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Induction treatment of ANCA-associated vasculitis with a single dose of rituximab

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Abstract

Objectives. Rituximab is effective in inducing remission in ANCA-associated vasculitis (AAV), with randomized evidence to support its use as four infusions of 375 mg/m^2 (the conventional lymphoma dosing schedule). As B cell depletion (BCD) appears to occur very rapidly after the first dose, we questioned the need for repeat dosing and adopted a standard single-dose protocol of 375 mg/m^2 to treat active AAV.

Methods. All consecutive cases with newly diagnosed or relapsing AAV for whom conventional immunosuppression was contraindicated or ineffective were enrolled. All were rituximab naive. Circulating CD19$^+$ B cells and clinical and serological markers of disease activity were recorded at regular intervals. Complete remission (CR) was defined as the absence of clinical features of AAV with a prednisolone dose $<$10 mg/day.

Results. Nineteen patients were included, 17 (89%) with generalized disease and 2 (11%) with severe disease (creatinine level $>$500 μM). Eight (42%) were on additional immunosuppression at the time of rituximab treatment. Satisfactory BCD ($<$0.005 cells/μl) was achieved in 89% of patients after a median of 13 days. Three-month BCD probability was 89%. Median time to CR following a single dose of rituximab was 38 days and the 3-month probability of CR was 80%. Median time to B cell repopulation was 9.2 months and to disease relapse/redose was 27 months. Use of this single-dose protocol saved an estimated £4533/patient (US$7103; €5276) compared with a 4 $\times$ 375 mg/m^2 dosing schedule.

Conclusion. Our single-centre experience suggests that a single dose of rituximab of 375 mg/m^2 is a reasonable and more cost-effective therapy for inducing remission in patients with AAV.

Key words: ANCA, anti-CD20, lupus nephritis, rituximab, vasculitis, monoclonal antibody.

Introduction

ANCA-associated vasculitis (AAV) is a chronic relapsing autoimmune disorder of unknown aetiology. It carries high morbidity and mortality that results not only from disease activity, but also from treatment complications [1]. Successful treatment requires induction of remission followed by maintenance therapy to prevent relapse. Multiple treatment modalities already exist that aim primarily to suppress the autoimmune response and are thus associated with infectious and other well-recognized side effects. Although the intensity of treatment is usually determined by disease severity, no clear consensus exists regarding optimal regimens.

Rituximab, a chimeric monoclonal antibody with anti-CD20 B cell–depleting activity, is emerging as an effective agent in AAV, with randomized trial evidence for its use as an induction agent [2, 3]. It causes rapid, specific and long-lasting B cell depletion (BCD) [4]. Until recently, rituximab had been used almost exclusively for the treatment of relapsed or refractory non-Hodgkin's lymphoma and lymphoproliferative disorders [5]. However, over the last decade it has been reported to be an effective agent in a range of autoimmune conditions [6], including SLE and AAV [7, 8]. Various dosing regimens have been used,

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and while large weekly doses are used for B cell lymphoma, evidence is emerging that smaller, less frequent doses also have good efficacy, fewer side effects and reduced cost in autoimmune conditions [9, 10]. Most early published series of rituximab use in AAV and SLE used four separate weekly infusions of 375 g/m^2, in line with the B cell lymphoma protocols [7, 11, 12]. However, in later series authors have reported equivalent success with fewer infusions in conditions such as pemphigus [13, 14], multiple sclerosis [15] and LN [16].

As rituximab emerges as an agent to both induce and maintain remission, issues of cost come to the fore, since it is far more expensive than conventional agents like CYC. In many centres it is becoming the first-line agent for the treatment of AAV, with the result that the cost of treating these patients increasing. Therefore there is strong rationale for addressing the need for the high-dose lymphoma protocol to treat these autoimmune diseases. For us, it quickly became apparent after the introduction of rituximab for the treatment of autoimmune disease that circulating CD19$^+$ BCD occurred rapidly after the first dose. Therefore the need for repeated doses was questioned and a treatment-to-target CD19 cell protocol was adopted. We describe here a single-centre experience with protocolized treatment of AAV with a single dose of 375 mg/m^2.

Subjects and methods

Study population

Rituximab was used in AAV as first-line therapy in cases of active disease where there was a contraindication to existing standard induction therapy (CYC, MMF or MTX), or as add-on therapy in cases refractory to conventional therapy. All patients gave informed consent for treatment and only ANCA-positive AAV cases that satisfied the Chapel Hill Consensus Conference definitions [17] were included. After adopting the approach of using a single dose of rituximab we enrolled all consecutive cases (both *de novo* and major relapses) in a rolling audit project, the results of which are presented here. Patients were followed from pre-dosing (baseline) until the end of the study, relapse/redose or treatment with an additional rescue therapy. Follow-up was censored in the event of a rituximab redose. All patients were rituximab naive at the time of treatment. The data analysed were collected as part of routine clinical care, thus this work did not require ethics approval.

Rituximab dosing schedule

For the treatment of active AAV we adopted a standard protocol of a single rituximab dose, with measurement of the CD19$^+$ B cell count after 1–2 weeks and at varying intervals thereafter. Rituximab was given as an i.v. infusion of 375 mg/m^2 over 4 h according to standard procedures.

Measurement of efficacy and disease activity

Absolute CD19$^+$ cell counts (to determine effective depletion of B cells) were determined. A level of $<0.005 \times 10^9$/l was taken to indicate full BCD. Serological markers of disease activity, including anti-PR3/MPO antibody levels, were recorded together with serum creatinine level {from which the estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation [18]} and urinary protein measurements. Established BCD was defined as a level $<0.005 \times 10^9$/l for at least 18 weeks. Complete remission (CR) was defined as the complete absence of clinical features of AAV (i.e. BVAS = 0) with a prednisolone dose <10 mg/day and partial remission (PR) was defined as improvement of clinical features without achieving CR.

We analysed the following endpoints: BCD ($<0.005 \times 10^9$/l), complete and partial clinical remission, B cell repopulation ($>0.005 \times 10^9$/l) and the combined endpoint of clinical relapse or redose with rituximab.

Estimation of drug cost

Current prices as indicated in the British National Formulary were used, which amounted to £2.10/mg (VAT inclusive). We assumed that that there was no wastage of rituximab during the course of preparation. The actual amount administered was compared with what would have been administered if a 4×375 mg/m^2 or 2×1 g dosing schedule was followed. We did not take into account the cost of actually delivering the drug by i.v. infusion (which would have increased the differential between actual and theoretical costs) or of measuring CD19$^+$ cell counts. We also did not account for the cost of rescue therapy in the case of rituximab failure.

Statistical methods

As the duration of follow-up varied between patients, and as there were censored cases, we used life table analysis to assess the probability of reaching a specified endpoint. Data are presented as the mean (S.E.M.) in the case of normally distributed data and the median [interquartile range (IQR)] or full range in the case of skewed data.

Results

A total of 19 patients with AAV were included, of whom 8 (42%) were receiving additional CYC or MMF at the time of rituximab infusion (Tables 1 and 2). Seventeen (89%) were considered to have generalized disease, but without imminent threat of loss of organ function; two (11%) had severe disease with a creatinine level >500 μM. Median duration of follow-up after rituximab infusion was 11.5 months (range 1.5–36.9). The BVAS scores at the time of treatment with rituximab are detailed in Tables 1 and 2.

Eighteen patients (95%) received additional treatment with prednisolone, three of whom received additional pulsed methylprednisolone (Tables 1 and 2).

The two patients with severe disease required dialysis (Table 1). One presented with newly diagnosed vasculitis with pulmonary haemorrhage and serum creatinine >500 μM. She was treated intensively with additional immunosuppression (oral CYC and methylprednisolone). The other patient was treated with rituximab for relapsed extrarenal disease and was already dialysis dependent

Table 1 Patient characteristics at the time of treatment with rituximab (n = 19)

PR3/ MPO	Presentation/ relapse	Extra-renal features	EUVAS disease category	Active nephritis time 0	BVAS time 0	Additional immunosuppression (at time of rituximab)	Category of BCD	CR/PR	BVAS during PR	Disease relapse?	Re-treatment with rituximab?
MPO	Presentation	Pulmonary haemorrhage	Severe	Yes	18	CYC 150 mg/day p.o., MP 3 × 500 mg i.v.	Sustained	CR > 18			
		No	Generalized	Yes	12		f/u <18 weeks	CR			
		Pulmonary haemorrhage	Generalized	Yes	18	MP 2 × 500 mg i.v.	Sustained	PR	2		
	Relapse	PNS, skin	Generalized	No	6		Transient	CR > 18			
		Mesenteric aneurysms affecting medium-sized vessels	Generalized	Yes	6		Sustained	CR > 18			
		ENT, skin	Generalized	Yes	10		Sustained	CR > 18			
		ENT, CNS	Generalized	No	3		Transient	CR > 18			
		No	Generalized	Yes	12		Sustained	PR	5		
		Eye, PNS, ENT	Generalized	No	13	MMF 2 g/day[a]	Sustained	PR	2	Yes	Yes
PR3	Presentation	ENT/skin	Generalized	Yes	18	CYC 150 mg/day p.o., MP 1 × 500 mg i.v.	Sustained	CR > 18			
		No	Generalized	Yes	13		Sustained	CR > 18			
	Relapse	Profound fatigue	Generalized	Yes	2	MMF 1.5 g/day[a]	Transient	CR > 18		No	Yes
		Pulmonary haemorrhage, arthritis, ENT, pituitary	Generalized	No	7	MMF 2 g/day[a,b]	Sustained	CR > 18		Yes	Yes
		ENT, PNS	Generalized	No	7	MMF 2 g/day[a]	Failed	CR > 18		No	Yes
		Pulmonary haemorrhage, ENT	Severe	No	2		Sustained	CR < 18		Yes	No
		Pulmonary nodules, ENT	Generalized	No	3		Failed	PR	0		
		CNS, ENT	Generalized	Yes	3		Sustained	CR > 18			
		Pulmonary haemorrhage, ENT	Generalized	No	5	MMF 1 g/day[a]	Sustained	CR > 18			
		ENT	Generalized	No	3	MMF 1.5 g/day[a]	Sustained	CR > 18		Yes	Yes

EUVAS: European Vasculitis Study Group; CR/PR: complete remission/partial remission; MP: methylprednisolone; IS: immunosuppression; CR > 18: CR >18 weeks duration; CR < 18: CR <18 weeks duration; sustained corresponds to >18 weeks; transient corresponds to <18 weeks; f/u: follow-up. [a]MMF continued for the duration of follow-up. [b]Transplant immunosuppression.

Table 2 Summary data for patient cohort ($n = 19$)

Age, median (range), years		61 (19–87)
Male, *n* (%)		5 (26)
Duration since diagnosis, mean (range), years		3.3 (0–12.6)
Ethnicity, *n* (%)	White	16 (84)
	Asian	3 (16)
ANCA positivity, *n* (%)	MPO	9 (47)
	PR3	10 (53)
Primary indication for rituximab, *n* (%)	Active nephritis	10 (53)
	Extra-renal disease	9 (47)
	First presentation	5 (26)
	Relapse	14 (74)
Dialysis dependent, *n* (%)		4 (21)
eGFR, mean (S.E.M.), ml/min		42.4 (6.8)
BVAS at time of rituximab, median (range)		7 (2–18)
Additional immunosuppression, *n* (%)	CYC	2 (11)
	MMF	6 (32)
	Corticosteroids	18 (95)
Mean prednisolone dose, mg	Rituximab treatment	20
	6 weeks	14
	12 weeks	9
	26 weeks	6
Re-treatment with rituximab, *n* (%)	Disease relapse	2 (11)
	PR	1 (5)
	Transient BCD	1 (5)
	Failed to deplete	1 (5)

eGFR: estimated glomerular filtration rate; PR: partial remission.

with suppressed bone marrow as a result of previous immunosuppression. He received low-dose AZA 50 mg/day in addition to rituximab.

$CD19^+$ cell count depletion

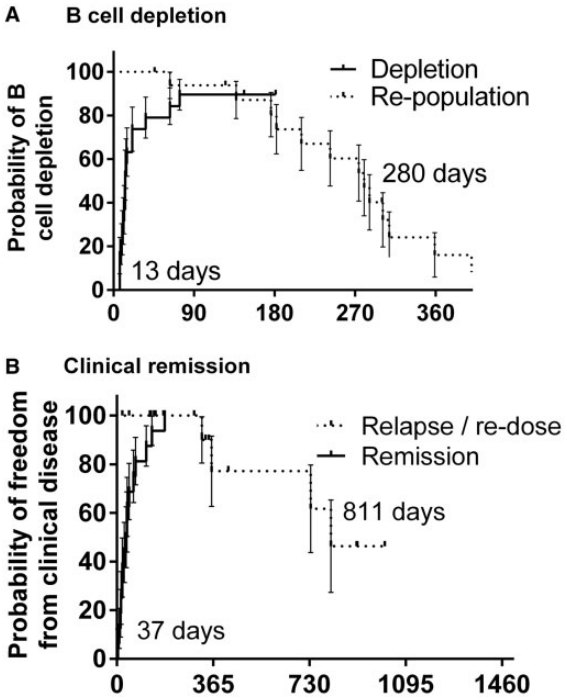
The median time to BCD ($<0.005/\mu l$) following a single dose of rituximab was 13 days and the 3-month actuarial probability of depletion was 89% (S.E.M. 7%) (Fig. 1A). Following a single dose of rituximab, 13 patients (68%) had established (>18 weeks) BCD, 3 (16%) had transient depletion (<18 weeks), 2 (11%) did not deplete and in 1 patient follow-up was <18 weeks. In those that depleted (89%), the median time to repopulation was 280 days (9.2 months) and 9 months after dosing the probability of persistent BCD was 54% (S.E.M. 13%). There was no difference in the probability or median duration of BCD between anti-MPO- and anti-PR3-positive patients [hazard ratio (HR) for depletion 1.7 (95% CI 0.7, 4.7), $P = 0.3$; HR for repopulation 1.1 (95% CI 0.3, 3.4), $P = 0.8$].

Disease activity

The median time to CR following a single dose of rituximab was 38 days and the 3-month probability of remission was 80% (S.E.M. 10%) (Fig. 1B). Following a single dose of rituximab, 13 patients (68%) achieved CR of >18 weeks duration, 1 (5%) achieved CR of <18 weeks duration, 4 (21%) achieved PR and 1 (5%) died (in CR) 51 days after treatment (Table 1). In no case was there a failure to respond at least partially to a single dose of rituximab. There was no difference in the probability of achieving remission between anti-MPO- and anti-PR3-positive patients [HR 1.8 (95% CI 0.6, 5.1), $P = 0.3$]. The median time to relapse or redosing was 811 days (27 months), and 9 months after achieving remission the probability of persistent remission was 89% (S.E.M. 7%) (Fig. 1B). There was no difference in the probability of relapse or redose between anti-MPO- and anti-PR3-positive patients [HR 0.4 (95% CI 0.1, 2.7), $P = 0.3$].

The patient who achieved transient CR of <18 weeks duration was not re-treated with rituximab upon disease relapse (Table 1). He had significant bone marrow suppression and was treated with an increased dose of prednisolone (20 mg/day) and AZA (100 mg/day). The four patients who achieved PR after treatment with a single dose of rituximab are identified in Table 1. One was re-treated with a second dose when her B cells repopulated and then went into prolonged CR. One patient had persistent low disease activity 15 weeks after treatment. The prednisolone dose was increased to 20 mg and his AZA to 150 mg, resulting in clinical remission. The remaining two patients had a limited follow-up period of 26 weeks during which neither patient was re-treated with rituximab. One was in clinical remission but remained on >10 mg/day prednisolone (hence considered to be in PR). The other patient had persistent low disease activity. She was not re-treated with rituximab during the period of follow-up, but was re-treated 8 months after her initial dose as she remained in PR. Both patients received maintenance immunosuppression (AZA 50 mg daily and MTX 20 mg weekly, respectively).

Fig. 1 BCD and clinical remission following treatment with a single dose of rituximab



(**A**) Probability of CD19$^+$ BCD (<0.005 cells/μl) and re-population over time following a single dose in rituximab in patients with vasculitis. The numbers beside the respective curves represent the median time to depletion and repopulation. (**B**) Probability of achieving full clinical remission and of developing further clinical features of vasculitis or of requiring a redose following a single dose of rituximab. The numbers beside the respective curves represent the median time to full clinical remission and relapse or redose. The error bars reflect the S.E.M.

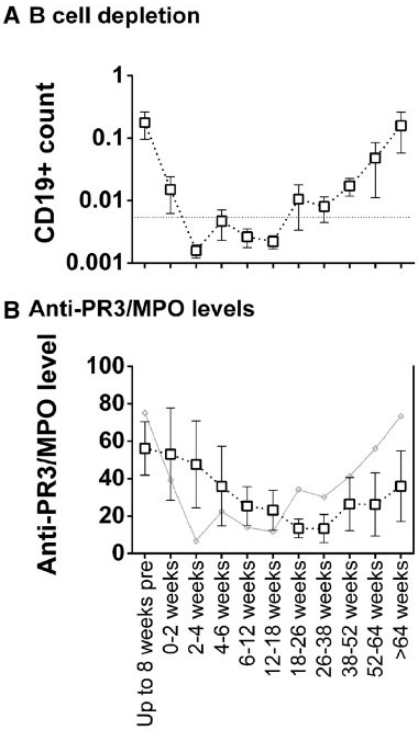
Four patients (21%) experienced disease relapse after treatment with a single dose of rituximab during the follow-up period. Three of these (75%) were re-treated with rituximab (Table 1). The remaining patient was treated with an increased dose of prednisolone and AZA as detailed above.

Overall, five patients (26%) were re-treated with rituximab during the follow-up period. The indications for re-treatment are summarized in Table 2. The two patients who received re-treatment for disease relapse had achieved prolonged CR of at least 2 years duration after their first dose of rituximab, before disease relapse and re-treatment. The mean anti-PR3/MPO antibody level pre-treatment was 56.1 (S.E.M. 14.2). There was a progressive decline in antibody level over 6 months to a mean nadir of 13.3 (S.E.M. 7.4), after which the mean level began to rise (Fig. 2).

Estimation of drug cost savings

Taking the study population under investigation, and not accounting for the differential requirement for further or

Fig. 2 Effect of a single dose of rituximab on peripheral CD19$^+$ B cell count and ANCA antibody titres



Mean levels of (**A**) CD19$^+$ B cells and levels of (**B**) anti-PR3 or anti-MPO antibodies at various time points following a single dose of rituximab. In (B) the light grey line depicts the respective CD19$^+$ B cell level. Error bars reflect the S.E.M.

rescue dosing, we estimated that the total actual drug costs were £28 715 (US$45 326, €33 667). If the dosing schedule had been 4 × 375 mg/m^2, this cost would have been £114 860 (US$181 307, €134 670). If the dosing schedule had been 2 × 1 g, the cost would have been £79 648 (US$125 700, €93 385). The respective drug cost savings for treating this population with vasculitis would therefore have been £86 146 (US$135 956, €100 985), a saving of 75%, and £50 933 (US$80 377, €59 706), a saving of 64%, for the four- and two-dose regimens, respectively.

Discussion

In a cohort of patients receiving rituximab therapy for active AAV, most of whom were experiencing a relapse, we found that a single dose of 375 mg/m^2 provides a duration of BCD that is comparable with those obtained in existing observational studies and an excellent clinical response. Half of patients achieved BCD within 2 weeks and the probability of depletion at 3 months was 89%, with an average of ~9 months of depletion. The probability of complete clinical remission was 80% at 3 months, with at least partial improvement in clinical parameters in all treated patients, which was durable in the majority of

patients, demonstrated by a median time to the combined clinical endpoint of relapse or redosing of >2 years.

Rituximab therapy has become an integral part of induction therapy in AAV, which is now supported by strong randomized controlled trial data [2, 3]. The published evidence describes the use of similar doses to those used for treatment of B cell lymphoma: either four weekly doses of 375 mg/m^2 or two fortnightly doses of 1 g. By employing a practice of frequent measurement of CD19$^+$ cell counts, we observed almost complete BCD after the first dose when we started using rituximab for this indication. We therefore developed a protocol comprising a single dose for both AAV and SLE, with subsequent measurement of the B cell count.

Review of our series of 19 consecutive patients with AAV treated in this manner indicates broadly similar results to the published literature. Previous studies mostly report BCD rates >95%, with the duration of BCD ranging on average from 9 to 12 months, after which most patients repopulate and some require redosing (Table 3). Although initial case series reported almost universal clinical response [7, 11, 19, 20], these were certainly prone to reporting bias of this novel therapy, and subsequent larger and controlled studies report remission rates ranging from 67% to 85% [2, 3, 8], depending on the definition of remission (Table 3).

This compares favourably with our observed CR rate of 79%. Thirteen patients in our cohort (68%) achieved sustained CR lasting >18 weeks and none of the treated patients with AAV failed to respond at least partially to the rituximab. It is difficult to directly compare this to the RAVE and RITUXVAS randomized controlled trials due to differences in study design and the definition of sustained remission. In the RITUXVAS trial, 76% patients entered sustained remission (defined as a BVAS score of 0 for >6 months), but all the patients in the rituximab arm were treated with CYC, more intensive immunosuppression than that received by the patients in our cohort. In the RAVE trial, 64% of patients had achieved CR at 6 months and were off steroid therapy [3]: 48% remained in remission at 12 months [21]. Although we observed relapse in 21%, this tended to be after the first year of follow-up. The median interval to relapse was similar to that reported in the literature, which ranged from 12 to 31 months. Therefore our data support the use of a single dose of rituximab for induction therapy of non-organ-threatening AAV and do not suggest that the use of a single dose risks more frequent or earlier disease relapse.

On average, we observed 9 months of BCD, which compares with the lower end of the reported intervals to B cell repopulation. Approximately one-quarter of our patients either failed to achieve BCD or achieved transient BCD lasting <18 weeks. However, none of these experienced disease relapse during the period of follow-up and only two were re-treated pre-emptively. Therefore failure to achieve prolonged BCD did not appear to correlate with a poor clinical outcome. Our experience suggests that patients without sustained BCD do not necessarily require early re-treatment with rituximab if they remain in clinical remission after a single dose. Clearly we need a longer follow-up period to be able to draw any conclusions about the long-term clinical outcome of these patients, but it is worth noting that two of the three patients with transient BCD were followed for >40 weeks and did not experience relapse during that time.

Similarly, the four patients in our cohort achieving PR did not necessarily require re-treatment with rituximab. Two were re-treated, but the other two achieved clinical remission with an increase in their doses of maintenance immunosuppression with AZA and/or prednisolone. However, both B cell and clinical responses in SLE were insufficient following this regimen, indicating a differential response between the two diseases. In a contemporaneous population of patients with SLE treated in our centre with a single dose of rituximab according to the same standard protocol as that used for the patients with AAV presented in this study, the median time to BCD was 31 days and the 3-month probability of depletion was only 67% (S.E.M. 12%). Following a single dose of rituximab, only 24% had established (>18 weeks) BCD. In those patients with SLE that depleted, the median time to repopulation was 150 days (5 months), and 9 months after dosing the probability of persistent BCD was 19% (S.E.M. 10%). Therefore the single-dose rituximab strategy was abandoned for treatment of active SLE.

The divergent response in SLE in the face of an identical dosing regimen is interesting and consistent with another series reported after we discontinued our single-dose practice in this patient group [22]. In this cohort ($n = 18$), 67% had active LN (mostly class IV) and patients were treated with rituximab 1 g 2 weeks apart: 22% did not deplete, the median time to repopulation was 5.6 months, 39% showed no clinical response to the first cycle of treatment and 39% had durable complete or partial disease remission at 12 months. There was an improved clinical response to re-treatment with a second cycle of rituximab in this cohort. It is possible that the higher prevalence of nephrotic-range proteinuria in SLE patients (resulting in possible loss of rituximab in the urine), Fc-receptor polymorphism in a population ethnically distinct from AAV or differences in the B cell subsets at relapse [23] may partially account for the difference between SLE and AAV responses to rituximab. Moreover, SLE is associated with polyclonal B cell abnormalities and diffuse B cell hyperreactivity with dysregulated homeostasis, resulting in more peripheral plasma cells that lack CD20 [24].

Our study has a number of limitations. First, the frequency of follow-up varied following treatment. This would have had an impact on the accuracy of some of our data, e.g. the duration of BCD and clinical response. However, only a minority of patients relapsed during the follow-up period and this was usually after at least 1 year of disease remission, so it was unlikely to have had a significant effect on our clinical outcome data. Second, the duration of follow-up for some patients was limited, so we are unable to confidently comment on the long-term outcome of patients treated with a single dose of

Table 3 Previous literature investigating the use of rituximab in systemic vasculitis

Study	Study design	No. of patients (disease type), renal involvement	Dose of RTX (no. of patients, no. of doses × amount)	BCD	Duration of BCD	ANCA serology	Clinical response (renal vasculitis)	Relapse	Duration of clinical remission, median (range), months
Eriksson [19]	Case series	9 (7 GPA, 2 MPA), 2 active renal vasculitis	6, 4 × 500 mg; 2, 2 × 500 mg; 1, 4 × 375 mg/m^2	9/9 depleted	6–12 months	0/7 became negative; no significant change in titre	8/9 (89%) CR, 1/9 (11%) PR, 2/2 improved	2/9 (22%) (at 12 and 13 months)	12 (6–25)
Keogh *et al.* [11]	Case series	11 (10 GPA, 1 MPA), 5 active renal vasculitis	4 × weekly doses 375 mg/m^2	11/11 depleted	4–12 months	8/11 became negative; significant decreased in titre in all patients	10/11 (91%) CR, 1/11 (9%) PR, 5/5 with renal vasculitis improved	2/11 (18%) (at 7 and 12 months); successful re-treatment with RTX	12 (7–19)
Omdal *et al.* [25]	Case series	3 (all GPA)	4 × weekly doses 375 mg/m^2	3/3 depleted	Median 12 months (range 8–13)	2/3 significant drop in titre, 1/3 negative pre-treatment	1/3 PR, 2/3 CR	3/3 (at 8, 13 and 15 months); all successfully re-treated with RTX	13 (8–15)
Henes *et al.* [20]	Case series	6 (all GPA), 2 active renal vasculitis	4 × weekly doses 375 mg/m^2	6/6 depleted	Median 10.6 months (range 8–18)	6/6 became negative	5/6 (83%) CR, 1/6 (17%) PR, 2/2 CR in renal vasculitis	1/6 (at 18 months); successful re-treatment with RTX	15 (12–21)
Keogh *et al.* [26]	POL	10 (all GPA), 7 active renal vasculitis	4 × weekly doses 375 mg/m^2	10/10 depleted	Median 9 months (range 9–15)	6/10 became negative; all had significant decrease in titre	10/10 CR, 7/7 with renal vasculitis improved	1/10 (10%) (at 9 months); successful re-treatment with RTX	12 (9–12)
Stasi *et al.* [12]	POL	10 (8 GPA, 2 MPA), 6 active renal vasculitis	4 × weekly doses 375 mg/m^2	10/10 depleted	Range 4–10 months	8/10 became negative; all had significant decrease in titre	9/10 (90%) CR, 1/10 (10%) PR, 6/6 with renal vasculitis improved	3/10 (30%) (at 12, 16 and 24 months); all successfully re-treated with RTX	31 (12–45)
Aries *et al.* [27]	POL	8 (all GPA), mainly granulomatous	4 × monthly doses 375 mg/m^2	8/8 depleted	Not reported	0/8 became negative; no significant decrease in titre	2/8 (25%) CR, 1/8 (13%) PR, 1/2 with renal vasculitis improved	Not reported	Not reported
Jones *et al.* [8]	Multicentre case series	65 (46 GPA, 10 MPA, 5 CSS, 4 unclassified)	32, 2 × fortnightly doses 1 g; 26, 4 × weekly doses 375 mg/m^2; 7, other regimens	65/65 depleted	Median 13 months (range 6–52)	Significant decrease in titres in all ANCA-positive patients	49/65 (75%) CR, 15/65 (23%) PR	36/65 (55%); majority successfully re-treated with RTX	Relapsing population 11.5 (range 4–37), not stated for non-relapsing population
Stone *et al.* [3], RAVE trial	Multicentre double-blind RCT	99 in RTX treatment group (74 GPA, 24 MPA, 1 unclassified), 51 active renal vasculitis	4 × weekly doses 375 mg/m^2	Majority depleted	At least 6 months (longer f/u required)	47/99 (45%) became negative	63/99 (64%) CR at 6 months, 31/51 (61%) CR in those with renal vasculitis	17/99 (17%) (within 6 months). Re-treatment with RTX not offered	Not stated; insufficient f/u
Jones *et al.* [2], RITUXVAS trial	Multicentre open-label RCT	33 in RTX treatment group (18 GPA, 12 MPA, 3 renal-limited vasculitis), all had renal disease	4 × weekly doses 375 mg/m^2	27/33 (82%) depleted	25/33 (76%) remained depleted at 12 months; timing of repopulation not detailed	33/33 became negative	30/33 (91%) CR, 25/33 (76%) sustained remission (BVAS = 0 for >6 months)	4/33 (12%) (within 12 months)	25/33 (76%) sustained remission at 12 months
This study	Open-label, observational	19 (9 GPA, 10 MPA), 18 had renal involvement (9 given RTX for active nephritis)	Single dose 375 mg/m^2	17/19 (89%) depleted	Median 9.5 months	Mean MPO/PR3 titre decreased from 56 to nadir of 13 at 6 months	15/19 CR (79%), 13/19 (68%) sustained remission (>18weeks), 4/19 (21%) PR	4/19 (21%)	89% probability persistent disease remission at 9 months; median time to relapse/redose 27 months

CR: complete remission; PR: partial remission; RTX: rituximab; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; CSS: Churg–Strass syndrome; POL: prospective open-label; RCT: randomized controlled trial.

rituximab. However, our median duration of follow-up was 11.5 months, which is comparable to the RAVE and RITUXVAS randomized controlled trials and reasonable for a case series.

The majority of patients received rituximab for treatment of relapsed disease. The RAVE trial reported that relapsed patients responded better to rituximab compared with CYC, and this may explain the favourable clinical response achieved with a single dose of rituximab in this study. However, in our cohort, 3 of 5 patients (60%) treated for new presentation of disease achieved sustained CR, compared with 7 of 12 patients (58%) treated for relapsed disease. Therefore our data do not suggest an improved clinical response to rituximab in those patients with relapsed disease. However, due to the small size of our study, it is impossible to make a statistically meaningful comparison between these two groups. Neither the RAVE trial nor this study were appropriately designed or statistically powered to determine whether relapsed disease responds better to rituximab. Future studies will be required to investigate this possible differential response more definitively.

Similarly, it is difficult to compare the clinical response of specific patient subgroups in this cohort (e.g. MPA *vs* GPA) or those with more severe disease manifestations disease (e.g. renal vasculitis or pulmonary haemorrhage) compared with those with less severe disease. A larger study is required to determine whether there is a differential response between these different disease manifestations to rituximab. However, although small, our cohort included a heterogeneous population of patients with AAV, representative of that seen in clinical practice. As no patient in our cohort failed to respond at least partially to a single dose of rituximab, this suggests that our proposed treatment protocol may be effective in treating a wide range of clinical manifestations of AAV in both newly diagnosed and relapsed disease.

The use of a single dose of rituximab, rather than the four- or two-dose regimens, resulted in very significant drug cost savings. Although we acknowledge that our estimates were relatively crude and did not take into account the cost of actually delivering the drug or the impact of the requirement for repeated dosing (which would have increased the cost differential further), we calculated a drug cost savings of >£4500 (US$6312, €4692) per patient if the single-dose regimen is used instead of the most commonly used four-dose regimen. In the case of AAV, the impact of unmeasured excess repeated dosing and relapse on this cost estimate would have been small, as these events were observed at a rate broadly similar to previous reports. Marked savings on rituximab drug costs would therefore be expected if single-dose therapy was adopted for treatment of non-organ-threatening AAV.

Our data suggest that a single dose of rituximab at a dose of 375 mg/m^2 is a reasonable and highly cost-effective induction therapy for AAV. It is highly unlikely that any further randomized trials of rituximab for induction therapy in AAV will be performed. However, trials of maintenance remission using rituximab, or of induction therapy using fully humanized rituximab successors, probably will take place. We propose that these are designed to allow us to answer the question of whether a single low dose is effective.

Rheumatology key messages

- A single 375 mg/m^2 dose of rituximab is effective induction therapy for ANCA-associated vasculitis.
- Induction treatment with a single dose of rituximab saved £4500/patient compared with the 4×375 mg/m^2 regimen.

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