RHEUMATOLOGY

doi:10.1093/rheumatology/keu452
Advance Access publication 3 December 2014

Original article

Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis

Federico Alberici[1,2,3], Rona M. Smith[1,2], Rachel B. Jones[1,2], Darren M. Roberts[1,2], Lisa C. Willcocks[1,2], Afzal Chaudhry[1,2], Kenneth G. C. Smith[1,2,4] and David R. W. Jayne[1,2]

Abstract

Objective. ANCA-associated vasculitis (AAV) is characterized by a chronic relapsing course. Rituximab (RTX) is an effective maintenance treatment; however, the long-term outcomes after its discontinuation are unclear. The aim of this study was to explore the long-term outcomes of AAV patients treated with repeat-dose RTX maintenance therapy.

Methods. AAV patients receiving a RTX treatment protocol consisting of an induction and maintenance phase were included. For initial remission induction, RTX was dosed at 1 g every 2 weeks or 375 mg/m^2 weekly for 4 consecutive weeks and for remission maintenance at 1 g every 6 months for 24 months. At the first RTX administration, ongoing immunosuppressives were withdrawn.

Results. Sixty-nine patients were identified, 67 of whom were failing other therapies. Nine relapsed during the RTX treatment protocol; however, all 69 were in remission at the end of the maintenance phase on a median prednisolone dose of 2.5 mg/day and 9% were receiving additional immunosuppression. During subsequent observation, 28 patients relapsed a median of 34.4 months after the last RTX infusion. Risk factors for relapse were PR3-associated disease ($P = 0.039$), B cell return within 12 months of the last RTX infusion ($P = 0.0038$) and switch from ANCA negativity to positivity ($P = 0.0046$). Two patients died and two developed severe hypogammaglobulinaemia.

Conclusion. This study supports the efficacy and safety of a fixed-interval RTX maintenance regimen in relapsing/refractory AAV. Relapses after discontinuation of maintenance therapy did occur, but at a lower rate than after a single RTX induction course. PR3-associated disease, the switch from ANCA negative to positive and the return of B cells within 12 months of the last RTX administration were risk factors for further relapse.

Key words: anti-neutrophil cytoplasm antibody, granulomatosis with polyangiitis, microscopic polyangiitis, vasculitis, B cells, biologic therapies, maintenance treatment.

CLINICAL SCIENCE

Rheumatology key messages

- Fixed-interval rituximab maintenance therapy appears effective in ANCA-associated vasculitis.
- After rituximab maintenance treatment, relapses are less frequent than after a single rituximab course in ANCA-associated vasculitis.
- B cell return within 12 months and ANCA reversal from negative to positive may predict relapse in ANCA-associated vasculitis patients.

[1]Department of Medicine, University of Cambridge School of Clinical Medicine, [2]Vasculitis and Lupus Service, Addenbrooke's Hospital, Cambridge, UK, [3]Department of Clinical and Experimental Medicine, University of Parma, Italy and [4]Cambridge Institute for Medical Research, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

Submitted 12 May 2014; revised version accepted 29 September 2014

Correspondence to: Federico Alberici, Lupus and Vasculitis Service, Box 57, Cambridge University Hospital, Cambridge CB2 2QQ, UK. E-mail: federico.alberici@gmail.com

Federico Alberici and Rona M. Smith contributed equally to this study.

Introduction

ANCA-associated vasculitides (AAVs), including granulomatosis with polyangiitis and microscopic polyangiitis, are small vessel vasculitides characterized by vasculitic and granulomatous manifestations [1]. ANCA positivity is reported in ~90% of cases [2] and their specificity may be directed against neutrophil PR3 or MPO. Classification has been historically performed according to the clinical phenotype together with ANCA positivity (but not specificity) or histological confirmation [3], although a recent GWAS study has challenged this convention by demonstrating that, from a genetic perspective, AAV is made up of two subgroups best defined by ANCA specificity rather than clinical features [4]. Disease severity ranges from life- or organ-threatening manifestations to milder forms. AAV is characterized, particularly in the PR3-associated group [5], by a chronic relapsing course leading to repeat exposure to augmented immunosuppression culminating in adverse events and damage [6].

Rituximab (RTX), an anti-CD20 monoclonal antibody, is an effective induction treatment in AAV in both newly diagnosed and relapsing patients [7, 8]. The efficacy of repeat dose RTX as maintenance therapy has been demonstrated both retrospectively in relapsing and refractory patients [9, 10] and prospectively by the preliminary results of a recent randomized trial comprising mainly patients with newly diagnosed AAV [11]. However, a number of factors remain unknown, including the ideal duration of maintenance treatment [12], the effect of cumulative RTX dose and whether or not redosing should be at a fixed time interval or driven by rising ANCA titre, B cell count or symptoms. Moreover, the long-term outcome after discontinuation of RTX-based fixed-term maintenance treatment is not known. Here we present the long-term follow-up of a retrospective cohort of AAV patients after 2 years of treatment with fixed-interval repeat-dose RTX maintenance therapy.

Patients and methods

In 2006, a 24-month fixed-interval RTX re-treatment regimen was implemented for patients with relapsing or refractory AAV at the Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge, UK. All patients with a diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis who have completed a RTX maintenance strategy since 2006 are analysed in this cohort. If ANCA was negative at the time of diagnosis, then histological confirmation of AAV was required. This cohort includes 53 patients from a previous report [9]. Patients' clinical and laboratory data were reviewed up to October 2013. In accordance with current UK ethical guidelines, ethical approval was not required because this work includes only retrospective data and all treatment decisions pre-date the collection of data.

Treatment protocol

The RTX treatment protocol included an induction and a maintenance phase. RTX was given at a dose of 1 g twice, 2 weeks apart or 375 mg/m^2 weekly for 4 consecutive weeks as induction therapy and then 1 g every 6 months as maintenance therapy for 24 months overall. For patients perceived to be at high risk of relapse or who had had severe disease flares, the maintenance treatment period was extended beyond 24 months; however, all such patients eventually discontinued RTX maintenance therapy and have been included in this cohort. Patients who had not completed the 24 month RTX treatment protocol (due to insufficient follow-up at the time of data analysis) were not included. Body surface area was calculated using the Mosteller formula [13]. At each RTX administration, all patients received premedication with i.v. hydrocortisone 100 mg, i.v. chlorpheniramine 10 mg and oral paracetamol 1 g before the infusion. Prophylactic trimethoprim–sulphamethoxazole was not routinely administered. At the time of first RTX dose, any pre-existing maintenance immunosuppressive agents were routinely withdrawn and the prednisolone dose was increased according to flare severity; other immunosuppressive treatments (e.g. i.v. CYC or plasma exchange) were considered only for life- or organ-threatening flares. The prednisolone dose was tapered during follow-up, aiming for complete withdrawal or <5 mg/day. Other immunosuppressive agents were not routinely introduced following completion of the RTX treatment protocol and patients were monitored during regular clinical assessment.

Assessments

Disease activity was assessed using the Disease Extent Index (DEI) score [14], the physician assessment of disease activity and the prednisolone dose. Recurrent disease (relapse) at the time of the first RTX infusion was defined as a DEI score $\geqslant 2$ and physician assessment of active disease requiring a therapeutic intervention in addition to an increase in steroid dose. Refractory disease was defined as a DEI score $\geqslant 2$ despite a full course of first-line immunosuppressive and CS treatment. Patients who received RTX for consolidation of remission included those with grumbling disease (low-grade disease activity based on clinical assessment) that did not fulfil the criteria for recurrent or refractory disease, patients unable to taper prednisolone to <15 mg/day and patients for whom steroid-free regimens were strongly advised (e.g. co-existent diabetes, severe osteoporosis or chronic infection). Disease response was assessed every 3–4 months during and after the RTX treatment protocol.

In terms of response to RTX treatment, we defined full remission as a DEI score $\leqslant 2$ with prednisolone dose $\leqslant 10$ mg and physician assessment of full remission and partial remission as a reduction of the DEI score $>50\%$ with physician judgement of partial remission. Relapses were classified as major or minor. Major relapses were those with life- or organ-threatening manifestations that would have historically been managed with CYC; minor relapses were those episodes of disease activity requiring an increase in therapy such as early RTX administration, addition of another immunosuppressive agent, i.v. methylprednisolone or oral prednisolone >20 mg/day.

Severe adverse events (SAEs) were defined as episodes requiring hospitalization, i.v. antibiotic therapy, malignancies or death. Patient follow-up was not censored at the time of the relapse in order to record subsequent SAEs. ANCA positivity required a positive ELISA for PR3 or MPO and B cell depletion with a $CD19^+$ cell count $<0.01 \times 10^9$/l. Hypogammaglobulinaemia was defined by an IgG level <6 g/l for at least 3 consecutive months and subclassified as either moderate (3–5.9 g/l) or severe (<3 g/l).

Statistics

Statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, NY, USA) and GraphPad version 5 (GraphPad Software, La Jolla, CA, USA). Results are expressed as value and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. Changes in variables including DEI, IgG level and prednisolone dose were compared by a related-sample Wilcoxon matched pairs test, paired *t*-test or Friedman test when appropriate. Proportions of patients were compared using a chi-squared, Fisher test or logistic regression. Time to relapse was assessed by Kaplan–Meier survival analysis, and if comparisons between populations were required, the log-rank test was used. *P*-values < 0.05 were considered significant.

Results

Patient characteristics

Sixty-nine patients were followed up for a median of 59.3 months (IQR 44.5–73.3), including a median of 19.9 months of post-relapse follow-up in the relapsing group. The total follow-up was 334.7 patient-years. The baseline characteristics of our cohort are reported in Table 1. Median DEI at the time of first RTX administration was 2.5; 47 of 69 patients (68%) had active disease while 20 of 69 (29%) received RTX for consolidation of disease remission. In the latter group, 16 patients were treated with RTX for low-grade disease activity (due mainly to persistent ENT symptoms); 3 due to an inability to taper the prednisolone dose to <15 mg/day and 1 because of a pulmonary aspergilloma, thus a steroid-free regimen was felt to be safer. In addition, in the subgroup with persistent low-grade disease activity, 5 of 16 patients required a steroid-free maintenance regimen due to significant steroid-related side effects. Two patients (3%) with a new diagnosis who received RTX induction followed by a repeat-dose maintenance course as a first-line therapeutic approach were also included. Sites showing active disease were ENT in 35 patients (57%), lung in 20 (29%), joints in 16 (23%), systemic symptoms in 15 (22%), kidney in 8 (12%), eye in 8 (12%), skin and peripheral nervous system in 5 patients each (7%) and CNS in 4 patients (6%).

Treatment

The median oral prednisolone dose at the first RTX administration was 10 mg/day (IQR 5–15). At study entry, 14 of 69 patients (20%) received other treatments in order to achieve rapid disease control: 8 i.v. methylprednisolone, 6 i.v. CYC, 2 plasma exchange, 1 AZA and 1 MMF. Median RTX treatment protocol length was 24.1 months (IQR 21–25.6), during which a median of five RTX cycles were administered corresponding to a median dose of 6 g (IQR 6–6.5). Seven patients had an overall treatment length >30 months with three treated for >40 months. The median overall dose of RTX per square metre of body surface area was 3154.9 mg (IQR 2743.4–3658.5).

Table 1 Demographic characteristics at the beginning of RTX maintenance treatment

Age, median (IQR), years	52.02 (40.12–62.87)
Sex, male	28/69 (41)
Diagnosis	
GPA	62/69 (90)
MPA	7/69 (10)
Prior disease duration, median (IQR), months	60.2 (20.7–120)
Prior CYC	63/69 (91)
Cumulative dose, median (IQR), g	13.45 (8.25–30)
Prior therapies	
MMF	53/69 (77)
AZA	48/69 (70)
MTX	24/69 (35)
RTX	15/69 (22)
Other[a]	15/69 (22)
IVIG	15/69 (22)
Anti-TNF-α	10/69 (15)
Plasma exchange	8/69 (12)
Alemtuzumab	6/69 (9)
Number of previous immunosuppressives	3 (2–4)
Historical ANCA status	
PR3	51/69 (74)
MPO	10/69 (15)
Indication	
Active disease	47/69 (68)
Consolidation of remission	20/69 (29)
New diagnosis	2/69 (3)
DEI at entry	2.5 (2–4)
ANCA at entry	
PR3	38/69 (55)
MPO	8/69 (12)

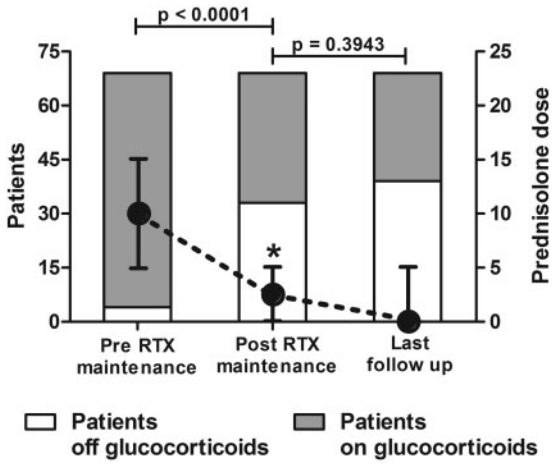
Results are expressed as *n*/*N* (%) unless indicated otherwise. DEI: disease extent index; GPA: granulomatosis with polyangiitis; IQR: interquartile range; MPA: microscopic polyangiitis; RTX: rituximab. [a]Other treatment: deoxyspergualin, LEF, anti-CD18, abatacept, HCQ, tacrolimus.

RTX maintenance treatment outcome

During the RTX maintenance treatment period, nine patients (13%) relapsed a median of 11 months after the first RTX infusion, including two major relapses. These episodes required an increased steroid dose in three, an early unplanned RTX infusion in one and five required the addition of another immunosuppressive agent (MTX in two, IVIG in one, AZA in one and LEF in one). In these

patients, the sites with active disease were the ENT in five, lung and joints in two, CNS in one and peripheral nervous system in one; systemic symptoms were reported by two patients. Despite these disease flares, all 9 patients continued the predetermined RTX treatment protocol and upon completion all 69 patients were in remission; 33 (48%) were not receiving glucocorticoids and 63 of 69 (91%) were not receiving other immunosuppressants. Two patients were receiving replacement IVIG for moderate hypogammaglobulinaemia and recurrent infections, one IVIG treatment for peripheral neuropathy, two immunosuppression following renal transplantation and one AZA started for relapse during the RTX maintenance treatment period. The median prednisolone dose was 2.5 mg/day (IQR 0–5), which was lower compared with the onset of RTX treatment ($P < 0.0001$) (Fig. 1). Fifteen patients (22%) were ANCA positive at the end of the RTX maintenance treatment compared with 46 of 69 (67%) at the beginning ($P < 0.0001$). The median IgG levels remained within normal range, although they decreased from 9.3 g/l (IQR 7.2–10.4) before RTX to 8 g/l (IQR 6–9.2) at the end of the treatment course ($P < 0.0001$) (Fig. 2).

Fig. 1 Glucocorticoid treatment during follow-up



Data include all 69 AAV patients who received RTX induction and maintenance treatment. Shown are the proportion of patients either receiving (grey bars) or not receiving (white bars) glucocorticoids before rituximab (RTX) maintenance treatment, immediately after RTX maintenance treatment and at the last follow-up (median 34.5 months since last RTX administration). The *P*-values reported above the histograms refer to comparison of the different proportion of patients at the different timelines (Fisher's exact test). Median prednisolone dose is represented with dots (median) and whiskers (25th–75th percentiles). Patient follow-up was censored at the time of the relapse considering the steroid dose at the assessment immediately before the relapse. *$P < 0.0001$ compared with the beginning of the RTX treatment protocol (Wilcoxon matched pairs test). AAV: ANCA-associated vasculitis; RTX: rituximab.

Follow-up post-RTX maintenance treatment

Following the completion of the 24 month RTX treatment protocol, all 69 patients were in remission and were therefore included in the post-treatment survey with a median post-treatment follow-up time of 34.5 months (IQR 19.2–47.2). Post-treatment follow-up of at least 6 months was available in 65 of 69 patients 94%).

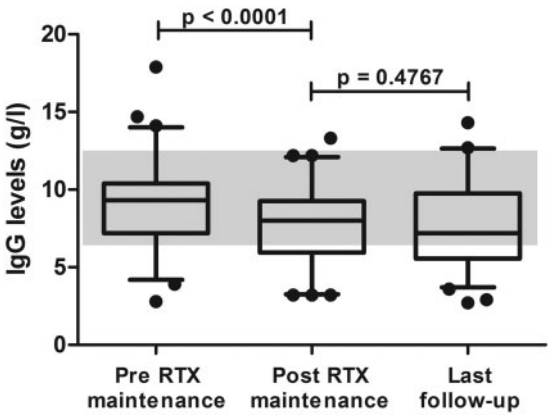
The median post-treatment relapse-free survival of our cohort was 34.4 months (Fig. 3). Twenty-eight patients experienced relapse after a median time of 15.5 months (IQR 12–22.9); 12 (43%) of these disease flares were classified as major. Within 1 year of post-treatment follow-up, 11% of the patients relapsed, 36% within 2 years, 51% within 3 years, 55% within 4 years and 55% within 5 years. Among the relapsing patients, 12 were re-treated with RTX monotherapy, 10 with RTX and corticosteroids and the remaining 6 patients received steroids alone, alemtuzumab, AZA, MMF or CYC. Six months after treatment for relapse, 19 of 28 patients (68%) were in complete remission, 6 (21%) in partial remission and 3 (11%) were showing active disease.

The median follow-up of the 41 non-relapsing patients was 27.3 months (IQR 17.1–45.4). At their last assessment, the median prednisolone dose was 0 mg/day (IQR 0–5), lower than at the end of the RTX treatment protocol ($P = 0.046$). Of these patients, 14 (34%) were ANCA positive and 28 (68%) had experienced B cell return.

Factors predictive of relapse

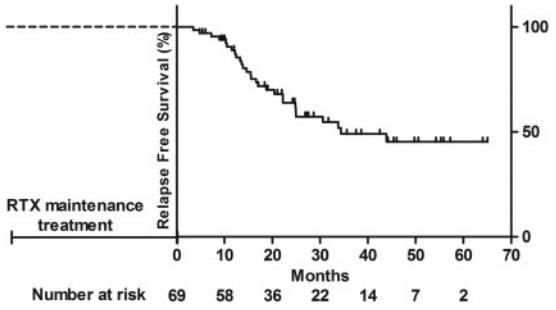
At the time of relapse, 14 of 28 (50%) were ANCA positive and 20 of 28 (71%) had experienced B cell return.

Fig. 2 Change in IgG level during follow-up



Data include all 69 AAV patients who received rituximab induction and maintenance treatment (paired *t*-test). The lines inside the boxes represent the median level, the edge of the boxes the 25th–75th percentiles, the whiskers the 5th–95th percentiles and the dots the outliers. The grey area represents the reference range. AAV: ANCA-associated vasculitis.

FIG. 3 Relapse-free survival after rituximab (RTX) maintenance treatment withdrawal



The dashed line represents the outcome during the RTX maintenance treatment. Although nine patients experienced relapse during this therapeutic course, all of them completed the RTX maintenance treatment and were in remission at the end of it and therefore were included in the subsequent analysis.

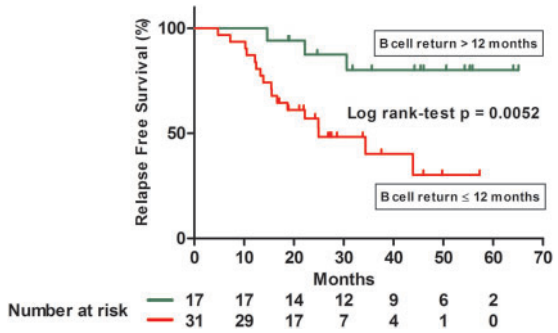
However, compared with the subgroup of non-relapsing patients, neither factor differed significantly ($P = 0.4984$ and $P = 1.000$, respectively). None of the patients' characteristics at the start of the RTX treatment protocol (disease duration, age, CYC cumulative dose, number of previous immunosuppressives, DEI score, sites showing active disease or the presence of granulomatous disease) were associated with the risk of relapse during post-treatment follow-up. Among baseline characteristics (age, sex, DEI score, sites showing active disease and antibody specificity), only PR3 ANCA positivity was associated with risk of relapse after RTX maintenance treatment ($P = 0.039$).

During post-treatment follow-up, among the 54 patients who were ANCA negative at the end of the RTX maintenance treatment period, 13 of 54 (24%) switched from ANCA negative to positive and 10 of 13 (77%) relapsed a median of 1.8 months following the ANCA switch, therefore ANCA switch from negative to positive was associated with an increased risk of relapse [odds ratio (OR) 7.04, $P = 0.0046$]. After stratification of the relapses according to severity, the ANCA switch was associated with the risk of major relapse ($P = 0.039$) but not minor ($P = 0.1655$). When the data were consistently available, patients whose B cells were detectable within 12 months of the last RTX maintenance infusion had a shorter time to relapse than those whose B cells returned after 12 months ($P = 0.0052$) (Fig. 4). Interestingly, two patients included in the analysis experienced B cell return shortly after relapse (4 months in both cases), with the difference between the two groups remaining significant also after their exclusion ($P = 0.00931$).

Severe adverse events

Ninety-three severe adverse events in 36 patients were recorded during the treatment and post-treatment follow-up period. Severe infections were documented in 20 (29%) patients, 57% affecting the lower respiratory tract. Fourteen (20%) patients were hospitalized for

FIG. 4 Relapse-free survival stratified by B cell return within or after 12 months of the last rituximab dose



reasons other than infection, most commonly orthopaedic: hip replacements in two cases and bone fracture in one. Malignancies (lung, bladder, peritoneal and breast) were recorded in four patients. Two patients developed self-limiting late-onset neutropenia: one required hospital admission for a fever and pre-emptive antibiotic treatment, but neither received granulocyte-stimulating agents. Two patients died: one as a result of peritoneal carcinoma and one of unknown cause 55 months after the last RTX infusion.

Twenty-eight (41%) patients developed IgG hypogammaglobulinaemia at some point during follow-up, with severe hypogammaglobulinaemia recorded in two (7%). Two patients with moderate hypogammaglobulinaemia required IVIG replacement for recurrent infections.

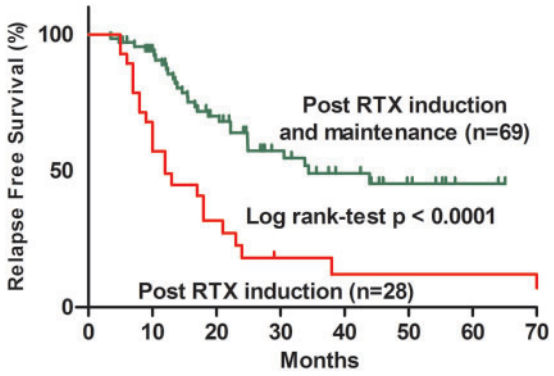
Discussion

AAV is characterized by a chronic relapsing course. Relapse leads to increased immunosuppressive exposure and consequent toxicity. Two randomized controlled trials have shown RTX to be an effective induction treatment in patients with both newly diagnosed and relapsing disease [7, 8]. However, the effect of a single course of RTX is not sustained, with 50% of the patients relapsing within 1 year, with a higher risk associated with PR3 ANCA positivity [9, 15].

Preliminary results suggest that repeat-dose RTX is effective as a maintenance therapy in AAV [9–11]. However, the optimal treatment duration and RTX dose remain unclear [12] and it is still debated whether to re-treat at a fixed time interval or on the basis of B cell count, ANCA titre or disease symptoms. Moreover, the identification of prognostic factors able to identify patients more likely to relapse on cessation of RTX treatment is still an area of unmet need.

In this retrospective study, we found that fixed-interval repeat-dose RTX was an effective maintenance strategy, both in terms of disease control, with only 13% of patients experiencing a relapse during the treatment period, and also in enabling steroid taper or withdrawal. Current evidence suggests that maintenance treatment in AAV should be continued for 18–24 months [16–18].

Fig. 5 Relapse-free survival in two cohorts of relapsing ANCA-associated vasculitis patients



The green line represents patients treated with rituximab (RTX) induction and maintenance treatment and the red line patients treated only with RTX induction (log-rank test).

However, despite successful remission induction, the risk of relapse is high (35%) with standard maintenance treatment with first-line agents (AZA/MTX), especially after cessation of immunosuppressive medication [19]. In 2006 we implemented a 2 year repeat-dose RTX maintenance regimen trying to find equipoise between the guidelines for duration of maintenance therapy and the debated long-term safety profile of repeat RTX dosing. Following cessation of this 2 year fixed-interval RTX maintenance treatment, we observed further relapses in 28 of 69 patients, with a median post-treatment relapse-free survival of 34.4 months. This median relapse-free survival was longer than that observed in our own refractory/relapsing patients historically treated with a single RTX course (12 months) (Fig. 5) [9].

In our population, relapses started to occur as early as 6 months after the last RTX infusion, but were more common between months 10 and 24. The majority of the relapsing patients were successfully re-treated with further RTX. These data suggest that RTX maintenance treatment may induce long-lasting remission of >24 months in 50% of patients, while for the remainder it may only be able to keep the disease inactive while ongoing dosing is employed. However, despite the long follow-up of our population, the number of patients at risk after the last recorded event at month 44 was small (12 patients), suggesting caution in the interpretation of these results.

The identification of factors predictive of relapse is necessary to pre-emptively identify the group likely to relapse after maintenance treatment. Several biomarkers and single nucleotide polymorphisms have been proposed, as well as the B cell phenotype, as potential prognostic factors in patients receiving RTX [20–22]: a memory $CD27^+$ B cell phenotype picture has been associated with relapse in SLE, while a decrease in regulatory $CD5^+$ B cells has been associated with relapses in AAV [23, 24]. However, for all of these potential biomarkers, validation is still required, and their use at the moment is limited to the field of research, with their application to clinical practice still somewhat distant.

We confirm in our cohort the higher risk of relapse in the PR3 ANCA-associated group. Notably, 78% of the patients were ANCA negative by the end of RTX maintenance. During the follow-up phase, a switch from ANCA negativity to positivity conferred a 7-fold increased risk of relapse, with a very short median time to flare (1.8 months), suggesting that very close follow-up is required to pre-emptively identify patients at risk of relapse on this basis. ANCA recurrence was associated with the risk of major relapse. In 90% of these patients, B cells had returned prior to ANCA recurrence, suggesting a consequential relationship between these events, with B cells producing ANCA as one of their many functions [25]. In addition, patients experiencing B cell return within 12 months of the last RTX dose relapsed significantly earlier than those whose B cells returned after 12 months. Depletion of tissue resident B cells may not necessarily be as effective as circulating B cells [26], and early repopulation might represent incomplete B cell depletion in tissues despite repeat dosing of RTX [27].

At the time of this study, safety concerns remained regarding the development of acquired immunodeficiency following long courses of repeated RTX treatment and therefore we decided to consider extending treatment beyond 2 years only in patients perceived to be at very high risk of relapse or in patients who had experienced life- or major organ-threatening manifestations previously. Reassuringly, in the reported cohort, the rate of severe adverse events was relatively low and in keeping with other relapsing/refractory AAV cohorts treated with different therapeutic approaches in our centre [28–30]. We should take into account that the relapsing and refractory nature of disease in this population, the prior high immunosuppressive burden and the very long follow-up may have influenced our SAE rate. Hypogammaglobulinaemia was common, occurring in 41% of patients at some point during follow-up, but was severe in only two patients. In addition, IVIG replacement was required in the context of recurrent infections in two patients with moderately low IgG levels, suggesting that IgG hypogammaglobulinaemia is only one component among the possible risk factors for recurrent infection in this group of patients. During the therapeutic course, the IgG levels decreased significantly, although the median value in the overall population remained within the normal range. Once RTX treatment was complete, IgG levels stabilized.

In conclusion, our results suggest that a fixed-interval RTX maintenance regimen in relapsing/refractory AAV effectively prevents relapse. Withdrawal of RTX after 2 years is possible, with 50% of patients remaining in long-lasting remission and 50% relapsing over 3 years; the relapse rate was significantly lower than that after a single RTX course. The relapse risk was higher in patients with B cell return within 12 months of the last RTX infusion, return of ANCA positivity and PR3-associated disease. In order to allow early identification of major relapses in patients not

on immunosuppression, we recommend monitoring B cells and ANCA after RTX withdrawal. Better biomarkers are required to identify patients at relapse risk after RTX maintenance therapy withdrawal.

Acknowledgements

F.A. has been supported by a European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) long-term fellowship between September 2012 and September 2013. D.M.R. was recipient of a fellowship funded by the University of Cambridge, Royal Australasian College of Physicians and Amgen (Australia) in 2012.

Funding: This study was supported by the National Institute of Health Research Cambridge Biomedical Research Centre.

Disclosure statement: R.M.S. has received lecture fees from Roche. R.B.J. undertook a part-time academic secondment to GlaxoSmithKline from 2011 to 2013. D.R.W.J. has received lecture fees and a research grant from Roche/Genentech. All other authors have declared no conflicts of interest.

References

1 Jennette JC, Falk RJ, Andrassy K *et al*. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187–92.

2 Mahr A, Katsahian S, Varet H *et al*. Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis 2013;72:1003–10.

3 Watts R, Lane S, Hanslik T *et al*. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007; 66:222–7.

4 Lyons PA, Rayner TF, Trivedi S *et al*. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012;367:214–23.

5 Walsh M, Flossmann O, Berden A *et al*. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:542–8.

6 Robson J, Doll H, Suppiah R *et al*. Damage in the anca-associated vasculitides: long-term data from the European Vasculitis Study group (EUVAS) therapeutic trials. Ann Rheum Dis 2013, Nov 15. doi: 10.1136/annrheumdis-2013-203927 [Epub ahead of print].

7 Jones RB, Tervaert JW, Hauser T *et al*. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.

8 Stone JH, Merkel PA, Spiera R *et al*. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.

9 Smith RM, Jones RB, Guerry MJ *et al*. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012; 64:3760–9.

10 Cartin-Ceba R, Golbin JM, Keogh KA *et al*. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770–8.

11 Terrier B. RTX versus azathioprine for maintenance in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (MAINRITSAN): follow-up at 39 months. 2013 Annual Meeting Abstract Arthritis Rheum 2013;65(suppl 10)Abstract 2783.

12 Pendergraft WF 3rd, Cortazar FB, Wenger J *et al*. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. Clin J Am Soc Nephrol 2014;9:736–44.

13 Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.

14 de Groot K, Gross WL, Herlyn K, Reinhold-Keller E. Development and validation of a disease extent index for Wegener's granulomatosis. Clin Nephrol 2001;55:31–8.

15 Specks U, Merkel PA, Seo P *et al*. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.

16 Jayne D, Rasmussen N, Andrassy K *et al*. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36–44.

17 Mukhtyar C, Guillevin L, Cid MC *et al*. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310–7.

18 Lapraik C, Watts R, Bacon P *et al*. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology 2007;46:1615–6.

19 Pagnoux C, Mahr A, Hamidou MA *et al*. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790–803.

20 Owczarczyk K, Lal P, Abbas AR *et al*. A plasmablast biomarker for nonresponse to antibody therapy to CD20 in rheumatoid arthritis. Sci Transl Med 2011;3:101ra92.

21 Ruyssen-Witrand A, Rouanet S, Combe B *et al*. Fcγ receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab. Ann Rheum Dis 2012;71:875–7.

22 Robledo G, Davila-Fajardo CL, Marquez A *et al*. Association between -174 interleukin-6 gene polymorphism and biological response to rituximab in several systemic autoimmune diseases. DNA Cell Biol 2012;31: 1486–91.

23 Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:613–20.

24 Bunch DO, McGregor JG, Khandoobhai NB *et al*. Decreased $CD5^+$ B cells in active ANCA vasculitis and relapse after rituximab. Clin J Am Soc Nephrol 2013;8: 382–91.

25 Alberici F, Jayne DR. Impact of rituximab trials on the treatment of ANCA-associated vasculitis. Nephrol Dial Transplant 2014;29:1151–9.

26 Gong Q, Ou Q, Ye S *et al*. Importance of cellular microenvironment and circulatory dynamics in B cell immunotherapy. J Immunol 2005;174:817–26.

27 Ferraro AJ, Smith SW, Neil D, Savage CO. Relapsed Wegener's granulomatosis after rituximab therapy—B cells are present in new pathological lesions despite persistent 'depletion' of peripheral blood. Nephrol Dial Transplant 2008;23:3030–2.

28 Koukoulaki M, Jayne DR. Mycophenolate mofetil in anti-neutrophil cytoplasm antibodies-associated systemic vasculitis. Nephron Clinical Practice 2006;102:c100–7.

29 Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). Ann Rheum Dis 2008;67:1322–7.

30 Flossmann O, Baslund B, Bruchfeld A *et al*. Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. Ann Rheum Dis 2009;68:1125–30.

Clinical vignette

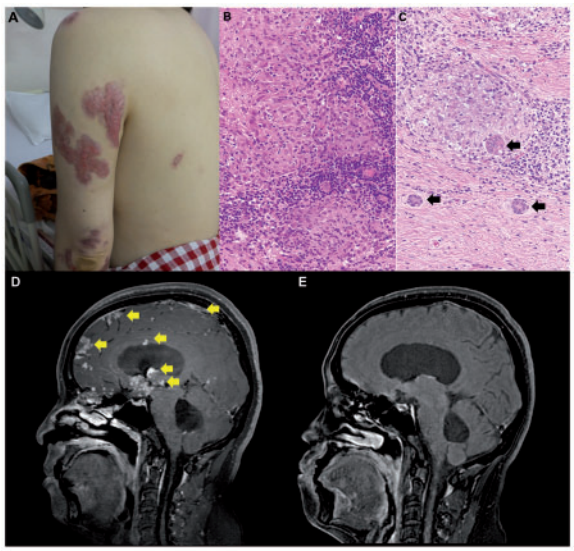
Rheumatology 2015;54:1160
doi:10.1093/rheumatology/kev109
Advance Access publication 8 May 2015

A case of relapsing neurosarcoidosis with brain nodules and hydrocephalus successfully treated by corticosteroid and methotrexate

Sir, A 45-year-old woman presented with a 2-month history of progressive cognitive dysfunction and red plaques on her extremities (Fig. 1A). She was diagnosed as having neurosarcoidosis (NS) by brain biopsy (Fig. 1B) 12 years before presenting and had been prescribed prednisolone 5 mg/day for the past 6 years. Laboratory examinations showed an increased serum angiotensin-converting enzyme level of 29.3 IU/l. Neither infection nor malignancy was detected. Skin biopsy of plaques revealed non-caseating epithelioid cell granuloma with giant cells (Fig. 1C, arrows), like the previous brain pathology. Contrast-enhanced MRI of the brain showed numerous high-intensity foci on the brain surface and hydrocephalus (Fig. 1D, arrows). Queckenstedt's sign was positive. She was diagnosed as a relapse of NS. She underwent methylprednisolone pulse therapy, followed by prednisolone 50 mg/day and MTX 12 mg/week. After 4 weeks from the initiation of therapy, the high-intensity foci disappeared (Fig. 1E), Queckenstedt's sign was negative and her cognitive function recovered.

NS develops in 5–13% of sarcoidosis patients [1]. Diagnosis of NS is challenging because of the variety of its clinical presentation and the difficulty of histological confirmation. Although hydrocephalus is a rare manifestation (5–7% of NS patients), it has a poor long-term prognosis [2]. In our case, multiple brain nodules and cognitive dysfunction improved remarkably, while hydrocephalus was unchanged after treatment.

Fig. 1 Neurosarcoidosis with brain nodules and hydrocephalus accompanied with skin plaques successfully treated by immunosuppressive therapy



(**A**) Red plaques on the extremities on admission. (**B**) Brain biopsy showing non-caseating epithelioid cell granulomas. (**C**) Skin biopsy of plaques showing non-caseating epithelioid cell granuloma with giant cells (indicated by arrows). (**D**) Contrast-enhanced MRI of the brain before treatment showing multiple high-intensity foci (indicated by arrows) and hydrocephalus. (**E**) Contrast-enhanced MRI of the brain 4 weeks after initiation of treatment showing disappearance of the high-intensity foci.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

Izumi Kurata[1], Hiroto Tsuboi[1], Hidenori Takahashi[1], Mizuki Yagishita[1], Saori Abe[1], Hiroshi Ebe[1], Hiroyuki Takahashi[1], Hiromitsu Asashima[1], Tomoya Hirota[1], Shinya Hagiwara[1], Naoto Umeda[1], Yuya Kondo[1], Hiroshi Ogishima[1], Takeshi Suzuki[1], Isao Matsumoto[1] and Takayuki Sumida[1]

[1]Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

Correspondence to: Takayuki Sumida, Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba-city, Ibaraki 305-8575, Japan.
E-mail: tsumida@md.tsukuba.ac.jp

References

1 Nozaki K, Judson MA. Neurosarcoidosis. Curr Treat Options Neurol 2013;15:492–504.

2 Brouwer MC, de Gans J, Willemse RB, van de Beek D. Neurological picture. Sarcoidosis presenting with hydrocephalus. J Neurol Neurosurg Psychiatry 2009;80:550–1.