurprising, but those assessing rituximab in the general lupus population have found improvement in CNS symptoms [19, 34]. Tokunaga et al. 2007 investigated use of rituximab in neuropsychiatric SLE, with rapid clinical improvement in a spectrum of manifestations including acute confusional states, seizure, psychosis and cognitive dysfunction. This was substantiated by reduced SLEDAI scores and MRI improvement. Effects were measured at one month, but persisted in half the group for 12 months [38].

#### Autoimmune haemolytic anaemia

As a manifestation of SLE, autoimmune haemolytic anaemia (AIHA) is a poor prognostic indicator [4], but has also been shown to be responsive to rituximab, with both platelet count and haemoglobin rising to normal levels within a few months. Although only evidenced by case studies and small open trials [39, 40] support also comes from non-SLE AIHA cohorts [41].

#### Other immunological associations

- CD40 and CD80 are costimulatory molecules expressed on B cells, up-regulated in active SLE, and integral to B- and T-cell interactions. Following rituximab, expression of CD40 and CD80 fall, suggesting that impediment of T lymphocyte activation is a second mode of action [19, 38].



- T regulatory cells increase in both number and regulatory activity (at days 30 and 90,  $p < 0.05$ ) [15].
- Natural killer cell numbers are reduced [42].
- The immunological milieu shifts in favour of a Th1 response (cellular immunity, activating macrophages and cytotoxic CD8+ T cells), although the significance of this is not clear [19].

### Safety

There is good safety data, as rituximab has been used since the 1990's in patients with lymphoma and since 2002 in SLE. Ceccarelli's safety study in SLE found adverse event rates comparable to placebo – the only differences being leukopenia (12.3% vs 4.2%), neutropenia (5.5% vs 1.4%) and hypotension (11% vs 4.2%) [43]. Most adverse events that are reported (Table 3) are mild infusion reactions e.g. fever [44]; however, rare but serious side effects include serum-sickness-like reactions, tumour lysis syndrome, and progressive multifocal leukoencephalopathy. The latter became a concern in 2006 when two rituximab-treated patients developed this progressive CNS demyelinating disease caused by JC virus reactivation [45]; though this is not specific to rituximab – immunosuppression and B cell proliferation are risk factors for this disease.

Indeed, concurrent immunosuppression remains an area of controversy in terms of both efficacy and safety; the majority of open studies giving a cyclophosphamide/rituximab combination, or adding rituximab to existing therapy. Such a study design prevents one differentiating the efficacy and safety of rituximab from concomitant medications. Interestingly, a recent RCT found that the addition of cyclophosphamide to rituximab conferred no additional clinical, histological or laboratory benefit in lupus nephritis [46]. A number of other studies excluding cyclophosphamide use (but allowing other immunosuppressant therapies to varying degrees) also demonstrated similar efficacy (Albert, 2008; Galarza, 2008; Sfikakis, 2005; Tokunaga, 2007). Other authors however (Lu, 2009; Jónsdóttir, 2008) have felt that the combination of rituximab and cyclophosphamide is synergistic.

Rituximab is not the only new monoclonal antibody (MAb) being tested in SLE: fully humanized Ofatumumab, Ocrelizumab and other anti-CD20 MAbs exist; Epratuzumab is humanized anti-CD22 antibody used alone or in combination with rituximab; B-Lymphocyte stimulator (BlyS) is a survival factor to which the MAb belimumab has been developed; abatacept (CTLA4-Ig) has been tested in renal and extrarenal SLE [47]; and anti-CD40L antibodies also reduce B cell load [48].

### Discussion

Methodological problems of any research involving patients with SLE include the heterogeneity of disease manifestations, study design and outcome measures. Breaking response down by disease manifestations suggests that some show better response rates to rituximab than others, for example cutaneous lesions/discoid lupus shows less improvement than neuropsychiatric or renal, and multi-system disease is more responsive than single organ [32]. Off-license, studies have inevitably included patients with severe refractory lupus, so any positive outcomes should be viewed favourably; however, the degree of severity and refractoriness is variable between the studies (e.g. baseline mean SLEDAI score varying from 8 to 24) [35, 49], and this will effect response rates. Similarly, variable regimens of rituximab and concurrent immunosuppressives complicate validation of efficacy.

Thirdly, EULAR (European League Against Rheumatism) [50] and OMERACT (Outcome Measures in Rheumatology) [51] have gone some way to standardizing outcomes, and SLEDAI and BILAG are validated assessment tools, but the issue of selecting valid and reliable outcome measures remains difficult given the multifarious disease processes and symptoms. For example, in lupus nephritis, abridging the outcome response to strictly defined “complete” or “partial remission” is too reductionist an approach, and too few studies have assessed the histological changes. Some have attempted to assess for, and found, disease activity change which SLEDAI and BILAG lacked sensitivity to discern [47].

Given the incongruence of the two RCTs to the rest of the published data, one has to consider whether publication bias of positive results is to blame. This possibility was assessed by constructing a Funnel Plot of response vs sample size (Fig. 2), which supports the reliability of the data search. The second possibility is industry bias, as at least 3 papers had financial links to Genetech, though had disclosed this conflict of interest in publication. Finally, the strength of the evidence is (as always) limited by the quality of the original research, in this case there is deficit of RCTs and most of the original evidence is grade C.

The diverse laboratory outcomes measured and discussed above is indicative of our lack of understanding of the disease process in SLE, and of the manifold actions rituximab has on these patho-physiological processes. Measuring the efficacy of rituximab will remain problematic until its impact on cells and systems is fully discerned. Older therapeutic agents for lupus have become established by anecdotal evidence, often without any scientific theorising that is the basis of newer proof-of-concept studies. This practice is no longer acceptable, but leaves us in the situation of needing evidence of superiority over unvalidated gold-standard agents.

**Table 3** Adverse effects documented following rituximab use

Author	Adverse effects	Concomitant immunosuppressants
Albert [35]	1× hypotension/bradycardia/fever; 1× serum sickness after 2nd dose, high HACA; 1× ?lupus cebritis, ?meningitis 8wks after RTX	None allowed 1 month prior to RTX; 100 mg MP before infusions to reduce risk infusion reaction
Galarza [39]	4 patients had adverse effects	MP; CYC stopped in all; MMF continued in 6 patients
Gottenberg [53]	2× neutropenia, 2× serum sickness	2 patients AZA, 1 HCQ, 2 MP, 1 CIC, 1 CYC
Gillis [18]	1× herpes zoster, 1× UTI	Steroids and existing (CYC, AZA, MMF)
Gunnarsson [37]	1× UTI, 1× neutropenic fever, 1× herpes zoster, 1× photosensitive eruption	CYC with 1st and last RTX; prednisolone (tapered)
Hernandez [56]	1× terminal renal failure and colitis	CYC, steroids+others “as necessary”
Lindholm [25]	1× osteitis in the jaw (possibly present before RTX), 1× serum sickness after 3rd RTX, 1× neutropenia and pseudomonas sepsis 2 months after last RTX, 1 patient died of pulmonary infection 23 months after RTX, 1 patient died of dilated cardiomyopathy 18 months after RTX	RTX added to regimen (CYC/MMF), maintained until remission
Looney [13]	1 mild infusion reaction; 1× herpes zoster 3 weeks after rituximab	Excluded CYC patients, others allowed
Lu [24]	1× serum sickness-like reaction (responded to steroids), 1× SLE-pericarditis–DIED (BCs repopulated), 1× pneumococcal pneumonia/sepsis, 1× hyponatraemia and seizure hrs after CYC, 1× ARDS after CYC–DIED	CYC 750 mg, MP 250 mg IVI to reduce risk infusion reaction
LUNAR [29]	overall incidence comparable between placebo and RTX; differences in rates of leukopenia (12.3% vs 4.2%), neutropenia (5.5% vs 1.4%) and hypotension (11% vs 4.2%)	MMF and corticosteroids; retreated at 6/12 with same
Melander [58]	5 infections, 4 moderate neutropenias	3 also got CYC
Merrill [30]	37.9% of the RTX group and 36.4% of the placebo had adverse effects (RTX: 4× serum sickness, more neutropenia)	RTX added to existing regimen; steroids tapered down
Shahrir [40]	2× anaphylaxis, both failed to have the study’s incorporated pre-medication	RTX and MP added to existing regimen
Smith [31]	Infusion reactions comon (resolved with hydrocortisone and antihistamine), 1× serum sickness after 3rd RTX dose (responded to MP), low rates of infection (2× pneumonia, 1× UTI, 1× abscess)	500 mg CYC with 1st RTX infusion, added to existing regimen (AZA or MMF)
Tamimoto [19]	1× infusion reaction; 5× bacterial infection; 1× candidiasis; 1 died renal failure from disease progression	All on prednisolone; 2 CIC; 1 CYC
Tanaka [34]	bacterial infections—1× pneumonia, 1× enteritis, 2× UTI, cystitis, URTIs	Prednisolone only; others not allowed
Tokunaga [49]	1 herpes zoster in patient with IgG drop	Prednisolone; 1 on CYC at outset, but stopped during study
Tokunaga [38]	pneumonia ×2, herpes zoster, infected ulcer	Variable pre-study, stopped during study; low-dose steroid throughout
Vigna-Perez [15]	1 invasive histocytosis (died)	RTX added to regimen

Determining an accurate safety profile for rituximab has been confounded in most studies, as the risk of infective complications is exacerbated by use of concomitant immunosuppressive drugs. There also remains a dearth long-term safety data; findings in lymphoma may not be translatable to SLE. Longitudinal studies and continuing surveillance are required. If evidence continues to accumulate in favour of rituximab, future consideration may be given to a combination approach with belimumab or epratuzumab, as the mechanisms of action of each are dissimilar. Furthermore, BLyS levels are inversely proportional to B-cell load, suggesting anti-BLyS may improve clinical response [52]. The obvious risk of a combination approach is of additional toxicity and susceptibility to opportunistic infections.

## Conclusion

No consensus yet exists regarding dosing, the majority follow a lymphoma schedule (375 mg/m<sup>2</sup> per week x 4 weeks), which achieves greater improvement in disease activity indices than 1 g two weeks apart (P 0.02). Dose-response relations require further elucidation. The most common adverse effects are mild infusion reactions, though serum-sickness reactions, hypotension, and immunosuppression-related complications can occur. In regard to the latter, there is evidence that rituximab is efficacious without concomitant immunosuppressive agents.

Rituximab shows an arsenal of immunological effects due to the diverse range of B cell actions. The effect on ds-DNA appears variable, presumably due to different measurement



time points and techniques. Immunoglobulin levels are maintained despite BCD, though response to new vaccines is suboptimal and live vaccines should be avoided. A quarter of patients developed HACAs, although there was again considerable variation between studies. Repeat rituximab dosing was used successfully, but with higher incidence of HACAs, more adverse reactions and shorter disease remission.

95 percent of patients achieved good B cell depletion with rituximab, duration being highly variable but on average 6 months. On clinical outcomes, two RCTs failed to meet primary or secondary endpoints. Combining the results of 27 small studies however demonstrates efficacy in renal and neuropsychiatric lupus and AIHA, and gives an average reduction in SLEDAI of 59% ( $P < 0.01$ ) and BILAG of 61% ( $P < 0.01$ ). Physicians continue to prescribe rituximab “off-label” [53] on the basis of these, and the paucity of alternatives for resistant disease.

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