

The efficacy of repeated treatment with B-cell depletion therapy in systemic lupus erythematosus: an evaluation

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Abstract

Objective. Since 2000, we have given B-cell depletion therapy (BCDT) with rituximab to 76 patients with active SLE refractory to standard immunosuppression. Twenty-four of these patients have now received repeated cycles of BCDT. The aims of the study were to: (i) assess the efficacy and safety of repeated cycles of BCDT in treating refractory SLE; and (ii) assess whether retreatment produced a more sustained clinical response.

Methods. BCDT was administered using CYC 750 mg, methylprednisolone 125–250 mg and rituximab 1 g given intravenously on two occasions, 2 weeks apart. Patients were reviewed at 1–2 monthly intervals and disease activity assessed using the BILAG activity index and serological markers. Clinical response was categorized as complete or partial remission, or no response, based on the change in BILAG scores.

Results. Eighteen patients had sufficient data for detailed analysis. All were female; mean age 29.9 years; mean duration of follow-up 58.7 months. Two patients died during follow-up and there were two infusion reactions. Disease activity was significantly reduced after both cycles of BCDT at 6 months. More patients achieved disease remission after the second cycle (82 vs 61% first cycle), which was maintained in 65% at 12 months (vs 39% first cycle). The time to disease flare was significantly longer after the second cycle ($P < 0.001$) and 33% of our patients have still not flared to date following retreatment (mean follow-up 24.5 months).

Conclusion. Repeated cycles of BCDT with rituximab are effective in treating refractory SLE and has a favourable safety profile. Retreatment may produce a more sustained clinical response.

Key words: Systemic lupus erythematosus, B cells, Biological therapies, Immunosuppressants, Immunotherapy, Autoantigens, Autoimmunity.

Introduction

Rituximab is a chimeric mAb against the B-lymphocyte marker CD20 expressed on immature, naïve and memory B cells, but not mature plasma cells or B-cell precursors. Since 2002, observational studies in 20 different units have produced data suggesting that rituximab is

effective in treating active SLE refractory to standard immunosuppression, reviewed in [1].

Although the pathogenesis of SLE is not fully understood, there is evidence that B lymphocytes play a central role [2], partly through the production of pathogenic auto-antibodies [3]. Therefore, specific depletion of B lymphocytes using rituximab may provide an effective treatment that is more specifically targeted at the underlying disease process compared with standard immunosuppressive therapy.

The efficacy of rituximab in the treatment of SLE demonstrated by numerous observational studies has not been confirmed by two recent randomized controlled trials EXPLORER [4] and LUNAR [5] (randomized double-blind, placebo-controlled trials of rituximab in

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Submitted 19 April 2010; revised version accepted 17 January 2011.

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non-renal and renal lupus, respectively). However, failure of these trials may be more attributable to study design than to the lack of efficacy of rituximab [1]. In particular, concomitant use of high-dose oral CSs and other immunosuppressive drugs may have masked any possible benefits of rituximab. Furthermore, evaluation of patient subsets is warranted as most of the open-label studies have focused on patients with very aggressive disease, who have failed conventional therapy with multiple immunosuppressive agents. In contrast, patients in the EXPLORER and LUNAR trials may have had less-active disease and it is possible that B-cell depletion therapy (BCDT) is simply more effective for patients with more aggressive disease. Nevertheless, BCDT with rituximab continues to be used to treat refractory SLE. Notably, a recent prospective cohort study demonstrated that rituximab is effective in inducing remission of lupus nephritis, allowing concurrent steroid therapy to be reduced or withdrawn completely and remission subsequently maintained with MMF [6].

We have used BCDT since 2000 to treat patients with refractory SLE and have shown that it is an effective and safe treatment [7–10]. To date, we have given BCDT to 76 patients with SLE, of whom 24 have received repeated cycles of treatment for flares in disease activity. To our knowledge, no studies have analysed in detail the effect of repeated cycles of BCDT in the treatment of active SLE. The aim of this study was to assess the efficacy and safety profile of repeated cycles of BCDT (using rituximab) in the treatment of active SLE. In particular, we wanted to investigate whether retreatment produced a better or more

sustained clinical response compared with initial treatment.

Methods

Identification of study population

Patients who had received at least two cycles of BCDT with rituximab for SLE refractory to treatment with other immunosuppressive agents (Table 1) were identified from our cohort of patients at University College London Hospital (UCLH). Between 2000 and June 2009, 24 patients have received repeated cycles of BCDT. All patients fulfilled the revised ACR criteria for SLE [11] and all gave informed consent for treatment.

Administration of BCDT

The treatment protocol for administering BCDT with rituximab at our institution has been described previously [10]. Standard treatment consists of 1 g rituximab, 750 mg CYC and 100–250 mg methylprednisolone administered intravenously on two occasions, 2 weeks apart. All patients received this protocol except two patients during the first cycle of treatment (who received only a single infusion of CYC) and three patients during the second cycle (two received rituximab alone and one received a single infusion of CYC). Treatment with other immunosuppressive agents was stopped before BCDT to reduce the risk of septic complications. Oral prednisolone was continued but the dose gradually tapered after BCDT. CD19 counts were monitored every 1–3 months after treatment and successful B-cell depletion (BCD)

TABLE 1 Baseline clinical characteristics of patient population

Patient/ethnicity	Previous therapies	Clinical indication for BCDT	Anti-ENA
4/C	Pred, HCQ, AZA, CYC, MMF	Arthritis, serositis, nephritis (WHO Class IV), skin vasculitis	Sm, RNP
5/AC	Pred, HCQ, AZA, CYC, MMF	Arthritis, serositis, nephritis (Class IV), skin vasculitis	RNP
7/AC	Pred, HCQ, MTX, AZA, CYC, CSA	Arthritis, serositis, nephritis (Class IV), skin vasculitis	Ro, La, RNP
10/AC	Pred, HCQ, AZA, CYC, MMF	Arthritis, nephritis (Class IV), skin rash	Sm, RNP
11/O	Pred, AZA, CYC, CSA, MMF	Fever, skin rash, serositis, nephritis (Class IV)	Ro
15/C	Pred, AZA, CYC, MMF	Fever, arthritis, CNS vasculitis, nephritis (Class IV)	Negative
17/AC	Pred, AZA, CYC, MMF	Nephritis (Class IV)	Negative
19/C	Pred, HCQ, AZA, CYC, MMF	Fever, arthritis, nephritis (Class IV), skin rash	Ro
22/C	Pred, HCQ, AZA, CYC	Arthritis, nephritis (Class IV)	Sm, RNP
25/A	Pred, HCQ, MTX, AZA, CYC	Fever, skin rash, arthritis, anaemia	Ro, La, Sm, RNP
27/O	Pred, HCQ, MMF	Skin rash, nephritis (Class IV)	Ro, La, Sm, RNP
29/A	Pred, HCQ, MTX, SSZ, ETC, IFX	Mouth ulcers, alopecia, arthritis, serositis	RNP
34/C	Pred, HCQ, MTX, AZA	Arthritis, nephritis (Class IV)	Ro, Sm, RNP
35/A	Pred, AZA, MMF, CYC	Arthritis, nephritis (Class IV)	Negative
39/AC	Pred, HCQ, MTX	Arthritis, fatigue	Negative
41/A	Pred, HCQ, MTX, CSA	Arthritis, skin rash, serositis	Negative
45/A	Pred, HCQ, AZA, CYC, MMF	Neuropsych (headaches, MRI lesions), arthritis	Ro, La
53/A	Pred, HCQ, AZA	Arthritis, skin rash, alopecia, pleurisy, haemolytic anaemia	Ro, La

C: Caucasian; AC: Afro-Caribbean; A: Asian; O: other; Pred: prednisolone; ETC: etanercept; IFX: infliximab; Sm: anti-Smith antigen; Ro: anti-Ro (SS-A); La: anti-La (SS-B).

defined as a fall in the absolute CD19 count to $<0.005 \times 10^9/l$.

Follow-up and repeat treatment

Patients were reviewed at 1–3 monthly intervals. SLE disease activity was assessed using the BILAG activity index [12] and serological markers of disease activity, including C3 and anti-dsDNA antibody titres. Data were collected prospectively and analysed retrospectively by reviewing the patients' medical records. A second cycle of BCDT was given for a flare in SLE disease activity following an initial positive response to the first cycle. A number of patients who showed no response to initial treatment were also retreated due to ongoing active, refractory disease. In all cases, retreatment was withheld until B-cell repopulation of the peripheral blood occurred (absolute CD19 count $>0.01 \times 10^9/l$).

Assessment of response to BCDT

The response of SLE disease activity to BCDT was evaluated at 6 and 12 months following each cycle of treatment. Response was categorized as complete remission, partial remission or no response based on the change observed in the patients' BILAG score, as described previously [10]. In brief, complete remission was defined as a change from a BILAG A or B score to a C or D score in every organ system. Partial remission was defined as a change from a BILAG A or B to a C or D score in at least one system, but with persistence of one BILAG A or B score in another system. No response was defined as a BILAG A or B score that remained unchanged after treatment. Global BILAG scores were calculated using a revised scoring system, where A = 12, B = 5, C = 1, D/E = 0 [13]. When it was not possible to assess response to treatment based on these formal BILAG criteria (in two patients), response was assessed and categorized by expert opinion following comprehensive review of the patient's medical records. Other data analysed to assess response included: duration of BCD, change in C3 and anti-dsDNA antibody titres and time to flare in disease activity. A flare in disease activity was defined as a new BILAG A score or two new consecutive B scores in any organ system.

Serological tests

Anti-dsDNA antibody titres were measured by ELISA (Shield Diagnostics, Dundee, UK) (normal $<50 IU/ml$) and serum complement (C3) levels by laser nephelometry (normal 0.90–1.80 g/l).

Statistical analysis

Data analysis was performed using the GraphPad Prism software program (San Diego, CA, USA). Data were assessed for normality of distribution using the Kolmogorov–Smirnov test. The *t*-test was used to compare parametric data (duration of BCD). Wilcoxon's matched-pairs signed-rank test was used to compare paired non-parametric numerical (C3 and anti-dsDNA antibody titres) and ordinal (global BILAG score) data. A chi-square test was used to compare categorical data including time to disease flare.

Results

Patient population

Eighteen patients had sufficient follow-up data for detailed analysis. Baseline clinical characteristics are summarized in Table 1 (patient numbers refer to all 76 patients in our cohort). Patients were excluded from the data analysis for the following reasons: two died after receiving their second cycle of treatment and hence lacked 6-month follow-up data. One patient was lost to follow-up after 3 months following their second cycle. Two only recently received their second cycle and have not yet completed 6 months follow-up. One patient was excluded because they had SLE with RA overlap and the BCDT was primarily given for active inflammatory erosive arthritis, considered to be a feature of their RA rather than their SLE. The mean age of 18 patients was 29.9 years (range 17–57 years) with a mean disease duration of 7.4 years (range 1–26 years) at the time of first BCDT. Six (33%) patients were Asian, five (28%) Afro-Caribbean, five (28%) Caucasian and two (11%) were of other ethnic origin. All patients were female. The mean duration of follow-up after first treatment with BCDT was 58.7 months (range 15–103 months).

Effect of BCDT on SLE disease activity

The response of SLE disease activity to each cycle of BCDT at 6 and 12 months follow-up is summarized in Table 2. Overall, at 6 months follow-up, 61% of patients achieved at least partial disease remission after their first cycle of BCDT, compared with 82% after retreatment. At 12 months follow-up, 39% of patients remained in at least partial disease remission after their first cycle, compared with 65% after their second cycle (Fig. 1). Global BILAG scores were significantly reduced after both cycles of BCDT, at both 6 and 12 months (Table 2).

A significant improvement in serological markers of disease activity was achieved following retreatment with BCDT at both 6 and 12 months (Table 2 and Fig. 2). Although a similar improvement was achieved following the first cycle, this was less marked: C3 titres increased significantly at 6 months but there was no significant improvement at 12 months and anti-dsDNA antibody titres did not decrease significantly at either 6 or 12 months. In contrast, our previous analysis based on a large number of patients did find a significant improvement in these serological markers at 6 months after initial treatment [10].

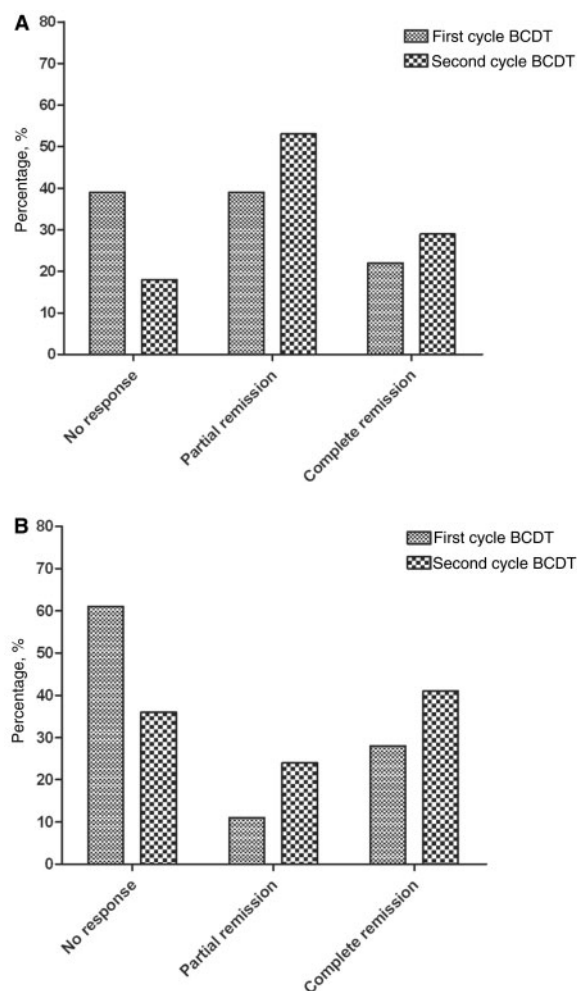
Flare in disease activity

Time to disease flare was significantly prolonged following the second cycle of BCDT compared with the first cycle ($\chi^2 = 32.39$, $P < 0.001$), shown in Fig. 3. Seven (38%) patients had a disease flare within 6 months and the majority [15 (82%) out of 18] flared within 12 months after their first cycle of treatment. By comparison, after retreatment, only eight (45%) patients flared within 12 months and six (33%) have still not flared to date (mean follow-up 24.5 months, range 11–45 months). Overall, 33% of patients received a third cycle of BCDT.

TABLE 2 Response of SLE disease activity to first and second cycles of BCDT

	6-month response		12-month response	
	First cycle BCDT	Second cycle BCDT	First cycle BCDT	Second cycle BCDT
Partial remission, <i>n</i> (%)	7 (39)	9 (53)	2 (11)	4 (24)
Complete remission, <i>n</i> (%)	4 (22)	5 (29)	5 (28)	7 (41)
No response, <i>n</i> (%)	7 (39)	3 (18)	11 (61)	6 (35)
Total, <i>n</i>	18	17 ^a	18	17 ^b
Global BILAG score, median	12.5 → 8**	13.5 → 8**	12.5 → 5*	13.5 → 4**
C3 titre, median (normal range 0.9–1.8), g/l	0.66 → 0.93**	0.68 → 0.82**	0.66 → 0.75	0.68 → 0.8***
Anti-dsDNA titre, median (normal range <50), IU/ml	136 → 42.0	119 → 31.5**	136 → 44.5	119 → 31*

^aPatient 35 excluded from analysis as no 6-month BILAG score was recorded (patient abroad at the time). ^bPatient 11 excluded from analysis as no 12-month follow-up data yet available. Significant difference compared with baseline: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Fig. 1 Response of SLE disease activity to first and second cycles of BCDT at (A) 6 months and (B) 12 months.

Duration of BCD

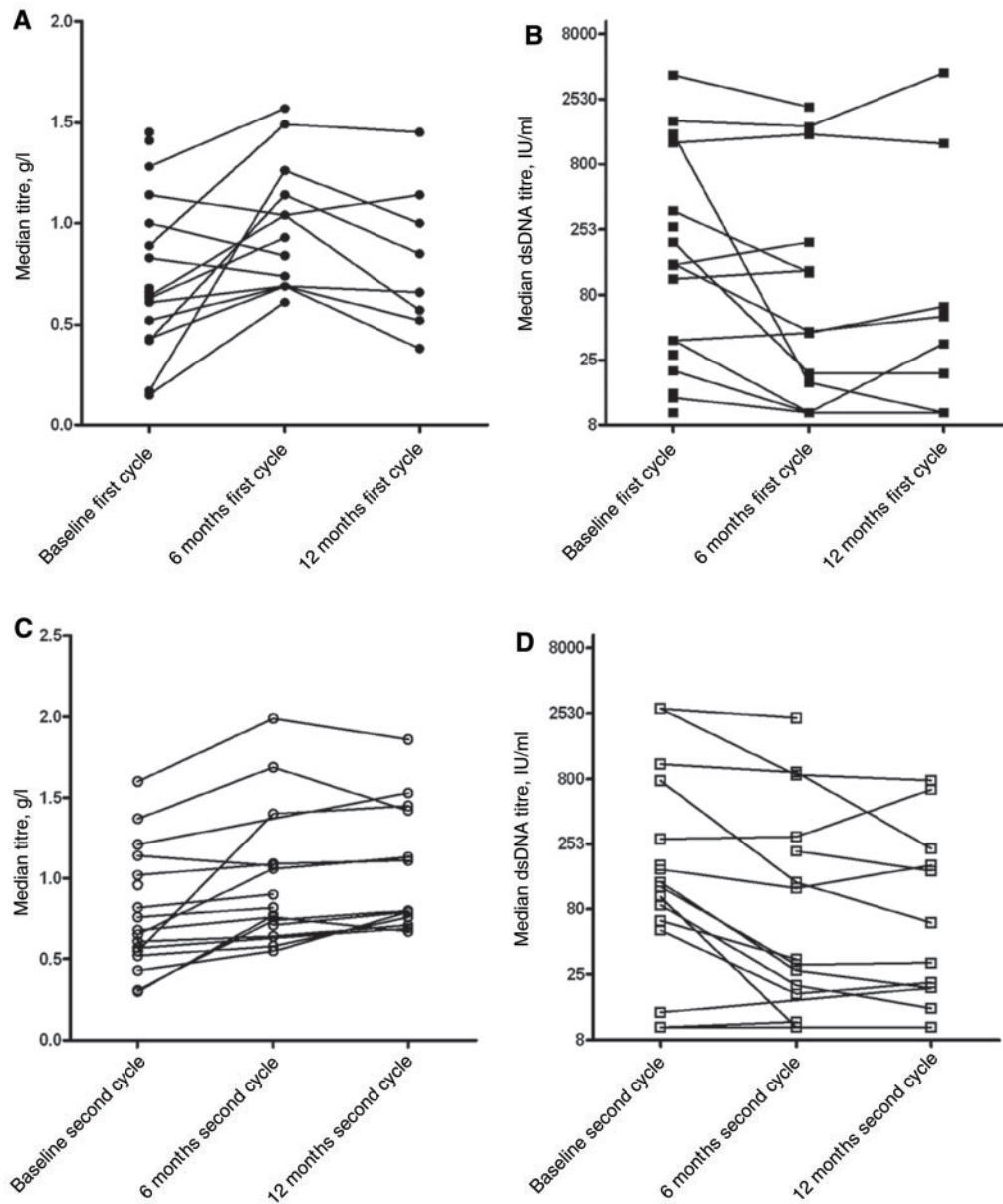
Fourteen (78%) patients achieved satisfactory BCD following their first cycle of BCDT. CD19 counts were not available for four patients (blood results before 2003 are not available on the electronic patient record and CD19 counts could not be identified in the hospital notes). After retreatment, 15 (83%) patients achieved BCD, 2 (11%) did not (second dose of rituximab incomplete due to infusion reaction). CD19 counts were not available for one patient. The mean time to B-cell repopulation (absolute CD19 count $>0.01 \times 10^9/l$) following the first cycle of BCDT was 5.6 months (range 2–10 months) compared with 7.1 months (range 3–12 months) after retreatment ($t = 1.42$, $P = 0.08$).

Safety profile

Six adverse events were observed. The rituximab infusions were generally well tolerated, but two patients experienced severe allergic reactions during their second cycle of BCDT. These reactions were characterized by dyspnoea and tachycardia occurring within minutes of starting the infusion, but resolved rapidly once the infusion was stopped.

Four patients died during the period of follow-up; two of which deaths were unrelated to BCDT. Patient 7 died following a road traffic accident, 6 years after their last cycle of BCDT. Patient 5 received four cycles of BCDT using three different anti-CD20 antibodies and unfortunately died from septicaemia 17 months after the last cycle of treatment. The first cycle of rituximab was given in March 2001 for a persistent vasculitic rash, polyarthritis, serositis, nephritis and haemolytic anaemia. Disease activity improved initially but then flared 9 months later, which coincided with B-cell repopulation. A second cycle of rituximab in January 2002 failed to achieve satisfactory BCD due to the development of human anti-chimeric antibodies (HACAs). Two further cycles of BCDT for persistently

Fig. 2 Effect of BCDT on serological markers of SLE activity: (A) C3 titres, first cycle BCDT, (B) anti-dsDNA titres, first cycle BCDT, (C) C3 titres, second cycle BCDT and (D) anti-dsDNA titres, second cycle BCDT.

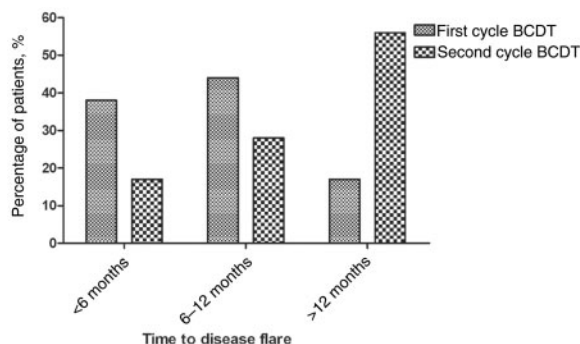


active disease were subsequently given using two other anti-CD20 mAbs (hA20 and ocrelizumab) [14]. At the time of death, the patient's B cells had repopulated and hence this death was not considered to be directly attributable to BCDT. The other two patients who died were excluded from the data analysis as they lacked 6-month follow-up data after the second cycle of BCDT. One patient died from suicide, 5 months after receiving their second cycle. Another patient died from varicella pneumonia, 7 months after their second cycle. Unfortunately, no CD19 counts were done in the month before this patient's tragic death and it is unclear whether their B cells had fully repopulated when they developed varicella pneumonia.

Discussion

Rheumatologists face a striking paradox when examining the evidence concerning the potential utility of rituximab in the treatment of SLE. Approximately 20 centres worldwide have reported considerable success in (mostly) small open-label studies [1]. More recently, a large prospective, multi-centre study of 136 patients with SLE has provided further open-label data suggesting that rituximab is a safe and effective treatment for these patients in the off-trial clinical setting [15]. It is hard to believe that all of these centres can be wrong about the use of rituximab in their patients.

Fig. 3 Time to disease flare following BCDT. Significant differences in time to disease flare between first and second cycles of BCDT ($\chi^2 = 32.39$, $P < 0.001$).



In contrast, however, two double-blind controlled trials—EXPLORER (which examined the effects of rituximab in non-renal lupus) and LUNAR (assessing patients with lupus nephritis)—failed to meet their primary end points. It is important to examine the design of these trials to seek potential clues to explain why they were unsuccessful. In both trials, patients were given substantial amounts of oral (and i.v.) steroids and continued immunosuppressant drugs while receiving treatment with either rituximab or placebo. In our view, the significant amount of concomitant therapy helps to explain why no benefit could be demonstrated for rituximab in these studies.

In this observational study, BCDT reduced SLE disease activity after both treatment cycles. Most patients had achieved at least partial disease remission at 6 months and at least partial disease remission was maintained in a substantial proportion of patients at 12 months, suggesting that BCDT produces a sustained clinical response: nearly two-thirds (65%) after the second cycle (with 41% in complete remission) and a smaller, but still substantial, proportion of patients (nearly 40%) following the first cycle. In our previous report [10], 12-month follow-up data were not presented so this is the first time we have demonstrated a sustained clinical response to BCDT beyond 6 months.

This positive clinical response to BCDT was accompanied by an improvement in the patients' global BILAG scores and serological markers of SLE disease activity. The degree of improvement was generally more significant after retreatment with BCDT compared with the first cycle, particularly at 12-month follow-up. The time to disease flare in our patient population was significantly prolonged following the second cycle of BCDT, compared with the first cycle ($P < 0.001$). Moreover, one-third of our patients have still not had a disease flare to date following retreatment.

The present observational study provides further evidence to suggest that BCDT with rituximab is effective in the treatment of active, refractory SLE. Although our study population is modest, our data also provide

provisional evidence that repeated cycles of rituximab remain effective in reducing SLE disease activity and may produce a more sustained clinical response compared with initial treatment: a greater proportion of patients remained in disease remission at 6 and 12 months and the time to disease flare was significantly prolonged following retreatment.

BCDT was administered using a combination of rituximab with CYC and methylprednisolone. This protocol aims to maximize BCD and is based on that used by our colleagues (J. Edwards and G. Cambridge) for the treatment of RA. The first 50 patients in our SLE cohort to be treated with this protocol showed a very positive clinical response [10], and hence we have continued to use it. However, there is no consensus regarding an optimal regimen for administering BCDT based on rituximab. Different disease manifestations may respond varying to slightly different regimens [1]. Our view is that for patients with severe, active lupus that has failed to respond to conventional immunosuppression (i.e. those included in the present study), maximizing BCD with concomitant CYC is likely to be more effective than using rituximab alone.

We have previously published data demonstrating that the use of the present BCDT protocol (with CYC) in the treatment of active SLE is safe [10]. Nevertheless, we recommend that standard vaccination against influenza and pneumococcus should be carried out before treatment and physicians must remain vigilant for adverse reactions. In the present study population, the infusions were well tolerated with only two patients experiencing allergic reactions, which quickly resolved once the infusion was stopped. Four patients (two excluded from analysis due to lack of follow-up data) died during follow-up, but only one of these deaths may have been attributable to BCDT. The patient concerned died of varicella pneumonia after her second cycle and we do not know whether her B cells had fully repopulated and hence whether she had increased susceptibility to disseminated varicella infection. This highlights the importance of regular monitoring of patients' CD19 counts after receiving BCDT, at least until B-cell repopulation has occurred.

Overall, our data suggest that administration of repeated cycles of rituximab to patients with active SLE has a favourable safety profile. However, there is a clear need for careful evaluation of side effects on an individual patient basis and, in all cases, the balance between the potential fatal effects of the disease and any serious sequelae from the rituximab must be weighed carefully. The risk of severe infection following BCDT is important to consider when assessing the potential risk:benefit ratio of treatment. There is some evidence that low serum IgG levels before treatment with rituximab are associated with an increased risk of severe infection during the first 12 months after treatment [16]. Measurement of baseline serum IgG titres may therefore enable a more individual assessment of the risk:benefit ratio of BCDT.

Most patients in the present study achieved satisfactory BCD after both cycles of treatment. There was a trend towards a longer duration of BCD following the second

cycle (7.1 months compared with 5.6 months for the first cycle), although this difference was not found to be statistically significant. However, patients tended to remain in disease remission for significantly longer following their second cycle of BCDT ($P < 0.001$). Our failure to detect a significant difference in the duration of BCD between the two cycles of BCDT may represent a Type II error due to our small study population. Alternatively, it is possible that the duration of clinical response may not depend critically on the duration of BCD and this may contribute to the favourable safety profile of repeated cycles of rituximab.

Interestingly, a poor clinical response to the first cycle of BCDT did not tend to predict a poor response to the second cycle. Five patients showed no clinical response to the first cycle of BCDT (three had active lupus nephritis, one had active serositis and one had a severe facial rash). All of them showed a positive clinical response to the second cycle: three patients (including two with lupus nephritis) were in complete remission 6 months after retreatment and two were in partial remission. Patients with active SLE who do not initially respond to BCDT may therefore benefit from retreatment. The decision to retreat these primary non-responders with rituximab was made following discussion with our colleague (J. Edwards) who had a similar experience in patients with RA. The five patients discussed here had severe, active lupus refractory to treatment with multiple immunosuppressive agents, leaving few alternative treatment options at the time.

The present study population includes patients with a diverse range of disease manifestations. Published observational data suggest that rituximab is effective in treating a wide spectrum of disease manifestations in SLE, but these may not all respond equally well, e.g. certain clinical features such as haematological abnormalities (anaemia or low platelets) often improve within the first 2 weeks after treatment whereas others, such as lupus nephritis, tend to respond more slowly [1]. Many patients in the present study population had refractory lupus nephritis. Therefore, the fact that the majority of these patients showed a good overall clinical response to rituximab suggests that BCDT is effective in treating renal lupus. We are analysing in detail the response of specific markers of renal disease, e.g. serum creatinine, albumin and proteinuria to treatment with rituximab in our lupus nephritis patients. Some of these data, in collaboration with the Karolinska Institute, comparing the effect of BCDT on membranous as opposed to proliferative glomerulonephritis, have recently been published [17].

There are a number of limitations to the present study. First, our study population was relatively small and included patients with a diverse range of disease manifestations, which limits the extent to which we can generalize our results. This is simply because only 24 patients at our institution have received at least two cycles of BCDT for refractory SLE and only 18 of these patients had sufficient follow-up data for inclusion in the present study. Secondly, the use of the BILAG index to determine the patients' response to BCDT is observer dependent and

it is likely that there was some variability between individual assessors in their assessment during the follow-up period. However, the objective serological improvements observed provide reassurance that any variability in clinical assessment was small. Thirdly, although only one patient was lost to follow-up completely, some of the follow-up data required for analysis were incomplete. In particular, data on CD19 counts required to assess the extent and duration of BCD following BCDT were not available for 4 of the 18 patients.

In conclusion, these preliminary data from a small but carefully observed cohort with a mean follow-up duration of 4.9 years provide evidence that administration of repeated cycles of rituximab is a safe and effective treatment for active, refractory SLE. Furthermore, patients who do not respond to initial treatment with rituximab may benefit from retreatment and a second cycle may produce a more sustained clinical response. Further study in a larger patient population is now warranted to confirm these findings. It is encouraging to note that even though the recent randomized clinical trials of rituximab in the treatment of SLE have failed [4, 5], success has been reported of its use in vasculitis [18, 19]. This encourages us to believe that better-designed clinical trials may confirm the benefits that our data help to support, i.e. that BCDT with rituximab may have a useful role to play in the treatment of patients with aggressive lupus.

Rheumatology key messages

- This observational study provides further evidence that rituximab is effective in treating refractory SLE.
- Administration of repeated cycles of rituximab is a safe and effective treatment for refractory SLE.
- Retreatment with rituximab may produce a more sustained improvement in SLE disease activity—further study is required.

Disclosure statement: D.A.I. has consulted for Roche, but does not accept any personal support, asking instead for the honoraria to be paid to a local arthritis charity. All other authors have declared no conflicts of interest.

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