Rituximab Therapy for Systemic Rheumatoid Vasculitis: Indications, Outcomes, and Adverse Events

Caitrin M. Coffey, Michael D. Richter, Cynthia S. Crowson, Matthew J. Koster, Kenneth J. Warrington, Steven R. Ytterberg, and Ashima Makol

ABSTRACT. ***Objective.*** To characterize the indication, outcomes, and adverse effects of rituximab (RTX) treatment in a large single-center cohort of patients with systemic rheumatoid vasculitis (RV).

Methods. We retrospectively reviewed the medical charts of 17 patients treated with RTX for systemic RV from 2000 to 2017. Clinical characteristics, outcomes, and adverse effects were analyzed.

Results. At RV diagnosis, mean age was 59 years, 59% were female, 94% were white, and 82% had positive rheumatoid factor. At the time of initiating RTX, median Birmingham Vasculitis Activity Score for rheumatoid arthritis was 4.0 (interquartile range 2.0–7.5). RV presented in the skin in 8 patients (47%), as mononeuritis multiplex in 2 (12%), inflammatory ocular disease in 2 (12%), and affected multiple organ systems in 5 (29%). RTX was used for induction therapy in 8 patients (47%), relapsing RV in 4 (24%), second-line therapy in 2 (12%), and salvage therapy or in combination with another agent in 3 (18%). At 3 months, 2 (13%) of 15 patients with available followup information achieved complete remission (CR), and 10 (67%) achieved partial response (PR). At 6 months, 6 patients (40%) achieved CR, 8 (53%) achieved PR, and one had no response. At 12 months, 8 of 13 patients with available records (62%) had CR and 5 patients (38%) had PR.

Conclusion. Systemic RV is difficult to treat effectively. CR of RV was achieved in 62% and PR in 38% of patients within 12 months of RTX use. Further evidence is needed to inform treatment for patients with RV. (J Rheumatol First Release November 15 2019; doi:10.3899/jrheum.181397)

Key Indexing Terms:
RHEUMATOID ARTHRITIS VASCULITIS BIOLOGICAL THERAPY

Systemic rheumatoid vasculitis (RV) is a rare inflammatory process affecting small- to medium-sized blood vessels that confers significant morbidity and mortality in patients with rheumatoid arthritis (RA). Up to 40% five-year mortality has been associated with development of RV, making it the most serious of all extraarticular manifestations of RA[1]. Development of RV in persons with RA has been associated with male sex, smoking at the time of RA diagnosis, longstanding disease, and vascular disease[2]. With the advent of biologic therapies and treat-to-target strategies, the incidence of RV has declined sharply over the past 2 decades[1]. However, the clinical presentation of RV has remained similar, and morbidity and mortality associated with RV remain high[1,2].

In the absence of treatment guidelines, the management of RV has been based largely on empiric evidence. In 1984 Scott and Bacon described the use of intravenous cyclophosphamide (CYC) combined with methylprednisolone[3]; a regimen that remains commonly used even today. In the Norfolk Vasculitis Register, 94% of patients with RV received high-dose glucocorticoids (GC) with intravenous CYC between 2001 and 2010[4]. At our institution between 2000 and 2010, 99% of patients received high-dose GC while 55% received a disease-modifying antirheumatic drug (DMARD), 29% received CYC, and 28% a biologic agent[1].

Rituximab (RTX), a B cell–depleting anti-CD20 monoclonal antibody, has proven effective in RA with active disease despite DMARD therapy[5]. The role of RTX and other biologic agents for RV has not been well established, though in the French Autoimmunity and Rituximab (AIR) registry a majority of patients treated with RTX either as first-line, relapse, or salvage therapy for RV achieved remission at 6 (71%) and 12 (82%) months[6]. RTX is also effective for the antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides, and now represents a mainstay of therapy[7,8,9].

From the Division of Rheumatology, Department of Internal Medicine, and Department of Health Sciences Research, College of Medicine and Science, Mayo Clinic, Rochester, Minnesota, USA.

C.M. Coffey, MD, Department of Internal Medicine, College of Medicine and Science, Mayo Clinic; M.D. Richter, MD, Department of Internal Medicine, College of Medicine and Science, Mayo Clinic; C.S. Crowson, PhD, Division of Rheumatology, and Department of Health Sciences Research, College of Medicine and Science, Mayo Clinic; M.J. Koster, MD, Division of Rheumatology, College of Medicine and Science, Mayo Clinic; K.J. Warrington, MD, Division of Rheumatology, College of Medicine and Science, Mayo Clinic; S.R. Ytterberg, MD, Division of Rheumatology, College of Medicine and Science, Mayo Clinic; A. Makol, MD, Division of Rheumatology, College of Medicine and Science, Mayo Clinic.

Address correspondence to Dr. A. Makol, Assistant Professor of Medicine, Consultant, Division of Rheumatology, Mayo Clinic, 200 First St. SW, Rochester, Minnesota 55905, USA. E-mail: makol.ashima@mayo.edu

Accepted for publication June 4, 2019.

To date, there are no randomized controlled trials evaluating RTX for the treatment of RV, and given the rarity of the condition, evidence to support its use remains limited. Our study aims to analyze indications, outcomes, and adverse effects of RTX use among patients with RV in a large single-center cohort.

MATERIALS AND METHODS

The Mayo Clinic Institutional Review Board approved this study (IRB #11-005042). Patients with systemic RV from 2000 to 2017 who were treated with RTX were retrospectively identified through direct medical chart review. Cases were identified by computer search for diagnosis of "rheumatoid arthritis" AND "vasculitis," with cases confirmed by study investigator (AM) as having RV based on histologic confirmation and/or based on strong clinical and/or radiological diagnosis of RV made by a rheumatologist at our facility, with no alternate explanation per the treating physician. For all potential subjects, computer search was performed for "rituximab" or its trade name in the medical chart. Search results were cross-referenced by study personnel (CMC) to remove duplicates, and all charts manually reviewed to confirm diagnosis of RV and indication of RV for RTX use as documented in clinical notes by the treating physician. Patients who received at least 1 infusion of RTX for first-line induction therapy, for relapsing RV after prior remission, or as salvage treatment after previous treatment failure were included. Patients were excluded if they received RTX for an indication other than RV, were treated at an outside institution, or if followup information was unavailable. Clinical characteristics, treatment, outcomes, and adverse effects were abstracted from electronic medical records.

The Birmingham Vasculitis Activity Score (version 3) for RA (BVAS/RA) without the item arthralgia/arthritis[10,11] is a validated scale for monitoring vasculitis activity. BVAS/RA was recorded or calculated for each subject if available data allowed at the time of RTX use and each followup thereafter. Partial response (PR) was defined as clinical improvement as documented by the provider. Complete remission (CR) was defined as BVAS/RA of zero and/or absence of signs and symptoms of disease as documented by a provider.

Descriptive statistics [mean (SD) or median (interquartile range; IQR)] for continuous variables and number (percentage) for categorical variables were used to summarize the characteristics of the cohort. Characteristics of patients who did and did not achieve CR by 6 months were compared using chi-square and rank-sum tests. Analyses were performed using SAS version 9.4 (SAS Institute Inc.).

RESULTS

Baseline characteristics. Between 2000 and 2017, 129 patients with RV were identified and of these, 17 patients were treated with RTX for RV and included in this cohort. Baseline characteristics are shown in Table 1. Mean age at RV diagnosis was 59.2 (SD 12.4) years. Fifty-nine percent were female, and 94% white. Fourteen of 17 patients (82%) were rheumatoid factor (RF)–positive and 13 of 17 (77%) anticitrullinated peptide antibody (ACPA)–positive. Mean duration of RA at time of RV diagnosis was 12.7 (SD 12.5) years. Mean length of followup after RV diagnosis was 6.9 (median 4.9) years. Fifteen patients (88%) were alive at the time of last followup.

RV was diagnosed by a rheumatologist at Mayo Clinic in 94% of patients; 100% were diagnosed clinically and of these, 8 (47%) had biopsy-proven vasculitis and 2 (12%) had other additional investigations (computed tomography angiography and electromyography). At the time of initiating RTX therapy, the median BVAS/RA was 4.0 (IQR 2.0–7.5), and median 28-joint count Disease Activity Score based on C-reactive protein (DAS28-CRP3) was 2.0 (IQR 1.7–2.3).

RV presented in the skin in 8 patients (47%, ulcers and/or leukocytoclastic vasculitis), as mononeuritis multiplex in 2 (12%), inflammatory ocular disease in 2 (12%), and affected multiple organ systems in 5 (29%; Table 1). Among patients with inflammatory ocular disease (IOD), one had panuveitis, one had ulcerative keratitis and corneal melt, one had posterior scleritis, and 2 had scleritis and episcleritis. None of the patients had renal or pulmonary vasculitis.

RTX use. RTX was used as first-line induction therapy in 8 of 17 patients (47%), relapsing RV in 4 (24%), and salvage therapy (defined as second-line or later) or in combination with another agent in 5 (29%). The administered dose was 1 g two weeks apart in 13 (86.7%), delayed to 7 weeks apart in 1 because of infection, and 375 mg/m^2 weekly for 4 consecutive weeks in 2 (12%; Table 1). GC were used in combination with RTX in 11 (65%). A DMARD was used in combination in 9 (53%), and CYC sequentially with RTX in 1 (6%).

Thirteen of 17 included patients received retreatment with RTX at least once after initial induction; 6 of them had received initial RTX induction as first-line therapy. Among the other 2 subjects who received RTX as first-line therapy, one (subject 6) changed therapy to tocilizumab because of PR, and one (subject 12) did not have followup or retreatment information available.

Treatment outcomes. Fifteen patients had followup information recorded at 3 and 6 months from RTX use, with 2 patients lost to followup. Outcomes are shown in Table 2. At 3 months, 2 patients (13%) had achieved CR and 10 (67%) had achieved partial response. Three patients (20%) had no response. At 6 months, 6 patients (40%) had achieved CR, 8 (53%) had achieved PR, and 1 had no response. At 12 months, 13 patients had followup visit information available for review. Eight patients (62%) had CR at 12 months, and 5 (38%) had PR.

Subjects were grouped by clinical presentation (Table 1) to describe outcomes based upon presenting features of RV. In those with vasculitis affecting the skin (Figure 1), 1 of 7 (14%) with available followup information had no response, 3 of 7 (43%) had PR, and 4 of 7 (57%) had complete response at 6 months. Two of 7 (29%) with available information had PR and 5/7 (71%) had complete response at 12 months. The patient with mononeuritis multiplex and available followup information had PR at both 6 and 12 months. Both of the patients with isolated IOD had PR at 6 months (100%). One of them was followed to 12 months and had PR at that time. Three of 5 patients (60%) with multiple organ systems affected by vasculitis had PR, and 2 of 5 (40%) had complete

Table 1. Baseline characteristics of 17 patients with rheumatoid vasculitis (RV) treated with rituximab (RTX).

Patient No.	Age/Sex	RF/ACPA Status	RA Duration at RV Diagnosis, yrs	Smoking Status at RV Diagnosis	Clinical Presentation	BVAS/RA at Time of RTX Use	RTX Regimen (Initial)	Indication	Prior Therapies for RV
1	77/F	RF+, ACPA+	33	Current	Lower extremity ulcers, digital/upper extremity ulcers	4	1 g × 2 weeks apart	First-line, induction	
2	61/M	RF–, ACPA–	3	Former	Lower extremity ulcers, digital/ upper extremity ulcers, inflammatory ocular disease (panuveitis)	6	1 g × 2 weeks apart	First-line, induction	
3	70/M	RF+, ACPA+	30	Former	Mononeuritis multiplex, lower extremity ulcers, digital/upper extremity ulcers, inflammatory ocular disease (ulcerative keratitis)	2	1 g × 2 weeks apart	Relapsing RV	CYC + CS
4	71/F	RF+, ACPA+	9	Never	Inflammatory ocular disease (posterior scleritis)	2	1 g × 2 weeks apart	Relapsing RV	MTX, HCQ, CS, IFX
5	64/M	RF+, ACPA+	20	Former	Mononeuritis multiplex, mesenteric vasculitis, lower extremity ulcers	9	375 mg/m^2 weekly × 4 weeks	Relapsing RV	CYC + CS
6	60/F	RF+, ACPA+	4	Former	Digital/upper extremity ulcers	2	1 g × 2 weeks apart	First-line, induction	
7	69/F	RF+, ACPA+	6	Never	Mononeuritis multiplex, lower extremity ulcers, digital/upper extremity ulcers, leukocytoclastic vasculitis	15	1 g × 2 weeks apart	First-line, induction	
8	70/M	RF+, ACPA+	19	Former	Leukocytoclastic vasculitis	2	1 g × 2 weeks apart	First-line, induction	
9	47/F	RF–, ACPA–	2	Never	Leukocytoclastic vasculitis	2	1 g × 2 weeks apart	Salvage therapy	CS, ETN, HCQ, AZA
10	50/M	RF+, ACPA+	11	Never	Inflammatory ocular disease (scleritis, episcleritis, uveitis), pericarditis	5	1 g × 2 weeks apart	Salvage therapy	MTX, LEF
11	60/M	RF+, ACPA unknown	5	Former	Lower extremity ulcers, digital/upper extremity ulcers	4	1 g × 2 weeks apart	Relapsing RV	CYC + CS
12	49/F	RF+, ACPA+,	2	Never	Mononeuritis multiplex	9	1 g × 2 weeks apart	First-line, induction	
13	43/F	RF+, ACPA+	4	Current	Inflammatory ocular disease (scleritis, episcleritis)	2	1 g × 2 weeks apart	Salvage therapy	CS, MTX, HCQ, LEF
14	52/F	RF+, ACPA+	1	Never	Leukocytoclastic vasculitis	Not available	1 g × 2 weeks apart	Salvage therapy	CYC + CS
15	69/F	RF+, ACPA+	6	Never	Lower extremity ulcers	4	1 g × 2 weeks apart	First-line, induction	
16	77/F	RF–, ACPA–	43	Former	Lower extremity ulcers	4	1 g × 7 weeks apart	First-line, induction	
17	50/M	RF+, ACPA+	17	Former	Mononeuritis multiplex	9	375 mg/m^2 weekly × 4 weeks	Salvage therapy	CYC + CS

RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: anticitrullinated peptide antibody; CS: corticosteroids; CYC: cyclophosphamide; ETN: etanercept; HCQ: hydroxychloroquine; IFX: infliximab; LEF: leflunomide; MTX: methotrexate; AZA: azathioprine; BVAS/RA: Birmingham Vasculitis Activity Score (version 3) for rheumatoid arthritis.

Table 2. Outcomes and adverse effects in 17 patients with rheumatoid vasculitis after treatment with rituximab.

Patient No.	Age/ Sex	Outcome, 6 Mos	Outcome, 12 Mos	Adverse Event	Event Type
1	77/F	Partial response	Complete remission	None	
2	61/M	Complete remission	Complete remission	None	
3	70/M	Partial response	Partial response	Yes	Infusion reaction
4	71/F	Partial response	Not available	None	
5	64/M	Partial response	Partial response	Yes	Hospitalization (for bleeding rectal ulcer), infection (candida urinary tract infection) requiring IV antibiotics, infection (possible Lyme disease) requiring oral antibiotics, infusion reaction
6	60/F	No response	Partial response	Yes	Infusion reaction
7	69/F	Complete remission	Not available	None	
8	70/M	Complete remission	Complete remission	None	
9	47/F	Partial response	Complete remission	None	
10	50/M	Complete remission	Complete remission	Yes	Rash
11	60/M	Not available	Not available	None	
12	49/F	Not available	Not available	None	
13	43/F	Partial response	Complete remission	None	
14	52/F	Complete remission	Complete remission	Yes	Hospitalization for *Pneumocystis carinii* pneumonia requiring oral antibiotics
15	69/F	Complete remission	Complete remission	None	
16	77/F	Partial response	Partial response	Yes	Infection (*Clostridium difficile* colitis) requiring oral antibiotics
17	50/M	Partial response	Partial response	Yes	Hospitalization for infection (pneumonia) requiring IV antibiotics

Complete remission is defined as BVAS/RA score of zero and/or the complete absence of clinical signs and symptoms of disease. IV: intravenous.

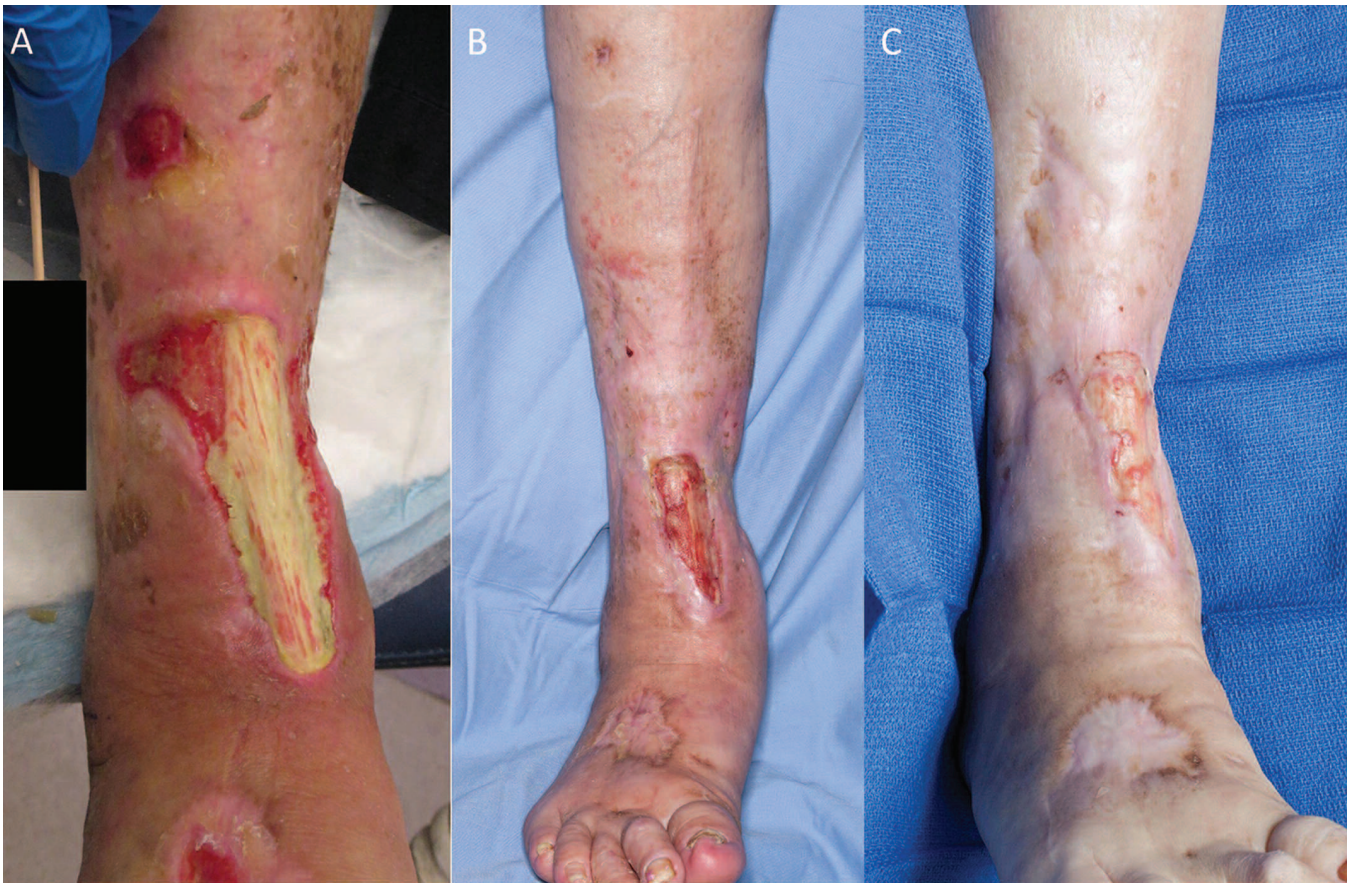

Figure 1. Clinical images of a patient (subject 16) with rheumatoid vasculitis presenting with right lower extremity ulcers, before and after treatment with rituximab (RTX). A. Forty days prior to first RTX treatment. B. About 7 months after first RTX treatment. C. About 11 months after first RTX treatment.

response at 6 months, while 2 of 4 available (50%) had PR and 2 of 4 (50%) complete response at 12 months.

Adverse effects. Ten (59%) of 17 patients tolerated RTX without adverse effects; 4 (24%) of 17 experienced mild adverse effects, including 2 with infusion reaction, 1 with rash, and 1 with *Clostridium difficile* colitis requiring oral antibiotic therapy. Three (18%) of 17 required hospitalization: 2 with infection (urinary tract infection, pneumonia) and 1 with *Pneumocystis carinii* pneumonia who had been prescribed prophylaxis. There were no deaths as a result of RTX use. None of the patients developed neutropenia, hypogammaglobulinemia, herpes simplex virus infection, opportunistic fungal infection, or tuberculosis.

Analysis. When compared between groups who did and did not achieve CR at 6 months, there were no significant differences in age, sex, smoking status, body mass index, duration of RA at RV diagnosis, baseline RA characteristics including RF and ACPA titers, DAS28-CRP3 or BVAS/RA baseline scores, medications used for RA prior to development of RV, or type of RV presentation. There was a nonsignificant trend toward higher inflammatory markers at the time of RTX use in those who achieved CR; median erythrocyte sedimentation rate was 63.5 versus 27.0 mm/h ($p = 0.32$) and CRP was 27.1 versus 13.2 mg/l ($p = 0.59$).

CYC use. In the current series, 7 of 17 patients received CYC at some time during their clinical course of RV. Three patients had been treated with CYC for an earlier episode of RV and received RTX for relapsed disease (subjects 3, 5, and 11), one of whom (subject 3) was receiving ongoing CYC therapy at the time of initiating RTX for relapsed disease. Two patients did not respond to CYC as first-line therapy, prompting transition to RTX (subjects 14, 17). One patient discontinued before any benefit was realized because of adverse effects (nausea, vomiting), prompting initiation of RTX (subject 15). One patient started CYC after response to RTX was inadequate (subject 4).

Followup. At the time of last followup at our institution, 15 patients (88%) were living and 2 patients (12%) had died. One patient died from metastatic melanoma. The other patient's cause of death is unknown.

DISCUSSION

Herein we report indications, outcomes, and adverse effects for 17 patients with systemic RV who received treatment with RTX. Of the 13 patients for whom followup information was available 12 months after initial RTX therapy, 62% experienced CR and 38% PR. Prior case studies[12,13] and a small case series[14] in 4 patients with cutaneous vasculitis refractory to other therapies have shown favorable results with RTX therapy in patients with RV. In addition, our results are in agreement with those from the French AIR registry, a multicenter, prospective cohort study in which CR was attained by 71% of patients at 6 months and 82% at 12 months[6]. To date, no randomized controlled trials have been performed and these are unlikely to be feasible because of the rare features of RV. Thus, treatment of RV continues to be based on clinical experience and cohort data, with no formal guidelines established. The present study adds to the small body of literature available regarding treatment of RV with RTX.

Currently, treatment for mild to moderate RV may include oral GC (20–40 mg/day prednisone equivalent) along with oral DMARD therapy. Severe RV, involving multiple organ systems or with 2 or more extraarticular manifestations, is typically treated with oral GC with or without 0.5–1 g/day intravenous pulse GC for the first 3 days, followed by CYC, RTX, or an anti-tumor necrosis factor (TNF) agent. RTX, an alternative anti-TNF agent, or another biologic agent is used in refractory or relapsed cases if not used for initial treatment[1]. In the current study, a majority of patients who received RTX as induction or as salvage therapy, after other treatments had failed, achieved CR at 1 year. Achievement of remission was not associated with differences in baseline characteristics or clinical features of RV presentation, though this case series with 17 patients was not designed to investigate predictors of response. There was a trend toward higher inflammatory markers at the time RTX was used in those who experienced CR, but this finding did not reach clinical significance.

The patients in this study developed systemic RV most commonly in the skin, eyes, or peripheral nerves. RV may involve any organ system but involves the skin or peripheral nerves in the majority of patients[15]. The median BVAS/RA score at the time of first RTX use in our study was lower than that reported in the French AIR group, and this may be because 8 patients (47%) presented only with cutaneous manifestations of systemic vasculitis. It has been suggested that isolated skin involvement carries a more favorable prognosis[15], and treatment response may differ among patients with different presentations of RV; thus our results may not be generalizable to a population with more severe multiorgan involvement. We note that of the 4 patients who had multiple organ systems involved and followup information available, 2 attained CR and 2 experienced PR at 1 year. Of 3 with mononeuritis multiplex who had followup information available, all had PR but none achieved CR at 1 year, which could suggest difference in treatment response or be related to the difficulty of assessing remission in patients who develop neuropathy. Of the 3 subjects with scleritis, a severe form of inflammatory ocular disease related to RA, 2 (subjects 10, 13) achieved CR at 1 year while 1 (subject 4) achieved partial remission at 6 months and did not have followup information available at 1 year.

Adverse events included hospitalization for 3 patients; one with *P. carinii* pneumonia requiring oral antibiotic therapy, and 2 with other infections requiring intravenous antibiotic treatment. One patient was treated on an outpatient basis for *Clostridium difficile* colitis. The safety profile observed is comparable to that seen in the French AIR registry, in which 3 of 17 patients experienced severe infection[6]. The safety of

RTX has not been directly compared to other agents such as CYC in patients with RV, though in groups with ANCA-associated vasculitis, rates of adverse events were not different between those who received CYC and RTX[8,9].

Limitations of our study include small sample size of 17 patients and retrospective design. Because of the retrospective features, followup was not standardized, and thus the timing, frequency, and data gathered at followup visits varied as in routine clinical practice. For instance, information about B cell depletion after initial RTX use was available in only 8 of 17 patients and thus conclusions about B cell depletion and clinical response could not be drawn. Two of the total 17 patients were lost to followup before 6 months and could not be included in the outcome analysis. The heterogeneity of the clinical scenarios in which some patients received CYC and RTX, and small sample sizes, preclude any direct comparisons between the 2 therapeutic agents. Additionally, relapse and retreatment after use of RTX were not specifically addressed, and information regarding maintenance therapy is limited.

Complete remission of systemic RV was achieved by 62% of patients at 1 year after treatment with RTX in this single-center, retrospective cohort. These findings are consistent with the existing literature. RTX appears to represent an effective option for inducing remission of RV, and has an acceptable safety profile. Further research is needed to inform use of RTX for RV.

REFERENCES

1. Makol A, Matteson EL, Warrington KJ. Rheumatoid vasculitis: an update. Curr Opin Rheumatol 2015;27:63-70.
2. Makol A, Crowson CS, Wetter DA, Sokumbi O, Matteson EL, Warrington KJ. Vasculitis associated with rheumatoid arthritis: a case–control study. Rheumatology 2014;53:890–9.
3. Scott DG, Bacon PA. Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. Am J Med 1984;76:377-84.
4. Ntatsaki E, Mooney J, Scott DG, Watts RA. Systemic rheumatoid vasculitis in the era of modern immunosuppressive therapy. Rheumatology 2014;53:145-52.
5. Edwards JC, Szezepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572-81.
6. Puechal X, Gottenberg JE, Berthelot JM, Gossec L, Meyer O, Morel J, et al; Investigators of the AutoImmunity Rituximab Registry. Rituximab therapy for systemic vasculitis associated with rheumatoid arthritis: results from the AutoImmunity and Rituximab registry. Arthritis Care Res 2012;64:331-9.
7. Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. Drug Des Devel Ther 2017;11:2891-904.
8. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al; European Vasculitis Study Group. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
9. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al; RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
10. 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.
11. Birmingham Vasculitis Activity Score (version 3). [Internet. Accessed October 3, 2019.] Available from: golem.ndorms.ox.ac.uk/calculators/bvas.html
12. Hellmann M, Jung N, Owczarcyk K, Hallek M, Rubbert A. Successful treatment of rheumatoid vasculitis-associated cutaneous ulcers using rituximab in two patients with rheumatoid arthritis. Rheumatology 2008;47:929-30.
13. Maher LV, Wilson JG. Successful treatment of rheumatoid vasculitis-associated foot drop with rituximab. Rheumatology 2006;45:1450-1.
14. Assmann G, Pfreundschuh M, Voswinkel J. Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers. Clin Exp Rheumatol 2010;28 Suppl 57:S81-3.
15. Bartels CM, Bridges AJ. Rheumatoid vasculitis: vanishing menace or target for new treatments? Curr Rheumatol Rep 2010;12:414-9.