Rituximab Maintenance Therapy for Granulomatosis with Polyangiitis and Microscopic Polyangiitis

CLAIRE ROUBAUD-BAUDRON, CHRISTIAN PAGNOUX, NADINE MÉAUX-RUAULT, ANNE GRASLAND, ABDELKADER ZOULIM, JULIEN LE GUEN, ANNE PRUD'HOMME, BORIS BIENVENU, MATHILDE de MENTHON, SANDRA CAMPS, VÉRONIQUE LE GUERN, ACHILLE AOUBA, PASCAL COHEN, LUC MOUTHON, and LOÏC GUILLEVIN, for the French Vasculitis Study Group

ABSTRACT. ***Objective.*** To evaluate the efficacy compared to the relapse risk and tolerance of systematic rituximab (RTX) infusions as maintenance therapy for patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), who entered remission taking conventional immunosuppressants or RTX.

Methods. A retrospective study of the main clinical characteristics, outcomes, and RTX tolerance of patients who had received ≥ 2 RTX maintenance infusions in our center, regardless of induction regimen, between 2003 and 2010.

Results. We identified 28 patients [4 MPA and 24 GPA; median age 55.5 yrs (range 18–78); 17 (60%) males] who received a median of 4 (range 2–10) RTX maintenance infusions, with median followup of 38 months (range 21–97) since diagnosis or last flare. None experienced a RTX infusion-related adverse event; 15 patients (among the 21 with available data) had hypogammaglobulinemia (predominantly IgM) prior to their last RTX maintenance infusion; 3 had infectious events (1 cutaneous abscess, 1 otitis, 1 fatal H1N1 flu). Two patients suffered pulmonary relapses shortly before a planned RTX maintenance infusion (both had increased antineutrophil cytoplasmic antibody levels and 1 had CD19+ lymphocyte reconstitution).

Conclusion. Rituximab maintenance therapy was well tolerated but did not completely prevent relapses and persistent "grumbling" disease. These preliminary results remain to be confirmed by a randomized controlled trial currently in progress. (First Release Nov 15 2011; J Rheumatol 2012;39:125–30; doi:10.3899/jrheum.110143)

Key Indexing Terms:
GRANULOMATOSIS WITH POLYANGIITIS MICROSCOPIC POLYANGIITIS RITUXIMAB MAINTENANCE THERAPY
ANTINEUTROPHIL CYTOPLASM ANTIBODY-ASSOCIATED VASCULITIDES

Rituximab (RTX) has reportedly achieved successful remission of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in 80%–100% of patients with severe and/or refractory diseases[1,2,3]. Recent results of the randomized RAVE[4] and RITUXVAS[5] trials demonstrated that an RTX-based regimen was as effective and safe as conven-

From the National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris; Department of Internal Medicine, Hôpital Jean Minjoz, Besançon; Department of Internal Medicine, Hôpital Louis-Mourier, Assistance Publique-Hôpitaux de Paris, Colombes; Department of Internal Medicine, Hôpital Côte de Nacre, Caen; Department of Respiratory Disease, Centre Hospitalier de Bigorre, Tarbes; Pharmacy, Université Paris-Descartes, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Paris; and Department of Adult Hematology, Université Paris-Descartes, Hôpital Necker Enfants-Malades, Assistance Publique-Hôpitaux de Paris, Paris, France.

C. Roubaud-Baudron, MD, MSc, Resident in Internal Medicine; C. Pagnoux, MD, MSc, MPH, Attending Physician, National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin; N. Méaux-Ruault, MD, Attending Physician; Department of Internal Medicine, Hôpital Jean Minjoz; A. Grasland, MD, Attending Physician, Department of Internal Medicine, Hôpital Louis-Mourier; A. Zoulim, MD, Attending Physician, Department of Internal Medicine, Hôpital Côte de Nacre; J. Le Guen, MD, Resident in Internal Medicine, National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin; A. Prud'Homme, MD, Attending Physician, Department of Respiratory Disease, Centre Hospitalier de Bigorre; B. Bienvenu, MD, PhD, Attending Physician, Department of Internal Medicine, Hôpital Côte de Nacre; M. de Menthon, MD, PhD, Attending Physician, National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin; S. Camps, PharmD, Hospital Pharmacist, Université Paris-Descartes, Hôpital Cochin; V. Le Guern, MD, Attending Physician, National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin; A. Aouba, MD, Attending Physician, Department of Adult Hematology, Université Paris-Descartes, Hôpital Necker Enfants-Malades; P. Cohen, MD, Attending Physician; L. Mouthon, MD, PhD, Professor of Medicine, Attending Physician; L. Guillevin, MD, Professor of Medicine, Head, Department of Internal Medicine, National Referral Center for Rare Systemic and Autoimmune Diseases: Necrotizing Vasculitides and Systemic Sclerosis, Department of Internal Medicine, Université Paris Descartes, Hôpital Cochin.

Address correspondence to Dr. C. Pagnoux, Department of Internal Medicine, Hôpital Cochin, 27 rue du faubourg Saint-Jacques, 75679 Paris Cedex 14, France. E-mail: christian.pagnoux@cch.aphp.fr

Accepted for publication September 7, 2011.

tional cyclophosphamide (CYC)-based regimens to induce remission in these patients[4,5]. Notably, in both those trials, no maintenance therapy was prescribed after RTX-induced remission.

However, results of previous retrospective studies[1,2], published after those randomized trials were started, indicated that, in populations of refractory/relapsing patients, relapses after RTX-induced remission could occur in more than half the patients[2], especially within the 9–12 months after the last RTX infusion, and independently of antineutrophil cytoplasmic antibody (ANCA) status or CD19+ lymphocyte immune reconstitution. We hypothesized that maintenance therapy was required after RTX-based induction therapy and that regular RTX infusions might represent an effective maintenance regimen. No recommendations are available yet concerning the need for maintenance therapy for these patients and, if so, with which agent. We report our retrospective analysis of 28 patients with ANCA-associated vasculitis (AAV) who received preemptive RTX infusions as maintenance.

MATERIALS AND METHODS

Patient selection. For this study, patients had to have GPA or MPA satisfying American College of Rheumatology and/or Chapel Hill consensus conference criteria[6,7]; to have received ≥ 2 RTX maintenance infusions (minimum followup of 12 months), regardless of their induction regimen; and to be followed (or been referred, at least once), between 2003 and 2010, in the Internal Medicine Department of Cochin Hospital, Paris. Patients may have subsequently received some or all of their RTX infusions in another hospital (in Besançon, Caen, Colombes, Paris, or Tarbes).

Study measures. We retrospectively analyzed patients' main characteristics (sex, diagnosis, age at diagnosis), clinical manifestations (duration of AAV since diagnosis, disease activity at the last flare), and treatments preceding and associated with RTX maintenance. We recorded why RTX maintenance was chosen (i.e., after RTX induction or because of contraindication and/or inefficacy of other conventional maintenance agents), the regimen (number, dose, timing), the efficacy of RTX at maintaining remission, tolerance for RTX, and patient outcomes. For the patients not followed entirely at our institution, information was updated by contacting the referral physicians (NMR, AG, AZ, AP, BB). Only the number of RTX maintenance infusions was counted. When available, we noted ANCA status and titer by immunofluorescence and enzyme-linked immunosorbent assay (ELISA; normal proteinase-3/myeloperoxidase values < 20 IU/ml), circulating CD19+ B lymphocyte counts by flow cytometry (normal range > 2%), and immunoglobulin levels (normal range 7.5–12 g/l) at diagnosis and during followup. Normal ranges of IgG and IgM were 6.8–15 g/l and 0.40–2.20 g/l, respectively. The normal CD19+ lymphocyte count exceeds 2% of the total lymphocyte population. CD19+ depletion is defined as below this normal value, and CD19+ reconstitution as the return of the CD19+ level towards normal.

Definitions. AAV activity was assessed using the Birmingham Vasculitis Activity Score (BVAS, version 3)[8] with complete remission defined as BVAS = 0 for ≥ 3 consecutive months (i.e., no active or persistent disease). The p-BVAS (for persistent BVAS) rated disease status when patients had some BVAS items that were not new or worsening (BVAS = 0) but persistent (regressing or unchanged) for ≥ 3 months, corresponding to "partial remission" (p-BVAS > 0) and represented by mainly "grumbling" ear-nose-throat (ENT) disease and/or scarring lung nodule. However, irreversible damage, like renal insufficiency or sustained, minor, and/or non-worsening sensory neuropathy, was recorded, when present, but did not exclude complete remission. Relapse meant the recurrence, worsening, or first appearance of ≥ 1 BVAS items attributable to active AAV after entering remission.

Disease duration was defined as the time from diagnosis of AAV to the onset of the last flare (0 for newly diagnosed patients; > 0 for relapsers). Followup duration was calculated from the start of induction treatment for the last AAV flare (either diagnosis or relapse for the relapsers) and last patient assessment visit.

Statistical analyses. Quantitative variables (mean ± SD) were compared using Wilcoxon tests for immunoglobulin levels. ANCA levels at last relapse, first RTX maintenance infusion, and last consultation were compared using one-way analysis of variance and pair-wise 2-sample t tests. All analyses were carried out with SPSS 16 software (SPSS Inc., Chicago, IL, USA). Significance was defined as $p < 0.05$.

RESULTS

Patient characteristics. This analysis concerned 28 patients (Table 1 and Appendix): 4 with MPA and 24 with GPA; 17 (60%) males; median age 40.5 years (range 13–70 yrs) at diagnosis and 50.5 years (range 19–78 yrs) at induction treatment for last flare. AAV disease was newly diagnosed in 3 patients, whereas 25 had relapsed (10 had had ≥ 2 relapses). Median disease duration (from diagnosis to last flare) was 84 months (range 15–222 mo). Median BVAS was 15 (range 6–26) before induction [at diagnosis for the former (n = 3) and

Table 1. Characteristics of the 28 patients at AAV diagnosis or last flare and their induction treatments.

Characteristic	Value
Diagnosis, n	
Granulomatosis with polyangiitis	24
Microscopic polyangiitis	4
Age, median yrs (range)	
At diagnosis	40.5 (13–70)
At induction treatment for last flare	50.5 (19–78)
Males, n (%)	17 (60)
AAV duration, median mo (range)	84 (15–222)
BVAS at last flare, median (range)	15 (6–26)
AAV history, n	
Newly diagnosed	3
1st relapse	15
2nd relapse	6
3rd relapse	3
4th relapse	1
Organ(s) involved at last flare, n (%)	
Ear, nose, throat	19 (68)
Lung	18 (64)
Arthralgias/myalgias	11 (39)
Fever	11 (39)
Kidney	9 (32)
Eyes	6 (21)
Peripheral or central neuropathy	3 (11)
Skin	3 (11)
Heart	1 (4)
Abdominal	1 (4)
Induction therapy (+ corticosteroid) for last flare, n (%)	
RTX	11 (39)
RTX + another immunosuppressant	10 (36)
CYC (intravenous or oral)	5 (18)
IVIG or MTX	2 (8)

RTX: rituximab; CYC: cyclophosphamide; IVIG: intravenous immunoglobulin; MTX: methotrexate.

at last flare for the others], with 19 patients having ENT involvement, 18 lung, 11 arthralgias, 11 fever, 9 kidney, 6 eyes, and/or 3 peripheral or central neuropathy. Lung manifestations were characterized by nodules for 11 patients, interstitial syndrome for 4, or both for 3. Eye manifestations were scleritis (n = 3) and, in 1 patient each, retrobulbar optic neuritis, lacrimal gland inflammation and scleritis, and retroorbital mass exophthalmia.

Induction and RTX maintenance regimens. All the patients had received CYC at least once in the past, with a cumulative CYC dose of 48 g/patient (range 5–250 g) before RTX maintenance therapy. Induction therapy before RTX-based maintenance included corticosteroids combined with RTX for 21 patients, with CYC for 5, with intravenous immunoglobulins for 1, or with intravenous immunoglobulins and methotrexate (MTX) for the remainder (Table 1). RTX induction regimens consisted of 2 infusions of 1 g each, given 2 weeks apart (for 4 patients), or 4 infusions of 375 mg/m^2 each, given once weekly (for 17 patients).

At the beginning of maintenance therapy, 6 patients were in complete remission (BVAS and p-BVAS = 0); 12 were in partial remission, with grumbling ENT disease (n = 12) and/or persistent lung nodules (n = 3); 10 were in complete remission with irreversible damage (including peripheral sensory neuropathy or renal insufficiency) from their last flare (n = 9) and/or an earlier flare (n = 3; Table 2).

RTX maintenance therapy was chosen for the 21 who had received RTX induction therapy. For the other patients, RTX maintenance was chosen for the following reasons: (1) side effects/intolerance of more conventional maintenance treatments for 2 patients [azathioprine (AZA)-related hepatitis and myelotoxicity; mycophenolate mofetil (MMF)-associated gastrointestinal intolerance]; (2) persistent and grumbling vasculitis manifestations after > 4 years of AZA or MMF in 1 patient each; or (3) previous relapse(s) under AZA therapy for 2 patients or (4) renal insufficiency for 1.

Patients had received 4 (range 2–10) RTX maintenance infusions over 38 months (range 21–97 mo) of followup since their diagnoses (in 3 patients) and since the last flare for the remaining 25. RTX doses were 375 mg/m^2 biannually for 13 patients, 1 g biannually for 4, 1 g annually for 3, and in different regimens for 8 (Table 2). Combined treatments at the time of the first RTX maintenance infusion included corticosteroids [median dose 5 mg/day (range 2–20)] for 23 (82%) patients and/or other immunosuppressants for 14 (50%; AZA for 6, MMF for 5, leflunomide for 1, and/or MTX for 4). Immunosuppressants were subsequently stopped for 9 patients, 8 months (range 2–26 mo) after their first RTX maintenance infusion. At last visit, all patients were still receiving RTX maintenance, 16 (57%) patients still took corticosteroids [median dose 5 mg/day (range 4–10)], and 7 (25%) received other immunosuppressant(s) (AZA for 3, MMF for 2, MTX for 2, and/or leflunomide for 1 patient).

Table 2. Characteristics of RTX maintenance treatment and outcomes of the 28 patients.

Characteristic	At 1st RTX Maintenance Infusion	At Last Evaluation
RTX maintenance therapy		
No. infusions, median (range)		4 (2–10)
Regimen, n		
375 mg/m^2 biannually		13
1 g biannually		4
1 g annually		3
Others		8
Combined agent		
Prednisone, n	23	16
Daily dose, median mg (range)	5 (2–20)	5 (4–10)
Azathioprine, n	6	3
Mycophenolate mofetil, n	5	2
Leflunomide, n	1	1
Methotrexate, n	4	2
Outcome		
Relapse, n	0	2
Complete remission, n	6	6
With sequelae, n	10	11
Renal insufficiency	6	6
Peripheral neuropathy	2	2
Ear, nose, throat	1	2
Pulmonary fibrosis	1	1
Partial remission (persistent disease), n	12	9
Ear, nose, throat	12	7
Lung (nodules)	3	2

Disease activity was assessed using BVAS version 3[8]. Complete remission: BVAS = 0 for ≥ 3 consecutive months (i.e., no active or persistent disease); partial remission: BVAS = 0 (no new or worsening items) but persistent (p) BVAS items present (regressed or unchanged; p-BVAS > 0) for ≥ 3 months. Complete remission with sequelae: presence of irreversible damage. Relapse: recurrence, worsening, or first appearance ≥ 1 BVAS items attributable to active AAV after entering remission.

Outcomes of AAV disease. Two patients had pulmonary relapses. A 65-year-old woman with MPA developed alveolar hemorrhage 6 months after RTX maintenance infusion, given biannually. Intravenous CYC and plasma exchange generated no response and she again received RTX induction treatment, before switching to RTX maintenance again (she died of H1N1 flu infection 16 months later). A 62-year-old man with GPA developed new lung nodules 11 months after his sixth RTX maintenance infusion (375 mg/m^2 every 6 months, then annually for the last 2). A new RTX induction regimen achieved remission, followed by RTX maintenance.

At last evaluation, 6 patients were in complete remission; 9 patients had partial remissions: 7 with persistent grumbling ENT manifestations, 2 with lung nodules; and 11 patients were in complete remission with irreversible damage: 6 with endstage renal disease, 1 hypoacousia, 1 subglottic stenosis, 1 pulmonary fibrosis, and 2 had residual peripheral neuropathy.

ANCA and CD19+ lymphocyte levels. CD19+ B lymphocytes were depleted before each of the RTX maintenance infusions in 12 of the 24 patients with available data (including the 2

who relapsed). CD19+ lymphocytes were never fully depleted before RTX infusions in 4 patients, and 8 had rising CD19+ lymphocyte levels at at least 1 determination before RTX infusion, but none of them subsequently relapsed. However, one relapser had CD19+ lymphocyte reconstitution at the time of relapse, 11 months after his last RTX infusion (this was not measured in the other patient).

Five patients were persistently ANCA-negative at time of diagnosis. At last flare, 5 of the remaining patients were ANCA-negative by ELISA (level < 20 IU/ml) and 18 were ANCA-positive. At the time of their first RTX maintenance infusion, 11 of these latter 18 were persistently ANCA-positive (including the 2 relapsers) and 6 remained so at their last evaluation. Mean titers for all 19 proteinase-3 ANCA-positive patients progressively declined, from the last flare to the first RTX infusion and last assessment (84.4 ± 93, 33.4 ± 58.6, and 14.3 ± 34.6 IU/ml, respectively; ANOVA, $p < 0.0001$), but they increased before at least 1 of the RTX maintenance infusions in 8 other patients. ANCA titers at relapse were higher than previous measurements in the 2 patients who relapsed (from 81 to 140 IU/ml and 157 to 240 IU/ml, by ELISA).

RTX tolerance/safety. No immediate RTX infusion-related reaction or serum disease was observed. No late-onset neutropenia was detected during followup. Among the 18 patients with available total gammaglobulin levels at 2 different times (i.e., just before starting RTX induction/maintenance and before the last RTX maintenance infusion), 11 were hypogammaglobulinemic before starting RTX induction/maintenance. Three patients developed hypogammaglobulinemia taking RTX, and total gammaglobulin levels decreased in 14 patients and normalized in 2 patients (Figure 1). Mean gammaglobulinemia was significantly decreased before starting and after RTX administration, i.e., at last evaluation (7.78 ± 2.5 g/l vs 6.97 ± 1.9 g/l, respectively; Wilcoxon test; $p = 0.041$). IgG and IgM levels were under the normal range at last RTX maintenance infusion in, respectively, 12 and 15 of the 21 patients with available data.

Three patients developed infections: 1 cutaneous abscess, 1 otitis media that resolved rapidly under antibiotics, and 1 fatal H1N1 flu infection. The latter patient had normal immunoglobulin levels at the time of her last RTX infusion 6 months before she died (not measured when she developed H1N1 flu), and the 2 others were hypogammaglobulinemic.

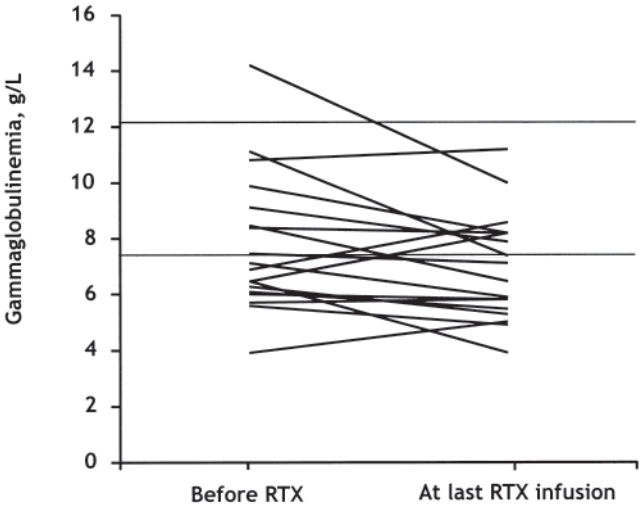

Figure 1. Gammaglobulin concentrations in patients with AAV (n = 18) before first RTX maintenance infusion and at last RTX maintenance infusion. Mean gammaglobulinemia decreased significantly during RTX treatment (Wilcoxon test: 7.78 ± 2.5 g/l vs 6.97 ± 1.9 g/l; $p = 0.041$). Horizontal lines indicate the normal range, 7.5–12 g/l.

DISCUSSION

Our results suggest that RTX effectively maintained remissions of GPA and MPA, with a good global safety profile. The results confirm those reported by Jones, *et al*[2] and Rhee, *et al*[9], who showed that patients who entered remission with RTX may need maintenance therapy, possibly based on RTX itself.

Among the 65 patients with refractory vasculitis analyzed retrospectively by Jones, *et al*[2], none of the 15 who had received preemptive 1-g RTX infusions biannually relapsed, in contrast to 57% of those not prescribed any maintenance therapy, with median followup at 11 months (range 5–23). Rhee, *et al*[9] treated 39 patients with RTX maintenance (1 g every 4 months), and among 20 patients at 24 months of followup, 3 had relapsed. With our longer duration of followup, 2 (7%) relapses have occurred, at 12 and 48 months after induction treatment. For comparison, at similar duration of followup, the WEGENT trial relapse rate was 35% for patients who had received AZA or MTX maintenance, after having achieved remission with corticosteroids plus CYC[10]. However, half our study patients were receiving additional concomitant immunosuppressive therapies during followup, making the interpretation that the low relapse rate was due to RTX less certain.

Based on our results and to further examine the potential place of RTX maintenance therapy compared to more conventional agents (e.g., AZA), we have started a prospective open-label trial (MAINRITSAN; ClinicalTrials.gov identifier NCT00748644) for patients with AAV who achieved remission with conventional CYC-based induction therapy[10,11]. Patients are enrolled at remission and randomized to receive maintenance therapy with either RTX (1 systematic infusion every 6 months for 18 months) or AZA (for 21 months).

Early identification of potential relapsers could help adjust therapy individually, thereby also limiting the risk of prolonged treatment toxicity. Unfortunately, to date, no reliable marker exists to do so[12,13,14]. Although our 2 relapsers had persistent ANCA positivity and increases of ANCA level at relapse, ANCA status and level do not seem sufficiently predictive of relapse to guide retreatment. Similarly, the CD19+ lymphocyte count does not seem to be a reliable predictor of relapse. Jones, *et al*[2] found no clear association between ele-

APPENDIX

Patient Characteristics				AAV Characteristics at Last Flare				Induction Treatment for Last Flare			Rituximab-maintenance Treatment				Outcome		
Dx	Age, yrs	Sex	Disease Duration (from Dx), mo	Organ(s) involved	BVAS*	ANCA titer IU/l†	Inducton regimen‡	CYC Cumulative Dose at Remission (from Dx)	ANCA Titer at Remission, IU/l	BVAS* at Remission	Dose	Infusions, n	Combined Drugs§	Time since Last Flare, mo	Relapse	BVAS* at Last Visit	Last ANCA Titer, IU/l
GPA	64	F	143	L, K, E	24	200	CS-CYC, CS-RTX	53	8	p3, E	375 mg/m²/6 mo	4	CTX-CS	28	0	p1, E	25
GPA	35	F	164	L, R, E, Fv	21	200	CS-RTX	75	200	p0	375 mg/m²/6 mo	4	CS	31	0	P0	105
GPA	62	F	77	L, E, K, Fv	20	119	CS-IFX, CS-RTX	20	0	p4, E	375 mg/m²/6 mo	8	CTX-CS-AZA	58	0	p3, E	0
GPA	51	F	85	L, R, E	10	96	CS-CYC IV, CS-CYC PO-IVIg, CS-RTX	45	0	p3, E	375 mg/m²/6 mo	2	CS	38	0	p3, E	3
MPA	23	F	42	S, R, L	9p2(K)	200 (MPO)	CS-RTX	24	640	p4,K	375 mg/m²/6 mo	3	CS	33	0	p4, K	160
MPA	78	M	65	L	6	200 (MPO)	CS-RTX	10	128	p2, L	375 mg/m²/6 mo	4	MMF (mo8)-CS	34	0	p2, L	62
GPA	48	F	45	E, N, Fv	21p3(N)	ø	CYC PO, CS-RTX-PE	18	ø	p5, N, K	375 mg/m²/6 mo	4	CS	54	0	p5, N, K	ø
MPA	65	F	55	K, R, Fv	15	67 (MPO)	CS-CYC IV, CS-RTX	25	157	p9, K, L	375 mg/m²/6 mo	3	CS	21	L, K	p9, K, L	0
GPA	44	M	90	L	7p3(N)	ø	CS-RTX	48	ø	p3, N	375 mg/m²/6 mo	2	CTX	33	0	p3, N	ø
GPA	29	F	172	L, E	12	65	CS-RTX	60	5	p0	375 mg/m²/6 mo	3	CS	23	0	p0	5
GPA	43	M	15	E, O	8	40	CS-RTX	24	20	p3, E	375 mg/m²/6 mo	3	AZA-CS	24	0	p3, E	0
GPA	52	M	178	H, S, L, E	20	ø	CS-RTX	30	ø	p3, E	375 mg/m²/6 mo	7	MTX (mo18)-MMF	53	0	p3, E	ø
MPA	60	M	0	R, L, K, Fv	18	190 (MPO)	CS-CYC	7	3	p4, K	375 mg/m²/6 mo	4	none	63	0	p4, K	0
GPA	75	M	186	L, K, R, Fv	16	160	CS-RTX	75	0	p3, K	1 g/6 mo	5	CS- MMF (mo2)	45	0	p2, K	0
GPA	52	M	228	N, E, Fv	17	10	CS-MTX-IVIg	250	4	p0	1 g/6 mo	6	CTX-MTX-AZA-CS	51	0	p0	6
GPA	57	M	29	K, O	18	200	CS-CYC	15	84	p0	1 g/6 mo	4	MMF (mo2)-CS	70	0	p0	49
GPA	40	M	114	E, O	12	27	CS-RTX	200	19	p6, E, O	1 g/6 mo	4	MMF-CS	45	0	p6, E, O	0
GPA	26	F	100	N, E, R, L	15	11	CS-CYC, CS-RTX	75	24	p4, E	1 g/yr	2	CTX-CS	26	0	p3, E	6
GPA	67	M	84	S, L	8	48	CS-IVIg	70	8	p3, E	1 g/yr	4	none	67	0	p3, E	0
GPA	56	M	50	A	9	1	CS-CYC, CS-RTX	5	5	p1, R	1 g/yr	3	CTX-AZA (mo3)-CS	56	0	p1, R	0
GPA	64	F	150	K, L, E, R, O	22	144	CS-RTX	81	53	p4, E, K	375 mg/m²/6 mo then 1 g/yr	4 + 1	CTX	33	0	p3, E, K	0
GPA	62	M	62	L, Fv, R, E	9	200	CS-RTX-MTX	48	70	p0	375 mg/m²/6 mo then 1g/yr	6+4	CTX-MTX (mo12)-CS	97	L	p0	0
GPA	57	M	62	E	6	5	CS-CYC PO, CS-RTX	68	0	p3, E	375 mg/m²/6 mo then 1 g/yr	3 + 1	CS-CTX	37	0	p3, E	0
GPA	55	M	0	R, E, L, K, O	20	ø	CS-CYC IV, CS-CYC PO	50	ø	p4, E, O	1 g/6 mo then 1 g/yr	4 + 1	CTX-CS-AZA (mo3)	57	0	p4, E, O	ø
GPA	18	F	26	L, E, Fv	15	5	CS-RTX	21	0	p3, E	1 g/6 mo then 375 mg/m²	2 + 1	CTX-CS-AZA (mo26)	37	0	p2, E	0
GPA	38	M	61	R, E, Fv	9	200	CS-CYC	–	200	p3, N	1 g then 375 mg/m²/6 mo	1 + 4	MTX-CS	38	0	p3, N	8
GPA	73	M	0	E, L, K, Fv	26	302	CS-CYC IV	–	97	p2, K	1 g/y then 375 mg/m²/6 mo	2 + 3	CS	63	0	p2, K	135
GPA	50	F	222	E, O	6	ø	CS-RTX-IVIg	80	ø	p0	375 mg/m²/yr	2	LEF-CS	33	0	p1, E	ø

*Scores indicate active BVAS or persistent (p) BVAS, if the vasculitis had not been active recently but, as defined by the BVAS, with some lingering grumbling symptoms. †ELISA specificity for proteinase 3, unless specified otherwise.‡Successive treatment lines are separate by commas. For example, CS-CYC, CS-RTX refers to a patient, who achieved remission with the combination of CS and RTX, after failure of CS and CYC. §Values between parentheses after drugs correspond to the month of their withdrawal after the first RTX-maintenance infusion. ØANCA negative at onset of disease (IF nor ELISA).A: abdominal; ANCA: antineutrophil cytoplasm antibodies; AZAA: azathioprine; BVAS: Birmingham Vasculitis Activity Score; CS, corticosteroids; CTX, co-trimoxazole; CYC, cyclophosphamide; Dx, diagnosis; E, ear, nose & throat; ELISA, enzyme-linked immunosorbent assay; F, female; Fv, fever; GPA, granulomatosis with polyangiitis (Wegener's); H: heart; IFX: infliximab; IV: intravenous; IVIg: intravenous immunoglobulin; K: kidney; L: lung; LEF: leflunomide; M: male; MMF: mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; MTX, methotrexate; N, central or peripheral neuropathy; –: no data available; O: ophthalmological; PO: per os; R: arthralgias & myalgias; RTX: rituximab; S: skin.

vated ANCA levels and relapse. Rhee, *et al*[9] reported complete CD19+ lymphocyte depletion in their 3 patients whose ANCA levels were positive but stable before they relapsed.

RTX, like corticosteroids and other immunosuppressants, carries a risk of infection, although the relationship between RTX maintenance and the 3 infectious events we observed remains hypothetical. Two of these 3 patients who developed infections were hypogammaglobulinemic. Hypogammaglobulinemia is common in patients treated with RTX, but most of our patients had also previously and/or concomitantly received other drugs such as CYC and corticosteroids, possibly further decreasing their gammaglobulin levels. Whether RTX associated hypogammaglobulinemia is associated with a higher risk of infections remains to be determined. Jones, *et al*[2] found no clear association between infections and gammaglobulin levels. In patients with rheumatoid arthritis, gammaglobulin levels before RTX appeared to be more closely associated with the risk of infection than during or after RTX therapy[15]. Longterm RTX safety in patients with AAV requires further investigation, especially if regular maintenance infusions are given.

We acknowledge that our study had limitations, including its retrospective design, thus the heterogeneity of induction treatments and RTX maintenance regimens, for which protocols had not been fully developed until recently. This preliminary study does not allow conclusions about the precise role of RTX in maintenance regimens for AAV or an optimal RTX regimen. The heterogeneity of treatments given in this exploratory and retrospective analysis precludes definitive conclusions, but no "red flag" was raised concerning safety of RTX or relapse rate. Moreover, not all patients had regular or systematic monitoring of ANCA levels, white cell counts, and immunoglobulins, which hampers understanding of the safety and tolerance of RTX maintenance therapy. However, no recommendations have been made concerning the need for maintenance therapy (or not) for those patients with AAV achieving remission with RTX, and if so, with which drug and regimen. Longer followup of patients in the RAVE[4] and RITUXVAS[5] trials who entered RTX-induced remission should provide some insight into these issues.

Our results and other available data suggest that RTX could probably be used as maintenance treatment for AAV. We must now determine whether RTX is as effective and safe as other maintenance agents such as AZA[10], and the optimal RTX maintenance regimen.

ACKNOWLEDGMENT

We thank Janet Jacobson for editorial assistance, and all French Vasculitis Study Group members who followed the patients and/or included them in the French Vasculitis Study Group database.

REFERENCES

1. Brihaye B, Aouba A, Pagnoux C, Cohen P, Lacassin F, Guillevin L. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: A study on 8 patients. Clin Exp Rheumatol 2007;25 Suppl 44:S23-7.
2. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009;60:2156-68.
3. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: Report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173:180-7.
4. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
5. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
6. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
7. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
8. Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.
9. Rhee EP, Laliberte KA, Niles JL. Rituximab as maintenance therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis. Clin J Am Soc Nephrol 2010;5:1394-400.
10. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790-803.
11. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310-7.
12. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med 2005;143:621-31.
13. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:262-8.
14. Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: Comparison of two independent cohorts. Arthritis Rheum 2008;58:2908-18.
15. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 2010;62:2625-32.