Efficacy and safety of rituximab as maintenance therapy for relapsing granulomatosis with polyangiitis—a case series

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Abstract The objective of this work was to study the efficacy and safety of pre-emptive rituximab (RTX) in a series of patients with severe relapsing granulomatosis with polyangiitis (GPA). GPA is a systemic vasculitis with a high relapse rate despite successful remission induction. Drug toxicity with repeated induction treatments and long-standing immunosuppression poses a problem. Based on the findings in reports on RTX for rheumatoid arthritis, we treated patients with severe relapsing GPA with pre-emptive RTX, 1,000 mg 2 weeks apart every 6 months, aiming at achieving sustainable remission. All patients at one centre with relapsing GPA in spite of traditional maintenance treatment, who had received more than or equal to three cycles of RTX as regularly repeated pre-emptive maintenance therapy every 6 months, were included in this retrospective study. Information on disease manifestations and activity, treatments, lab parameters and adverse events was extracted from the medical files. Of the 12 included patients, all with a positive proteinase 3–antineutrophil cytoplasmic antibodies, generalised disease and a median disease duration of 35 months (21–270), 92 % (11/12) achieved sustainable remission during a median follow-up time of 32 months (range 21–111) from first RTX treatment. Concomitant immunosuppressants were reduced. Infections were the most common adverse events, but infections were an issue also before the start of RTX. RTX administered every 6 months seems to be an effective maintenance treatment in a population with severe, relapsing long-standing GPA. Granulomatous as well as vasculitic manifestations responded equally well. Infections are a problem in this patient group but no new safety problems were identified.

Keywords Granulomatosis with polyangiitis · Infections · Maintenance therapy · Rituximab · Safety

Introduction

Granulomatosis with polyangiitis (GPA) is a systemic necrotizing vasculitis, typically engaging the upper airways, kidneys and lungs and often associated with circulating antineutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 (PR3). The well-established standard treatment for remission induction in GPA has been cyclophosphamide (CY), in combination with corticosteroids (CS) [1, 2]. This treatment regimen, introduced in the 1970s, has dramatically improved the outcome for GPA patients but with a risk of considerable side effects, including infections, sterility and bladder cancer [3]. Maintenance treatment is usually given with methotrexate (MTX), azathioprine (AZA) or mycophenolate mofetil (MMF), but as at least 50 % of patients have one or several relapses, repeated induction treatment is often necessary with the risk of high cumulative doses of CY [4, 5]. Recently, rituximab (RTX) has been approved by the FDA and the European Medicines Agency (EMA) for induction treatment of GPA and microscopic polyangiitis (MPA) in combination with CS, using the lymphoma protocol of 375 mg/m² once weekly for 4 weeks. However, the efficacy and safety of repeated RTX courses as maintenance treatment has not yet been established.

B lymphocytes play an important role in many autoimmune diseases, including GPA [6–8]. Induction therapy with RTX has reported successful remission of GPA in two
randomised trials comparing CY and RTX [9, 10], but relapses after RTX-induced remission still occurred in a significant number of patients. A retrospective study of 59 patients with refractory GPA [11] described successful induction of remission, response or stabilisation of disease in 67% of patients given two to three RTX treatments, but 33% of patients were refractory to treatment and this failure to respond was mainly due to the persistence of granulomatous manifestations. Also, the relapse rate during a median follow-up time of 13.5 months was 44%. Several other studies report successful remission induction with RTX also in previously refractory disease [12–14]. Two smaller retrospective studies have addressed RTX as maintenance therapy after achieving remission [15, 16], both reporting successful results with less frequent relapses. Just recently, two larger retrospective studies have been published reporting RTX as remission and/or maintenance therapy [17, 18]. Both these studies showed reduced relapse rate during ongoing RTX treatment and also prolonged remission after cessation of RTX. However, in these studies, different treatment regimens were employed, three of the studies included patients with a mixture of diagnoses within the concept of “anti-neutrophil cytoplast antibody-associated vasculitides” [15, 16, 18], and one study included induction treatment as well as maintenance therapy [17]. Two review articles on B cell depletion therapy for vasculitides have also recently been published [19, 20].

In rheumatoid arthritis (RA), pharmacokinetic studies of RTX have shown drug concentrations below the level of detection, evidence of returning peripheral B cells and recurrence of symptoms from 24 weeks after a given RTX course [21]. Long-term treatment with RTX (courses of 500 or 1,000 mg 2 weeks apart) repeated after 24 weeks has shown good disease control and an acceptable safety profile in patients with RA [21].

Further knowledge about the use of RTX in patients with GPA is essential before recommendations can be made on maintenance treatment, including optimal dosage, and clinical trials may reflect neither the efficacy nor the adverse reaction rates observed in clinical practice.

This study is a retrospective analysis of actual performance of repeated RTX cycles in a clinical setting of consecutive GPA patients all treated at the same clinic. Based on the positive experience of repeated treatment with RTX in RA and the knowledge of B cell return after approximately 6 months after treatment, and as an alternative to the registered dosing based on the lymphoma protocol suggested for induction treatment, we treated patients with severe relapsing GPA using the RA regimen with 1,000 mg RTX 2 weeks apart every 6 months, aiming to achieve sustainable remission. We report efficacy and safety data from all treated patients with a median follow-up of 32 months and longest follow-up of 111 months, suggesting this treatment regimen as a possibility for relapsing GPA.

Patients and methods

All patients with relapses of GPA in spite of traditional maintenance treatment and having received more than or equal to three cycles of RTX as regularly repeated preemptive maintenance therapy every 6 months between January 2003 and February 2013 were included in the study. The patients had to fulfil the American College of Rheumatology criteria [22] and/or the definition of the Chapel Hill Consensus Conference [23] for GPA. Information on patient characteristics (sex, age at diagnosis of GPA, duration of GPA, smoking habits), clinical manifestations at diagnosis, Birmingham Vasculitis Activity Score (BVAS) [24] at diagnosis and at follow-up, ANCA status at diagnosis and follow-up and all treatments given before RTX and all treatments given concomitantly with RTX, as well as dose of other treatments including CS and of RTX was extracted from the patient files. Information on infections and other adverse events before and after the introduction of RTX and immunoglobulin (Ig) levels before and after RTX treatment, when analysed, was likewise collected.

Disease activity was measured using the BVAS, version 3 [24] with assessments performed 4–6 months after first and latest RTX infusion. Remission was defined as BVAS of 0 with a dose of prednisolone of 7.5 mg or less/day, according to EULAR recommendations [25]. Patients achieving BVAS of 0, but still on more than 7.5 mg prednisolone/day were registered as responders. Relapse was defined as a recurrence of symptoms attributable to vasculitis plus a therapy escalation; either unscheduled RTX, any other immunosuppressant or an increase in CS of more than 20 mg. PR3-ANCA was analysed with an ELIZA kit with a cut-off value of <20 kE/l. Response in orbital mass was defined as reduction of mass on magnetic resonance imaging. Infections treated with antibiotics, antiviral therapy or anti-fungals have, in this study, been considered as “significant infections” and are included in the follow-up.

Follow-up of RTX treatment was defined as the time from date of first infusion until termination of follow-up (31 March 2012). Ethical approval was obtained from the regional ethics committee.

Statistics

After Friedman ANOVA test, Wilcoxon rank test with Bonferroni correction was used to compare changes in BVAS, prednisolone dose and C-reactive protein (CRP) values before and after RTX treatment. Statistica version 10 was used for statistical analyses. P values <0.05 were considered statistically significant.
Results

Patient characteristics and follow-up

The study includes 12 patients (seven females, five males) with relapsing GPA treated with repeated cycles of RTX from January 2003 through February 2013. The median age at GPA diagnosis was 44 years (range 16–61 years). The patients were followed for a median of 32 months (range 21–111 months) after initiation of RTX. At diagnosis, all patients were PR3-ANCA-positive and had involvement of the upper respiratory tract and lungs. Biopsy-proven granulomatous manifestations were present in seven patients: three with retrobulbar granulomas, two with laryngeal stenosis and two with pulmonary granulomas. Apart from the patients with retrobulbar granulomas, one further patient had CNS involvement (hypophyseal granulomas) and two had mononeuritis. Renal manifestations included one patient with biopsy-verified nephritis, and a further five patients with pathological urine sediment compatible with nephritis. All patients had generalised disease defined as involvement of kidney and/or lungs (Table 1).

The patients had all received CS and CY, either orally or as repeated CY pulses, as induction therapy. Seven patients had received induction therapy with CY more than once (median number of treatment periods with CY 2; range 1–3), and a majority of the patients were treated with CY over long periods; the total median treatment time with CY was 19 months (range 2–54 months) and the median cumulative CY dose before RTX was 61.5 g (range 11–105 g). CY was followed by maintenance treatment with CS in all patients, and 11 of the 12 patients had also received AZA, nine MTX, eight MMF and four intravenous gammaglobulin. One of the patients, with refractory GPA in spite of conventional treatment including repeated CY cycles, had a bone marrow transplant, followed by remission for 6 months. The clinical appearance of this patient does not differ from the other patients in the series in any other aspects, and the effect of RTX is also comparable; for detailed characteristics of all patients, see Table 2.

Rituximab treatment

For all patients, the main indication for pre-emptive treatment with RTX was treatment failure with disease relapses under ongoing conventional maintenance treatments. In addition, several of the patients had a history of repeated and high cumulative CY doses and three of the patients were young females where the long-term negative effects of CY on fertility were taken into account. One of the patients also experienced liver toxicity on MTX as well as on AZA and MMF. One patient developed necrosis of the head of femur on CS as well as liver toxicity on AZA. The patients’ median disease duration before the initiation of RTX treatment was 35 months (range 19–270) (mean 84 months) and the median number of relapses before RTX was 4.0 (range 1–8). Ten of 12 patients were persistently PR3-ANCA-positive at first RTX treatment.

The first patient was treated in 2003 with RTX according to the lymphoma protocol (four doses of 375 mg/m² at weekly intervals), but thereafter, RTX treatment was given to all patients as two infusions of 1,000 mg 2 weeks apart (with methylprednisolone 100 mg on the day of infusion) repeated at 6-month intervals. Four patients have been kept on this regimen, but the dose has been lowered to 1,000 mg every 6 months in four patients, to 500 mg twice every 6 months in two patients and to 500 mg once every 6 months in two patients. Reduction of the RTX dose has been done at the discretion of the treating clinician and in all cases because remission has been maintained. However, RTX on a pre-emptive basis has been continued in all patients.

Table 1 Baseline characteristics of the patients with relapsing granulomatosis with polyangiitis (GPA) before the initiation of rituximab (RTX)

| Number of patients, n | 12 |
|----------------------|----|
| Gender (female/male), n (%) | 7/5 (58/42) |
| Age at GPA diagnosis, median (range), years | 46 (16–61) |
| Males | 46 (37–61) |
| Females | 37 (16–62) |
| Disease duration before RTX, median (range), months | 35 (19–270) |
| PR3-ANCA-positive at GPA diagnosis, n (%) | 12 (100) |
| PR3-ANCA-positive at RTX initiation, n (%) | 10 (80) |
| Organ involvement/activity, cumulative before RTX, n (%) | 8 (67) |
| Ear, nose, throat | 12 (100) |
| Lung | 12 (100) |
| Arthritis/arthralgia | 7 (58) |
| Kidney* | 6 (50) |
| Skin | 6 (50) |
| Eye (keratitis, conjunctivitis) | 4 (30) |
| Central nervous system (hypophyseal & retrobulbar granulomas) | 4 (30) |
| Peripheral nervous system | 2 (17) |
| Smoker, ever, n (%) | 8 (67) |
| Cumulative treatment before RTX, n (%) | 12 (100) |
| Cyclophosphamide | 12 (100) |
| Corticosteroids | 12 (100) |
| Azathioprine | 11 (92) |
| Methotrexate | 9 (75) |
| Mycophenolate mofetil | 8 (67) |
| Intravenous gammaglobulin | 4 (33) |
| Bone marrow transplant | 1 (8) |
| Cumulative dose cyclophosphamide before RTX, median (range), g | 61 (11–105) |

*Including one patient with biopsy-verified glomerulonephritis and five with pathological urine sediment

ANCA anti-neutrophil cytoplasmic antibody

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| N | M/F | Age at diagnosis (years) | ANCA before/after RTX | Previous treatments | Disease duration at the start of RTX | RTX dose last follow-up | Other drugs last follow-up | BVAS before/after RTX | CS before/after RTX | IgG before/after RTX | IgA before/after RTX | IgM before/after RTX | Significant infection before/after RTX |
|---|-----|--------------------------|------------------------|---------------------|-------------------------------------|------------------------|--------------------------|------------------------|------------------|------------------|------------------|------------------|--------------------------|----------------------------------------|
| 1 | F   | 50                       | 129/neg                | cy, aza, mmf, mtx   | 25                                  | 1,000×2 mtX            | 12/0                     | –                      | –                | –/–              | –/–              | –/–              | –/–                      | –/–                      |
| 2 | F   | 16                       | 263/neg                | cy, aza, mtx, ivig  | 99                                  | 1,000×2               | –                        | 10/0                   | 0/0              | 10.1/7.6         | 2.4/1.7          | 1.7/0.8          | 60/20                     | 10/5                     |
| 3 | F   | 52                       | 104/neg                | cy, aza             | 19                                  | 1,000×1 aza           | 8/0                      | 5/0                    | 7.3/5.6          | 0.9/0.8          | 0.8/0.4          | 10/0             | 60/20                     | –/–                      |
| 4 | M   | 59                       | 200/neg                | cy, aza, mmf       | 20                                  | 1,000×1               | –                        | 9/0                    | 15/7.5           | 8.6/7.5          | 3.5/3.3          | 0.5/0.4          | 26/0                      | –/–                      |
| 5 | M   | 61                       | 470/neg                | cy, aza, mtx        | 17                                  | 500×2 aza             | 15/0                     | 10/0                   | 9.3/6.5          | 2.0/0.8          | 0.9/0.6          | 0/0              | –/–                      | –/–                      |
| 6 | F   | 18                       | 260/neg                | cy, aza, mmf, mtx, ivig | 174                                  | 1,000×2 mtX          | 10/0                     | 5/5                    | 6.2/2.2          | 1.4/1.2          | 0.5/0.3          | 0/0              | –/–                      | –/–                      |
| 7 | M   | 46                       | 250/neg                | cy, aza, mmf, ivig  | 73                                  | 1,000×1               | –                        | 9/0                    | 7.5/5            | 8.2/7.8          | 1.2/1.0          | 0.8/0.7          | 0/20                     | –/–                      |
| 8 | F   | 37                       | 156/85                 | cy, aza, mmf, mtx   | 270                                  | 1,000×2 mtX           | 7/0                      | 10/5                   | 11.2/8.6         | 2.0/1.7          | 0.7/0.6          | 1/0              | 0/20                     | –/–                      |
| 9 | F   | 18                       | 82/neg                 | cy, aza, mmf       | 20                                  | 500×2                 | –                        | 6/2                    | 10/7.5           | 15.1/10.5        | 2.6/1.6          | 1.6/1.3          | 0/10                     | –/–                      |
| 10 | M | 46                       | 125/neg                | cy, aza, mmf, mtx  | 30                                  | 500×1                 | –                        | 4/0                    | 20/7.5           | 5.4/5.0          | 1.6/1.4          | 0.3/0.3          | 1/0                      | –/–                      |
| 11 | M  | 37                       | 49/neg                 | cy, aza, mmf, mtx, BMT, ivig | 40                                  | 500×1 ivig           | 10/0                     | 17.5/10              | 10.6/–           | 0.9/–            | 0.2/–           | 0/0              | –/–                      | –/–                      |
| 12 | F  | 47                       | 550/neg                | cy, aza, mmf, mtx, ivig | 456                                  | 1,000×1 aza         | 6/0                      | 10/2.5                | 6.8/5.6          | –/1.8            | –/–             | –/–            | 0/0                      | –/–                      |

The time of follow-up after the start of RTX is expressed in months

M male, F female, GPA granulomatosis with polyangiitis, RTX rituximab (in milligrams), ANCA anti-neutrophil cytoplasmic antibody (in kU/L, with a cut-off value of < 20), cy cyclophosphamide, mtx methotrexate, aza azathioprine, ivig intra venous immunoglobulins, BMT bone marrow transplant, BVAS Birmingham vasculitis score, CS corticosteroids (in milligrams),

a Infection treated with antibiotics, anti-fungals or anti-viral therapy

b Sinusitis
c Pneumonia
d Herpes Zoster
e Influenza
f Empyema
g Fungal infection
h Cystitis
Rituximab treatment results

At follow-up (28 Feb 2013), a total of 75 RTX treatment courses had been administered to the 12 patients (median six courses/patient, range 3–13). After the first course of RTX, four of the 12 patients (30 %) achieved remission defined as BVAS 0 and prednisolone <7.5 mg/day, seven achieved response (58 %) and one did not respond, according to the definitions of remission and response used. The symptoms and signs that remained in the eight patients who did not achieve complete remission after the first course of RTX were peripheral neuropathy, sensori-neural hearing deficit, arthralgia and pulmonary cavities. With continuous treatment, 11 of the 12 patients (92 %) were in remission at last follow-up and one showed clinical response (BVAS of 0 but 12.5–15 mg prednisolone/day) (Table 2). All granulomatous manifestations responded well in two of the cases after the first treatment cycle. During follow-up, only one patient experienced a minor relapse (nasal blockage and bloody discharge, sinusitis, rise in PR3-ANCA level from 86 to 129 kE/l). The relapse occurred 2 months after the patient’s second course of RTX and was successfully treated with oral CS and continued RTX.

In the cohort, the median BVAS was reduced from 9 to 0 (p=0.002), median CRP from 6.0 to 2.6 (p=0.01) and 11 of 12 patients have become ANCA-negative (Table 3). The ANCA level of the positive patient has been reduced but is still above the cut-off value of 20 kE/l. Concerning other medications, over time, the prednisolone dose was reduced from median 10 to 3.75 mg/day (p=0.003). Concomitant immunosuppressant use has in six cases been completely omitted and has been reduced in a further two patients. The RTX dose has been reduced in eight patients after a median of 4.5 (range 1–6) RTX courses of 1,000 mg twice. The patients with reduced RTX have been followed for a median of 9 months (range 3–38) (mean 15.6 months), so far without any disease deterioration or relapse (Table 2).

Adverse events and safety aspects

Rituximab was overall well tolerated. There were two patients who experienced three minor infusion reactions (non-urticarial rash and prurigo; occurring at infusion 1, 1 and 3, respectively) which could be treated with antihistamines before continuing the infusions.

There were seven infections that needed antibiotics, antifungals or anti-viral therapy in four patients after the initiation of RTX, (seven infections during 41 patient-years) including one Pneumocystis jiroveci pneumonia. This is to be compared with 14 verified infections treated with antibiotics in seven patients before the initiation of RTX treatment (14 infections during 79 patient-years). However, all the infections occurring early in the disease course i.e. before RTX treatment have most likely not been recorded as some patients were treated at other hospitals in earlier stages of disease, which underestimates the “background” infection incidence before RTX treatment.

Three of the four patients who developed infections after RTX were on concomitant steroids and other immunosuppressive drugs (MTX and MMF); the forth patient has insulin-dependent diabetes mellitus since the age of 11. The P. jiroveci infection occurred in a young female 6 weeks after her first RTX course, and the patient was at that time also on CS (methylprednisolone 20 mg/day) and MTX 20 mg/week. P. jiroveci prophylaxis was not given in conjunction with RTX treatment as this was not routinely recommended at the time. Smoking is known to be a risk factor for respiratory infections. Of 14 mainly respiratory infections that occurred before RTX, 13 affected smokers and of 7 infections after RTX, 2 occurred in smokers. Ig levels before RTX treatment were normal or

| Table 3 Effect of rituximab (RTX) on disease activity, prednisolone dose and laboratory parameters |
|---------------------------------------------------------------|
|                  | Before RTX | After first RTX course | P*a  | Last follow-up | P*b |
| BVAS, median (range)       |           | 9 (4–15)              | 0.002| 0 (0–0)       | 0.002|
| Prednisolone dose (mg/day), median (range)               |           | 10.0 (0–18)           | ns   | 3.75 (0–15)  | 0.003|
| CRP, mg/l, median (range)          |           | 6.0 (0.3–96)         | ns   | 2.6 (0.3–9.2)| 0.01 |
| Remission, n (%)                                             |           | 0                    | 3 (25)| 11 (92)      |      |
| Response, n (%)                                               |           | 8 (67)               | 1 (8)   |             |      |
| No response, n (%)                                           |           | 1 (8)                | 0 (0)    |             |      |
| Immunoglobulin levelsc                                     |           |                      |       |              |      |
| IgG g/l, median (range)                |           | 8.98 (5.4–15.1)     |       | 6.81 (4.1–10.5) |      |
| Ig A g/l, median (range)                   |           | 1.85 (0.87–3.5)     |       | 1.52 (0.78–3.3) |      |
| IgM g/l, median (range)                     |           | 0.81 (0.23–1.7)     |       | 0.54 (0.2–1.3) |      |

BVAS Birmingham Vasculitis Activity Score [22], ns non-significant

*a Comparison before RTX and after first RTX course

*b Comparison before RTX and at last follow-up

c Measured at variable time points after the start of RTX, reference values: IgG, 6.7–14.5 g/l; IgA, 0.88–4.5 g/l; IgM, 0.27–2.1 g/l
just below normal (three patients had IgG and one patient IgA just under reference level). Information on Ig levels after RTX was retrieved and related to the total dose of RTX that each patient had received at the time point of Ig testing (Tables 2 and 3). The three patients who had received the highest doses of RTX also had the lowest IgG and IgM levels. Among the four patients who had infections during follow-up, two had subnormal Ig levels (IgG and IgG+IgM, respectively).

B cell levels have not been measured in all patients as this is not recommended in routine care. As expected, B cell levels were undetectable in those who were tested after RTX administration (three patients). All patients were screened negative for hepatitis B before RTX treatment was initiated and there were no cases of hepatitis B after the start of RTX.

Discussion

Untreated GPA is a disease with high mortality and morbidity. The current well-established therapeutic options (mainly CY in combination with CS) achieve high rates of remission, but the problem of relapsing disease and treatment toxicity remains. RTX is now approved in the USA as well as in Europe for induction treatment of GPA and MPA, with a recommended dose of 375 mg/m² given once weekly for 4 weeks. There are no recommendations on maintenance therapy or concomitant immunosuppressive treatment. In this case series of 12 patients with relapsing GPA in routine clinical care, we report efficient and well-tolerated maintenance treatment with repeated pre-emptive RTX infusions given every 6 months, a regimen which has proven effective in RA. The patients have received a median of six RTX treatment courses (range 3–13) with a median total dose of 9,000 mg RTX (range 6,000–21,500 mg), and during a median follow-up period of 32 months (range 21–111 months), 11 of the 12 patients (92 %) have achieved and maintained remission, 1 has achieved response (stable BVAS of 0 but prednisolone 12.5–15 mg/d) and only 1 patient has had a (minor) relapse during follow-up.

These results support those previously reported for ANCA-associated vasculitides by Rhee et al. [15] and Roubaud-Bauldron et al. [16] and are consistent with the recently published, larger studies by Cartin-Ceba et al. [17] and Smith et al. [18], although patient characteristics and treatment regimens partly differ between the studies. In the study by Smith et al., RTX dosage was 1,000 mg every 6 months in one treatment arm (similar to the regime in our study), but in this study, RTX was discontinued after 24 months in all patients. Three of the previous studies include patients with GPA as well as MPA [15, 16, 18], which represent two different diseases [26] making evaluation of treatment results difficult as response to treatment may differ between the diseases.

Generally, the patients in our study seem to have a more severe and long-standing disease than those in the previous studies. In the study by Rhee et al., the patients had a median BVAS of 1, and in the Cartin-Ceba study, the median BVAS was 5 at RTX initiation. The patients in the Smith study (group B) had received a median dose of 14.9 g CY and the median disease duration was 43 months compared to our study where median BVAS was 9, the median cumulative CY dose was 61 g and the median disease duration was 35 months (mean 84 months). In the present study, there was no difference in effect of RTX on granulomatous and vasculitic disease manifestations. This is in contrast to the previous study where granulomatous manifestations, especially orbital masses, responded less well than vasculitic manifestations to a regimen of RTX as four doses of 375 mg/m² at weekly intervals [11].

Apart from different doses and dose intervals for RTX in previous studies, also strategies for co-medication have differed. In one study, all immunosuppressive agents were stopped and CS dose reduced at start of RTX [18]. In another study, CS at a dosage of 1 mg/kg/day was introduced at RTX initiation followed by stepwise reduction of CS [17]. In our study reflecting clinical routine, RTX was added to the ongoing maintenance therapy of immunosuppressants and CS when relapse occurred. In patients who achieved stable remission, concomitant immunosuppressive drugs were omitted or reduced and CS was tapered at the discretion of the treating physicians. Notably, with this regimen, only four of the 12 patients obtained remission after the first course of RTX and repeated courses were needed for the majority of patients to achieve and maintain remission. Achieving disease control with RTX enabled reduction or withdrawal of other immunosuppressive drugs (Table 2). In the FDA and EMA, approval of RTX for GPA suggested dosages are copied from the lymphoma protocol. Our study supports that a regimen with 1,000 mg twice every 6 months is efficient and well tolerated and that RTX doses can be reduced over time. Optimal dosage and dose intervals of RTX need to be further investigated, but possibly according to our preliminary results and others, dosing of RTX can be reduced once stable remission has been achieved. In seven of the patients in this study, the RTX dose was reduced without relapses occurring, but follow-up is still short (median 9 months; mean 15.6 months). In one of the previously mentioned studies [18], an initial course of 1,000 mg RTX 2 weeks apart was followed by a single dose of 1,000 mg RTX every 6 months for a total of 24 months reporting a relapse rate of 12 % over 2 years. Comparisons between studies regarding optimal RTX regimen are however hampered by the differences in study populations and study designs.

Biomarkers, in particular B cell levels and ANCA titres, have been suggested to be used to predict relapse and guide retreatment with RTX, but studies have been conflicting, and so far there is little support for the use of these markers to guide optimal time point for retreatment with RTX. No conclusions regarding biomarkers can be drawn from this study, but it can be noted that the only patient with a relapse had a
infections in the patients before and after the initiation of RTX, we made special effort to scrutinise the medical files to find all infections of CD 19+ cells (as a possible measure of disease activity) have not been consistently analysed, as this is not standard of routine.

As infections have been reported in previous trials on RTX, we made special effort to scrutinise the medical files to find all infections of CD 19+ cells (as a possible measure of disease activity) have not been consistently analysed, as this is not standard of routine.

There was one opportunistic infection (P. jiroveci pneumonia) which occurred after the first RTX treatment with a concomitant relatively high dose of CS. At this time, prophylaxis for P. jiroveci was not given, but is now recommended by the FDA and EMA for patients with GPA treated with RTX, and we have changed our routines accordingly. Infections were not consistently correlated to low immunoglobulin levels (Table 2). Smoking did not emerge as a main predisposing risk factor for infections during RTX treatment in these patients. None of the patients developed late-onset neutropenia previously reported in patients with RA, SLE and vasculitis receiving RTX [27], neither have we experienced progressive multifocal leukoencephalopathy (only previously reported in patients with RA and SLE receiving RTX [28]). The infection rate after RTX was considerably higher in our patient group than that reported for RA patients (4.3/100 patient-years), treated with similar RTX treatment regimen [29]. However, and as was evident in our study, it is plausible that the background infection risk in GPA in general is higher than in RA because of the systemic nature of the disease, damage of upper and lower airways predisposing for airway pathogens and the immunosuppressive treatments, including CY, given over time. This emphasises that pattern and incidence of adverse events in RTX-treated GPA patients may differ from what is reported in other RTX-treated patient groups.

The strength of this study lies in the setting in normal clinical practice and in the relatively long follow-up time, also that the patients have been followed at the same clinic with easily accessible and comprehensive electronic medical files for follow-up. The initial treatment regimen has been consistent, and all patients with GPA treated with repeated RTX infusions at our clinic have been included, which eliminates any risk of selection bias.

However, there are several limitations to our study, mainly the small study population and the retrospective design, hence the heterogeneity in treatments given before start of RTX. Also, the patients initially continued previous immunosuppressive drugs during RTX treatment, and concomitant medications have been gradually withdrawn, which may also influence relapse rate. The relatively low age in the population may have influenced the infection risk. Follow-up time is too short to yield information on possible delayed unexpected effects of long-term B cell depletion and the possible late effects of hypogammaglobulinemia seen in some patients. The role for concomitant immunosuppressive treatment is still unclear. Possibly, continuing MTX or AZA may allow for a regimen with RTX given at lower dose or greater interval, reducing the risk of hypogammaglobulinemia. On the other hand, reduced doses of CS and other immunosuppressive drugs most likely have long-term beneficial effects on infection risks.

In conclusion, this study adds to our knowledge on RTX as maintenance treatment in patients with severe, relapsing GPA and indicates that RTX, given pre-emptively every 6 months as initially described in RA, can prevent relapses, allows for reduction of concomitant immunosuppressive drugs and CS and is well tolerated under a median observation period of 32 months. Extended studies are needed to further establish the place of RTX in maintenance therapy and the role of concomitant immunosuppression.

Disclosures None.

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References

1. Hoffman GS, Kerr GS, Leavitt RY et al (1992) Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 116:488–498
2. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W et al (2009) for the European Vasculitis Study Group. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 68:310–317
3. Knight A, Askling J, Granath F, Sparen P, Ekbom A (2004) Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis 63:1307–1311
4. Jayne D, Rasmussen N, Andrassy K et al (2003) A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44
5. Pagnoux C, Hogan SL, Chin H et al (2008) Predictors of treatment resistance and relapse in anti neutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. Arthritis Rheum 58:2908–2918
6. Martin F, Chan AC (2004) Pathogenic roles of B cells in human autoimmunity: insights from the clinic. Immunity 20:517–527
7. Popa ER, Stegeman CA, Bos NA, Kallenberg CG, Tervaert JW (1999) Differential B- and T-cell activation in Wegener's granulomatosis. J Allergy Clin Immunol 103:885–894
8. Cupps TR, Edgar LC, Fauci AS (1982) Suppression of human B lymphocyte function by cyclophosphamide. J Immunol 128:2453–2457
9. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS et al (2010) Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 363:221–232, for the RAVE-ITN Research Group
10. Jones RB, Tervaert JWC, Hauser T, Luqmani R et al (2010) Rituximab versus cyclophosphamide in ANCA associated renal vasculitis. N Engl J Med 363:211–220
11. Holle JJ, Dubrau C, Herlyn K et al (2012) Rituximab for refractory granulomatosis with polyangiitis (Wegener’s granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. Ann Rheum Dis 71:327–333
12. Jones RB, Ferraro AJ, Chaudhry AN et al (2009) A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 7:2156–2168
13. Wendt M, Gunnarson I, Bratt J, Bruchfeld A (2012) Rituximab in relapsing or refractory ANCA-associated vasculitis: a case series of 16 patients. Scand J Rheumatol 41:116–119
14. Eriksson P (2005) Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J Intern Med 257:540–548
15. Rhee EP, Laliberte KA, Niles JL (2010) Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitides. Clin J Am Soc Nephrol 5:1394–1400
16. Roubaud-Baudron C, Pagnoux C, Méaux-Ruault N, Grasland A, Zoulim A, LE Guen J et al (2012) Rituximab maintenance therapy for granulomatosis with polyangiitis (Wegener’s): ten-year experience at a single center. Arthritis Rheum 64:3760–3769
17. Specks U (2012) Biologic agents in the treatment of granulomatosis with polyangiitis. Cleve Clin J Med 79(Suppl 3):50–53
18. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A et al (2012) Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 64:3760–3769
19. Tesfà D, Ajeganova S, Hägglund H, Sander B, Fadeel B, Hafström I, Palmblad J (2011) Late-onset neutropenia following rituximab therapy in rheumatic diseases: association with B lymphocyte depletion and infections. Arthritis Rheum 63:2209–2214
20. Carson KR, Evens AM, Richey EA et al (2009) Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the research on adverse drug events and reports project. Blood 113:4834–4840
21. Vollenhoven RF, Emery P, Bingham CO et al (2010) Long-term safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 37:558–567