

Original Article

Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients

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Abstract

Background. B-cell depletion with rituximab, a chimeric anti-CD20 antibody, is a novel treatment for refractory and relapsing ANCA-associated small-vessel vasculitis. Data are limited and most reports describe single patients or small numbers of patients followed prospectively.

Methods. We report a single-centre experience with 15 patients who received rituximab for refractory or relapsing ANCA-associated vasculitis. All patients had been treated with corticosteroids and cyclophosphamide and a variety of other second-line immunosuppressive agents. None of the patients had evidence of infection and received four infusions of 375 mg/m² of rituximab. Disease activity was assessed in accordance with the Birmingham Vasculitis Activity Score (BVAS). BVAS, C-reactive protein and ANCA titres were recorded at baseline and during follow-up.

Results. B-cell depletion was achieved in all patients. Partial or complete remission was seen in 14 of 15 patients with a significant decline in BVAS compared to baseline ($P < 0.007$). One patient with granulomatous ANCA-associated vasculitis did not respond to rituximab. There were no side effects during rituximab infusion. Transient leucopenia was observed in two patients. One patient with bronchial stenosis died of pneumonia 5.5 months after the initiation of rituximab treatment. One initially anti-HBc-positive/HBsAg-negative patient experienced a reactivation of hepatitis B, developed end-stage renal failure and died after refusal of dialysis.

Conclusions. We report the largest case series of rituximab use for ANCA-associated vasculitis so far. Our data support that the drug is capable of inducing partial or complete remission in refractory or relapsing patients. Leucopenia and infectious complications remain a matter of concern.

Keywords: ANCA-associated vasculitis; B-cell depletion; rituximab

Introduction

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen [1]. CD20 is found on the surface of normal and malignant B lymphocytes but not on plasma cells. Rituximab was first licensed for the treatment of B-cell lymphoma and achieves depletion of CD20 positive B cells for a period of 6–9 months [2]. B cells rapidly become undetectable in the peripheral blood after a successful rituximab infusion, followed by a gradual reconstitution after 6 months. The notion that B cells might be critical to the development of autoimmune disease led to the extension of the use of B-cell depletion to a variety of diseases, such as rheumatoid arthritis [3] and lupus [4].

The role of B lymphocytes in systemic vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) is poorly understood. Renewed interest in these cells, however, was sparked by proof that ANCA have a direct pathogenic role [5] and by demonstration of ANCA-producing B lymphocytes in peripheral blood of vasculitis patients [6]. Accordingly, rituximab has been used in ANCA-associated vasculitis although most reports describe single patients or small series of patients. Most of these reports have reported a favourable outcome with remarkably few side effects, but lack of efficacy in refractory granulomatous disease has also been described [7]. The largest series of patients reported included 11 patients. More recently, infectious complications, such as reactivation of hepatitis B [8] or progressive multifocal leucoencephalopathy [9], have been described as rare complications in association with rituximab use.

We have been using rituximab in patients with ANCA-associated vasculitis since 2004. Here, we report

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single-centre experience in 15 patients with refractory or relapsing ANCA-associated vasculitis. We report clinical data, pre-treatment and side effects as well as response to treatment, outcomes and follow-up in what is currently the largest case series of patients with ANCA-associated vasculitis treated with rituximab.

Patients and treatment protocol

Between March 2004 and May 2007, 15 patients with ANCA-associated vasculitis were treated with rituximab (8 males, 7 females, age 19–73 years, median 45 years) (Table 1). Fourteen of those showed a relapsing course of the disease despite intensive immunosuppression (median number of relapses 2, range 1–5) and one patient had developed cyclophosphamide intolerance. Thirteen patients had granulomatous ANCA-associated vasculitis (Wegener's granulomatosis). One patient had microscopic polyangiitis and one patient had the Churg-Strauss syndrome. Disease activity was assessed in accordance with the original Birmingham Vasculitis Activity Score (BVAS) [10], but every active manifestation was scored. All patients had active, severe disease with a median BVAS 12 (range 6–21) at baseline as well as an increase in disease activity prior to rituximab therapy. Organ involvement which leads to rituximab treatment is shown in Figure 1. Five patients had renal activity defined as either red blood cell casts or new microhaematuria with >5% acanthocytes in spot urine with or without increased proteinuria and/or an increase in creatinine of >20%. Two patients were already on maintenance dialysis for end-stage renal failure, one due to renal vasculitis. The median serum creatinine in those with renal disease but without end-stage renal failure was 98.5 $\mu\text{mol/l}$ (range 57–376 $\mu\text{mol/l}$). Three patients had pulmonary involvement, nine had granulomatous disease of the upper respiratory tract, one had cutaneous vasculitis, one had vasculitis of the central nervous system, one had disease of the peripheral nervous system and four had eye involvement. Six patients had arthralgias and eight had constitutional symptoms and two patients each had gastrointestinal vasculitis and cardiac involvement. Eleven patients presented with a positive c-ANCA (all anti-proteinase 3-ANCA), three patients with a positive p-ANCA (all anti-myeloperoxidase-ANCA) and one patient was ANCA negative. The median C-reactive protein value was 10 mg/l (range 1–228 mg/l) while all patients lacked evidence of bacterial or viral infection. All patients had already received standard treatment for induction (cyclophosphamide and corticosteroids) and maintenance of remission (corticosteroids and either azathioprine, mycophenolate mofetil or methotrexate) as well as a variety of second-line or rescue modalities, such as plasma exchange, immunoglobulins, deoxyspergualin, cyclosporine or TNF blockade (Figure 2). The median dose of prednisolone at the time of rituximab infusion, at the time of remission and at the last follow-up was 20 mg (range 8.75–80 mg), 10 mg (range 5–50 mg) and 7.5 mg (range 3.75–9 mg), respectively.

All patients gave informed consent to the off-label use of rituximab. The protocol included four weekly doses of 375 mg/m² rituximab (MabTheraTM, Roche, Grenzach-Wyhlen, Germany). Supportive treatment included 50 mg

ranitidine, 2 mg clemastine and 100 mg prednisolone intravenously prior to the administration of rituximab. B-cell depletion was confirmed by flow cytometry (less than one CD19⁺ cell per microlitre). Following rituximab infusions, all patients received prednisolone 0.5–1 mg/kg/day, which was tapered in the following weeks. Concomitant to prednisolone therapy, six patients continued to receive azathioprine or mycophenolate mofetil, one patient continued to receive cyclophosphamide and one patient remained on cyclosporine during rituximab use. Three patients continued to receive trimethoprim/sulfamethoxazole, infliximab or methotrexate, respectively.

All patients were seen for follow-up. Clinical status and CRP and ANCA titres were obtained as well as serum creatinine, liver function tests and differential blood count. Disease activity was assessed by BVAS and partial remission was defined as a reduction of BVAS to at least 50% of their baseline values. Complete remission was defined as a BVAS of 0. Side effects during administration of rituximab and during follow-up were also recorded. Statistical analysis was performed by using the non-parametric Mann-Whitney *U*-test. Data are presented as median with interquartile ranges. Differences were considered significant if $P < 0.05$.

Results

No immediate side effects were observed during infusion of rituximab. B-cell depletion was achieved in all patients.

A total of 267 patient-months of follow-up after treatment with rituximab were completed (median 15 months, range 3–39 months). BVAS at baseline confirmed active disease (median 12, range 6–21). Complete remission was achieved in six patients and partial remission was achieved in eight patients. The median time to remission was 4 months (range 6 weeks to 6 months). Complete renal remission was achieved in all patients with renal involvement who had not been dialysis dependent. Renal remission in non-dialysis patients was defined as no red blood cell casts and no more than three to five red blood cells per high-power field (400 \times magnification), stable or improving renal function and stable or improving proteinuria. One patient with severe involvement of the central nervous system also achieved rapid improvement and total regression of symptoms (Figure 3). BVAS declined significantly to a median of 2 (range 0–12, $P < 0.007$ when compared to baseline, Figure 4, Table 1). One patient, a 32-year-old female with c-ANCA-associated vasculitis involving the upper respiratory tract and eyes, did not respond to rituximab treatment. She had previously received treatment with corticosteroids, methotrexate and intravenous as well as oral cyclophosphamide. Following failure of rituximab, she received infliximab as well as mycophenolate mofetil and corticosteroids and eventually achieved partial remission.

ANCA titres decreased in all patients except the one patient with granulomatous disease who did not respond to rituximab treatment (Figure 5). Median CRP values declined from 10 mg/l to 6 mg/l, but the decline failed to achieve statistical significance.

Table 1. Clinical data, pre-treatment and outcomes

	Age/gender/ disease	Disease duration prior to RTX (month)	Treatment prior to RTX	Prednisolone dosage at time of RTX (mg/day)	BVAS score prior to RTX	Relapses prior to RTX	BVAS score after RTX	Follow-up after RTX (month)	ANCA-titre at last follow-up	Lymphocytes [% of leucocytes] at last follow-up	Status after RTX	Comment
1	19/f/GAV	44	CP, P, PE, IG	40	21	2	0	39	1:16	9.8	Full remission	–
2	50/m/GAV	421	CP, P, MTX, CO, AZA, MMF	12.5	10	2	2	18	Negative	8.1	Partial remission	–
3	67/m/GAV	234	CP, P, D, AT, CI, AZA	8.75	20	5	5	5	Negative	n.d.	Partial remission	Leucopenia; death due to post-stenotic pneumonia
4	73/m/GAV	43	CP, P, CO, MMF, AZA, DAP	10	15	3	4	16	Negative	10.4	Partial remission	Relapse and successful rituximab re-treatment
5	47 f/GAV	85	CP, P, MTX, AT	40	12	4	1	28	Negative	9.0	Partial remission	–
6	32/f/GAV	131	CP, P, MTX	40	13	3	12	28	Negative	5.9	Failed	–
7	28/m/GAV	17	CP, P, MTX, CO	80	12	3	2	30	1:64	24.	Partial remission	–
8	45/f/GAV	50	CP, P, AZA, PE	20	16	2	0	34	1:32	10.0	Full remission	Relapse and successful rituximab re-treatment
9	73/m/GAV	08	CP, P, AZA	40	7	1	2	15	Negative	2.	Partial remission	Hepatitis B reactivation; death after refusal of dialysis
10	36/m/MPA	26	CP, P, AZA	60	15	2	0	14	1:64	7	Full remission	–
11	72/f/CSS	115	CP, P, AZA, CO	40	9	4	3	10	Negative	7	Partial remission	Relapse with cutaneous vasculitis
12	30/f/GAV	145	CP, P, CO, MMF	20	11	2	0	03	Negative	9.5	Full remission	Leucopenia probably due to metamazole
13	40/m/GAV	57	CP, P, AZA, CI, MMF	16	8	4	0	11	1:4	7.0	Full remission	–
14	70/m/GAV	14	CP, P	12.5	6	1	2	08	1:16	11.3	Partial remission	–
15	39/f/GAV	140	CP, P, AZA, CO, MTX, IG	7.5	7	2	0	08	Negative	18.9	Full remission	–

AT = anti TNF biologicals (infliximab or etanercept), AZA = azathioprine, CP = cyclophosphamide, CI = cyclosporine, CO = Trimethoprim/sulphamethoxazole, CSS = Churg-Strauss syndrome, DAP = dapsone, D = deoxyspergualin, GAV = granulomatous ANCA-associated vasculitis, IG = immunoglobulins, MMF = mycophenolate mofetil, MPA = microscopic polyangiitis, MTX = methotrexate, P = prednisolone, PE = plasma exchange; n.d. = not detected.

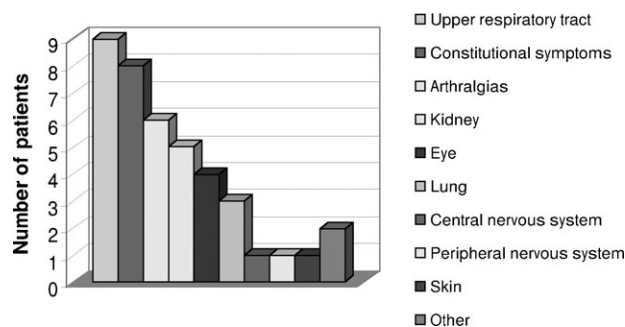


Fig. 1. Organ involvement prior to rituximab treatment.

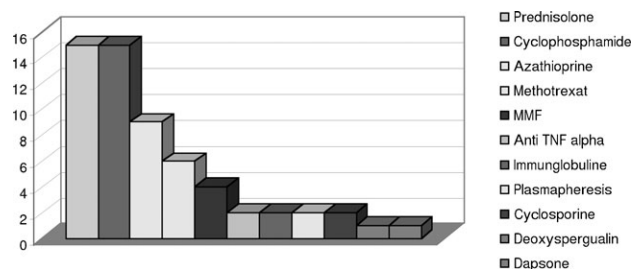


Fig. 2. Immunosuppressive treatment prior to rituximab treatment.

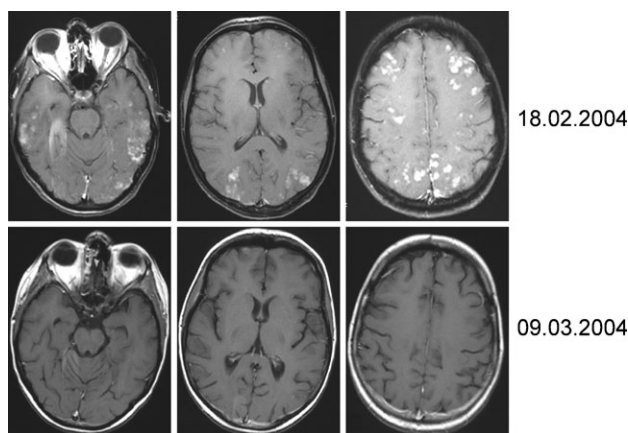


Fig. 3. MRT scan before and about 3 weeks after rituximab treatment in a young woman with central nervous system involvement.

Three patients relapsed. Two of those relapses occurring at 11 and 14 months after initiation of rituximab treatment were re-treated successfully with rituximab. The third patient sustained a cutaneous relapse 7 months after rituximab treatment, necessitating corticosteroid treatment. ANCA-titres for all three patients did not change before/or with the relapse and two patients remained ANCA negative.

During treatment, transient leucopenia was observed in two patients 2 and 11 weeks, respectively, after the initiation of rituximab treatment (Table 2). In one of these two patients, leucopenia (1300/ μ l leucocytes, neutrophils < 100/ μ l) was later attributed to daily use of metamizole, a peripheral analgesic capable of causing bone marrow depression and concurrent medication with mycophenolate mofetil; white blood cell counts normalized after both were stopped. In the second patient, leucopenia (2500 leucocytes/ μ l with 1200/ μ l neutrophils and 600/ μ l

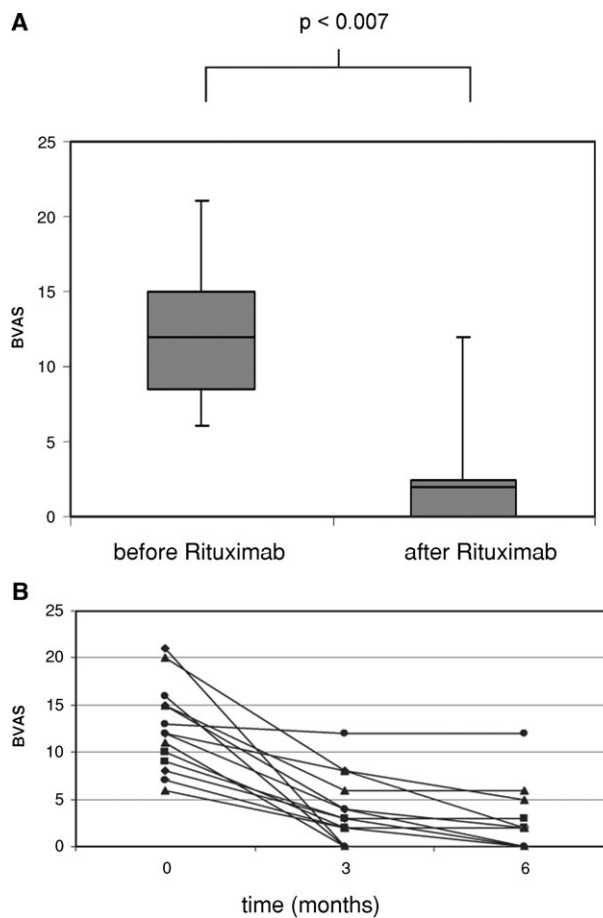


Fig. 4. BVAS before and after rituximab treatment. (A) Box plot with upper and lower quartiles. Solid lines denote medians and whiskers denote ranges. (B) Individual BVAS before and after rituximab treatment.

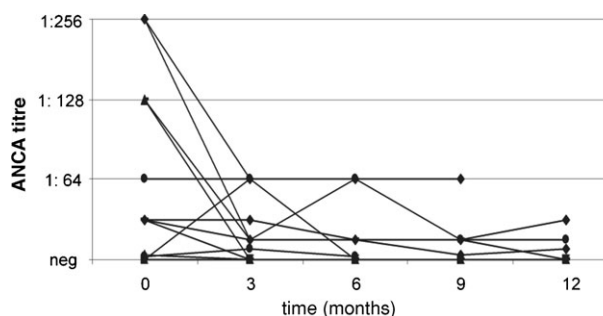


Fig. 5. ANCA titres before and after rituximab treatment.

lymphocytes) was believed to be due to concomitant treatment with trimethoprim/sulfamethoxazole and white blood counts normalized after the drug had been stopped.

Two patients died (see Table 2). One patient with severe pre-existing bronchial stenosis due to granulomatous ANCA-associated vasculitis died of pneumonia in another hospital 5.5 months after initiation of rituximab treatment despite of clinical improvement of the vasculitis. General conditions, dyspnoea and tracheal lesions improved. A transbronchial biopsy showed no evidence of granulomatous inflammation or vasculitis after rituximab treatment. At the time of death, the

Table 2. Case descriptions

Patients with leucopenia	Timepoint after rituximab (weeks)	Leucocyte count (cells/ μ l) (4400–11 300/ μ l)	Neutrocyte count (cells/ μ l) (1200–8000/ μ l)	Lymphocyte count (cells/ μ l) (1500–4000/ μ l)
(a)				
Patient 3	2	2500	1200	600
Patient 12	11	1300	<100	900
Patients who deceased	Ig G levels (7–16 g/l) before/after rituximab	Ig A levels (0.7–4 g/l) before/after rituximab	Ig M levels (0.4–2.3 g/l) before/after rituximab	Treatment
(b)				
Patient 3	5.29/4.76	4.32/1.79	1.06/0.59	2 \times 175 mg/day cyclosporine A and alternating 10 mg/day and 7.5 mg/day prednisolone
Patient 9	11.40/7.71	2.28/1.88	0.89/0.74	125 mg/day azathioprine and 10 mg/day prednisolone

patients received 2 \times 175 mg/day cyclosporine A and alternating 10 mg/day and 7.5 mg/day prednisolone. An autopsy was not performed.

Another patient who was anti-HBc-positive but HBsAg-negative at the time of initiation of rituximab treatment presented with elevated liver function tests 11 months after initiation of rituximab treatment. Viral serology revealed HBsAg positivity and high levels of HBV (hepatitis B virus)-DNA ($>110 \times 10^6$ IU/ml). Analysis of stored sera with a highly sensitive Taq-Man PCR (Roche Cobas TaqMan, Detection limit 6 IU/ml) showed low but positive levels of HBV-DNA (1650 IU/ml) 4 months earlier, when HBs antigen had been undetectable, antiHbc was positive and liver function tests had been normal. He received 125 mg/day azathioprine and 10 mg/day prednisolone. The patient deteriorated clinically, developed end-stage renal failure and died after refusal of dialysis despite comprehensive counselling of the patient and his relatives. An autopsy was not performed.

Discussion

There is increasing evidence that B lymphocytes play a crucial role during the pathogenesis of ANCA-associated vasculitis. The direct pathogenic role of ANCA has been shown in animal models [5] and subsequent studies were able to demonstrate ANCA-producing lymphocytes in peripheral blood [6] and granulomatous lesions [11]. These studies and the recognition of self-reinforcing interactions between T [12] and B cells as a crucial event in autoimmune disease [13] have rekindled the interest in B lymphocytes in vasculitis [14].

Rituximab [1], a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen, was originally approved by the Food and Drug Administration (FDA) for the treatment of lymphoma [2]. It has now been used in a variety of autoimmune diseases, such as rheumatoid arthritis [3] and lupus [4]. In Europe, it is currently licensed for the treatment of lymphoma and rheumatoid arthritis. Interestingly, the mode of action by which rituximab ameliorates autoimmune disease is not

entirely clear. Plasma cells, which are traditionally held responsible for the synthesis of auto-antibodies, do not harbour the CD20 antigen. Others have attempted alternative explanations, such as the immune complex decoy hypothesis [15]. According to this concept, binding of rituximab molecules to B cells generates decoy cellular immune complexes. These decoy complexes attract Fc gamma receptor-expressing T cells and thereby downregulate the autoimmune response elsewhere.

Several smaller studies have explored the use of rituximab in ANCA-associated vasculitis and a total of just over 50 patients have been treated to this date. Most studies have reported good efficacy with remarkably few side effects [16]. A very recent report described the successful use of rituximab in post-transplant relapse of ANCA-associated vasculitis [17]. In our study, 14 out of 15 patients achieved partial or complete remission. Our patients were severely ill at presentation as evidenced by a median BVAS of 12; in addition, they had received considerable pre-treatment. Finally, five patients had renal activity and two were on maintenance dialysis.

Our data add further proof to the impression that rituximab is capable of inducing remission in a majority of these difficult patients. Relapses have been described after rituximab use but these have been re-treated with rituximab, with good success [16]. We, too, re-treated two relapses with rituximab, again with good success. The use of rituximab re-treatment in this setting remains ill defined. Some authors have described the use of the drug after a rise in ANCA titres and after B-cell restoration without clinical disease activity whereas others would only re-treat with rituximab when clinical signs of relapse become apparent. Finally, the long-term effects of repeated rituximab treatment are unclear. Further studies are clearly needed to define the role of rituximab re-treatment.

Whereas a study of 11 patients with rituximab treatment reported success in all patients [18], one report has voiced concern about the efficacy of rituximab in ANCA-associated vasculitis, describing treatment failure in granulomatous disease [7]. We, too, saw failure of rituximab in one patient with granulomatous disease while others have described good efficacy in granulomatous disease [19]. It

should not be forgotten that cases of treatment failure may not be published and hence introduce bias in the interpretation. It has been speculated that lack of efficacy is due to survival of long-lived autoreactive plasma cells, which do not harbour the CD20 antigen, but this assumption remains unproven [20]. In summary, it is not quite clear whether different manifestations of the disease show a differential response to rituximab.

With 7 years of post-marketing surveillance experience and >370 000 patient exposures, the safety profile of rituximab is well defined [21]. A number of side effects have been reported during rituximab use. These include infusion reactions, which were not observed in our study, presumably due to comprehensive pre-medication with ranitidine, clemastine and prednisolone. Haematological events have also been reported and we observed two cases of transient leucopenia although these patients were also receiving other drugs that cause leucopenia. Rituximab-associated interstitial lung disease is rare but responds well to corticosteroids [22]. Cytokine storm has been reported as a rare but potentially fatal complication in a patient with relapsed acute lymphatic leukaemia [23], but it is difficult to attribute this to the drug itself since tumour lysis cannot be excluded.

Infectious complications have been reported in a number of cases [8,24–27]. One of our patients died of pneumonia 5.5 months after rituximab treatment. This patient, however, had severe, pre-existent multi-focal bronchial stenosis due to granulomatous disease. He had also experienced a transient leucopenia, which was attributed to his concomitant medication with co-trimoxazole. Furthermore, the patient had been treated with many potent immunosuppressive drugs, including oral cyclophosphamide, infliximab and deoxyspergualin, prior to rituximab. His tracheo-bronchial inflammation, however, persisted despite heavy immunosuppression and only improved after rituximab administration. We find it difficult to ascertain the degree to which rituximab contributed to the fatal outcome in this case. Severe and fatal infections with rituximab have been reported previously. These include cytomegalovirus reactivation [28], pneumonia [27] and rare infections, such as adenovirus hepatitis [25] acantamoeba encephalitis [26] or progressive multifocal leucoencephalitis (PML) due to BK virus [9,29]. The latter is of particular concern because it is difficult to diagnose and almost uniformly fatal. Interestingly, PML has been described in association with another biological, anti- α 4-integrin antibody natalizumab [30].

Another patient in our study experienced reactivation of hepatitis-B. The patient eventually died after he reached end-stage renal failure and refused dialysis. However, it is conceivable that reactivation of hepatitis-B contributed to the clinical deterioration. Similar cases of hepatitis-B reactivation have been reported previously: Hernandez and co-workers reported a case of fulminant hepatitis-B reactivation in association with rituximab and other chemotherapy for lymphoma [31]. Westhoff and others described another case of fulminant hepatitis with fatal outcome after rituximab use [8]. Reactivation of hepatitis B may occur as late as 1 year after rituximab treatment [32]. The precise mechanisms of hepatitis-B reactivation due to rituximab and the time course of this complication remain unknown, but impairment of humoral immune responses against HBV is

likely to be involved. In addition, it is difficult to compare previous cases [8,31] with our report in that most reports so far describe patients with lymphoma who received not only rituximab but also other chemotherapy. To our knowledge, we describe the first patient with non-malignant, autoimmune disease who sustained a reactivation of hepatitis-B with rituximab use. We detected a significant HBV viraemia 7 months after rituximab treatment when HBs-AG was still negative and liver enzymes were normal. Abnormal liver function tests were only seen 11 months later in conjunction with the onset of constitutional symptoms. Tsutsumi and others demonstrated loss of anti-HBs antibodies with rituximab and speculated that this leads to an environment that facilitates hepatitis-B reactivation [33]. The same authors have described the use of lamivudine prophylaxis for HBsAg-positive patients undergoing rituximab treatment. Of note, patients who are hepatitis-B antigen negative may also be at risk [24]. The risk of hepatitis-B reactivation with chemotherapy has been reviewed in great detail elsewhere [34]. We emphasize the need for comprehensive virological studies prior to rituximab treatment and for close monitoring of virus DNA. Our data confirm that reliance on HBsAg and liver function tests alone may confer a false sense of security. Reports of late reactivation of hepatitis-B as late as 1 year after rituximab use [32] highlight the need for prolonged follow-up using virus screening DNA testing. An early antiviral prophylaxis with lamivudine or other HBV polymerase inhibitors should be initiated in patients with detectable HBV viraemia independent from the level of HBV-DNA before the pathological liver function test is performed [33,35].

In summary, vigilance towards infectious complications is certainly warranted. It must be emphasized, however, that patients in these studies were desperately ill with few or no therapeutic alternatives. Finally, it is hoped that complications will diminish with more experience with the drug and supportive medication.

The risk of malignancy is another concern with the use of rituximab as with any other potent immunosuppressive agent. Patients with ANCA-associated vasculitis have an elevated risk of malignancy [36], presumably due to immunosuppressive treatment and cyclophosphamide in particular. It is unclear whether additional treatment with rituximab may affect the risk of malignancy in the long run.

Another area of uncertainty is that of concomitant immunosuppressive medication during rituximab use. Some studies have used a variety of other immunosuppressants during rituximab treatment while others [16–18] have used only corticosteroids during that time. This issue, however, may not be very amenable to standardization since the choice of concomitant immunosuppression may reflect severity of disease as well as the extent of pre-treatment.

In summary, we report the largest case series of rituximab use in the ANCA-associated vasculitis so far. Our data are consistent with previous reports and give support that the drug is capable of inducing partial or indeed complete remission in refractory or relapsing patients. Two out of 15 patients died although it is difficult to directly attribute their death to the use of rituximab. This mortality rate, we believe, is not surprising, given the severity of disease, previous immunosuppression and lack of other therapeutic alternatives

in these patients. We reckon that a similarly invasive treatment, such as TNF-alpha blockade, would incur the same magnitude of complications, including severe infectious, in a comparable group of patients. Leucopenia and infectious complications, such as pneumonia, reactivation of hepatitis B and PML, remain a particular concern. Further case series should be encouraged to gauge the incidence and severity of these and other side effects. Results of double-blind, placebo-controlled trials are eagerly awaited before a more widespread use of rituximab in ANCA-associated vasculitis can be encouraged.

Conflict of interest statement. Marion Haubitz has previously received financial support for giving lecture from Roche, the manufacturer of rituximab (MabTheraTM) in Germany. All other authors declare no conflict of interest.

References

- Press OW, Appelbaum F, Ledbetter JA *et al*. Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas. *Blood* 1987; 69: 584–591
- McLaughlin P, Grillo-Lopez AJ, Link BK *et al*. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* 1998; 16: 2825–2833
- Edwards JC, Szczepanski L, Szechinski J *et al*. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004; 350: 2572–2581
- Sfikakis PP, Boletis JN, Tsokos GC. Rituximab anti-B-cell therapy in systemic lupus erythematosus: pointing to the future. *Curr Opin Rheumatol* 2005; 17: 550–557
- Xiao H, Heeringa P, Hu P *et al*. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J Clin Invest* 2002; 110: 955–963
- Clayton AR, Savage CO. Production of antineutrophil cytoplasm antibodies derived from circulating B cells in patients with systemic vasculitis. *Clin Exp Immunol* 2003; 132: 174–179
- Aries PM, Hellmich B, Voswinkel J *et al*. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann Rheum Dis* 2006; 65: 853–858
- Westhoff TH, Jochimsen F, Schmittel A *et al*. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. *Blood* 2003; 102: 1930
- Freim Wahl SG, Folvik MR, Torp SH. Progressive multifocal leukoencephalopathy in a lymphoma patient with complete remission after treatment with cytostatics and rituximab: case report and review of the literature. *Clin Neuropathol* 2007; 26: 68–73
- Luqmani RA, Bacon PA, Moots RJ *et al*. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Q J Med* 1994; 87: 671–678
- Voswinkel J, Mueller A, Kraemer JA *et al*. B lymphocyte maturation in Wegener's granulomatosis: a comparative analysis of VH genes from endonasal lesions. *Ann Rheum Dis* 2006; 65: 859–864
- Clayton AR, Savage CO. What you should know about PR3-ANCA. Evidence for the role of T cells in the pathogenesis of systemic vasculitis. *Arthritis Res* 2000; 2: 260–262
- Shlomchik MJ, Craft JE, Mamula MJ. From T to B and back again: positive feedback in systemic autoimmune disease. *Nat Rev Immunol* 2001; 1: 147–153
- Walsh D, Jayne DR. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. *Kidney Int* 2007; 72: 676–682
- Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease—the immune complex decoy hypothesis. *Nat Clin Pract Rheumatol* 2007; 3: 86–95
- Keogh KA, Ytterberg SR, Fervenza FC *et al*. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med* 2006; 173: 180–187
- Geetha D, Seo P, Specks U *et al*. Successful induction of remission with rituximab for relapse of ANCA-associated vasculitis post transplant: report of two cases. *Am J Transplant* 2007; 7: 2821–2825
- Keogh KA, Wylam ME, Stone JH *et al*. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 262–268
- Tamura N, Matsudaira R, Hirashima M *et al*. Two cases of refractory Wegener's granulomatosis successfully treated with rituximab. *Intern Med* 2007; 46: 409–414
- Lamprecht P, Till A, Steinmann J *et al*. Current state of biologicals in the management of systemic vasculitis. *Ann NY Acad Sci* 2007; 1110: 261–270
- Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. *Arthritis Res Ther* 2005; 7 (Suppl 3): S19–S25
- Wagner SA, Mehta AC, Laber DA. Rituximab-induced interstitial lung disease. *Am J Hematol* 2007; 82: 916–919
- Seifert G, Reindl T, Lobitz S *et al*. Fatal course after administration of rituximab in a boy with relapsed acute lymphoblastic leukemia: a case report and review of literature. *Haematologica* 2006; 91: ECR23
- Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. *J Infect Chemother* 2005; 11: 189–191
- Iyer A, Mathur R, Deepak BV *et al*. Fatal adenoviral hepatitis after rituximab therapy. *Arch Pathol Lab Med* 2006; 130: 1557–1560
- Meersemann W, Lagoru K, Sciort R *et al*. Rapidly fatal Acanthamoeba encephalitis and treatment of cryoglobulinemia. *Emerg Infect Dis* 2007; 13: 469–471
- Mercader P, Rodenas JM, Pena A *et al*. Fatal pseudomonas pneumonia following rituximab therapy in a patient with epidermolysis bullosa acquisita. *J Eur Acad Dermatol Venereol* 2007; 21: 1141–1142
- Suzan F, Ammor M, Ribrag V. Fatal reactivation of cytomegalovirus infection after use of rituximab for a post-transplantation lymphoproliferative disorder. *N Engl J Med* 2001; 345: 1000
- Harris HE. Progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus treated with rituximab. *Rheumatology (Oxford)* 2007
- Berger JR. Natalizumab and progressive multifocal leukoencephalopathy. *Ann Rheum Dis* 2006; 65(Suppl 3): iii48–iii53
- Hernandez JA, Diloy R, Salat D *et al*. Fulminant hepatitis subsequent to reactivation of precore mutant hepatitis B virus in a patient with lymphoma treated with chemotherapy and rituximab. *Haematologica* 2003; 88: ECR22
- Perceau G, Diris N, Estines O *et al*. Late lethal hepatitis B virus reactivation after rituximab treatment of low-grade cutaneous B-cell lymphoma. *Br J Dermatol* 2006; 155: 1053–1056
- Tsutsumi Y, Tanaka J, Kawamura T *et al*. Possible efficacy of lamivudine treatment to prevent hepatitis B virus reactivation due to rituximab therapy in a patient with non-Hodgkin's lymphoma. *Ann Hematol* 2004; 83: 58–60
- Yeo W, Johnson PJ. Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. *Hepatology* 2006; 43: 209–220
- Wedemeyer H, Cornberg M, Protzer U *et al*. German Guidelines on diagnosis and therapy of hepatitis B. *Dtsch Med Wochenschr* 2007; 132: 1775–1782
- Pankhurst T, Savage CO, Gordon C *et al*. Malignancy is increased in ANCA-associated vasculitis. *Rheumatology (Oxford)* 2004; 43: 1532–1535

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