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Long-Term Safety of Rituximab in Granulomatosis With Polyangiitis and in Microscopic Polyangiitis

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Objective. The present study was undertaken to conduct a phase IV, open-label, prospective study to characterize the long-term safety of rituximab in a 4-year observational registry of adult patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) within the US.

Methods. Patients initiating treatment with rituximab were evaluated every 6 months for up to 4 years. Outcomes included the incidence of serious adverse events (SAEs), infusion-related reactions (IRRs), and SAEs of specific interest, including serious infections, serious cardiac events, serious vascular events, and malignancies.

Results. Overall, 97 patients (72 with GPA and 25 with MPA) received rituximab through a median of 8 (range 1–28) infusions and were followed up for a median of 3.94 years (range 0.05–4.32 years). The estimated incidence rates (95% confidence interval [95% CI]) of serious infections, serious cardiac events, and serious vascular events were 7.11 (4.55–10.58), 5.03 (2.93–8.06), and 2.37 (1.02–4.67) per 100 patient-years (PYs), respectively. No IRRs or SAEs occurred within 24 hours of an infusion of rituximab. None of the 9 deaths reported (crude mortality rate 2.67 [95% CI 1.22–5.06] per 100 PYs) were considered to be related to use of rituximab.

Conclusion. The safety profile of long-term treatment with rituximab in patients with GPA or MPA was consistent with that of rituximab administered for shorter durations and with rituximab's known safety profile in other autoimmune diseases for which it has received regulatory approval. These findings provide clinicians with long-term, practice-level safety data for rituximab in the treatment of GPA or MPA.

INTRODUCTION

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are 2 forms of systemic vasculitis that affect small to medium-sized blood vessels and are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs). If left untreated, GPA and MPA can result in organ damage or death. Serious infections, cardiovascular disease, and malignancy are important causes of morbidity and death in patients with GPA or MPA (1).

Prior to regulatory approvals in 2011 for the use of rituximab in combination with glucocorticoids for the treatment of patients with GPA or MPA, the standard-of-care treatment (since the 1970s) for severe disease was cyclophosphamide in combination with glucocorticoids (2). Rituximab is an anti-CD20 monoclonal antibody that targets and depletes CD20+ B cells and is approved for the treatment of GPA and MPA (3–6). Rituximab, in combination with glucocorticoids, is recommended by both the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology as an alternative to cyclophosphamide for induction of remission of new-onset, organ-threatening, or life-threatening GPA or MPA (2,7). Rituximab is also effective for the maintenance of remission in patients with GPA or MPA (2,8–10).

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Qualified researchers may request access to individual patient-level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available at https://vivli.org/members/ourmembers/. For further details on Roche's global policy on the sharing of clinical information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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SIGNIFICANCE & INNOVATIONS

- This study reports long-term safety data following treatment with rituximab in 97 patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) in a prospective observational manner outside of a controlled clinical trial and in a real-world setting.
- In patients with GPA or MPA, long-term treatment with the anti-CD20 antibody rituximab was consistent with that of rituximab administered for shorter durations and with rituximab's known safety profile in other autoimmune diseases for which it is approved.
- The findings in this study provide clinicians with long-term, practice-level safety data for rituximab in the treatment of GPA or MPA.

Given the improved survival of patients with GPA or MPA over the past decades (11) and the potential short- and long-term toxicities associated with standard-of-care treatments (12), the Rituximab in ANCA-Associated Vasculitis registry (RaVeR) was developed to address the need for data on the long-term outcomes of patients with GPA or MPA treated with rituximab and other immunosuppressive therapies in routine clinical practice. The primary objective of this study was to characterize the long-term safety of rituximab, including repeated administrations, in the treatment of GPA or MPA in a real-world setting (observational cohort).

PATIENTS AND METHODS

Study design and patients. RaVeR was a phase IV, multicenter, prospective, observational study to characterize the long-term safety of rituximab in patients with GPA or MPA (ClinicalTrials.gov identifier NCT01613599). The study was a post-marketing requirement requested by the US Food and Drug Administration (FDA). Patients were recruited from June 2012 to July 2015 from 15 centers in the US. Inclusion criteria for this study were the following: age ≥18 years, diagnosis of GPA or MPA consistent with the Chapel Hill Consensus Conference definitions for MPA or the ACR 1990 criteria for the classification of GPA (13,14), and disease severity requiring treatment with rituximab per the investigators' assessment. Only patients receiving rituximab for the first time (or who started during screening) were eligible for enrollment in the registry. Exclusion criteria included hypersensitivity to any component of humanized or murine monoclonal antibody or diagnosis of eosinophilic granulomatosis with polyangiitis. There was no protocol-mandated dose or regimen for the treatment with rituximab. The specific rituximab regimen administered was either the FDA-approved dose of 375 mg/m^2 once weekly for 4 weeks in combination with glucocorticoids or any modification by the treating physician. After induction of remission, patients could be retreated with rituximab and/or administered other treatments for the management of GPA or MPA, per the physician's discretion. Although prophylaxis to prevent *Pneumocystis jirovecii* infection is recommended for patients with GPA and MPA during treatment with rituximab, this was not mandated in the protocol.

This study was approved by the institutional review boards and independent ethics committees of the investigational centers. All patients provided written informed consent in accordance with the Declaration of Helsinki. See Appendix A for a list of colleagues and investigators who contributed to this study.

Assessments. Protocol-specified assessments were completed at screening, at baseline, and at follow-up visits every 6 months (±45 days). Follow-up was up to 4 years or until death, study withdrawal, or loss to follow-up. Safety assessments included adverse events (AEs) and severe flares of GPA or MPA. The primary outcome was the incidence of serious infections, defined as infections that were serious AEs (SAEs), or nonserious infections that were treated with intravenous antimicrobials. Secondary outcomes were the proportion of patients experiencing SAEs, including infusion-related reactions, the incidence rate (IR) of SAEs of specific interest (serious infections, serious cardiac events, serious vascular events, and malignancies [excluding nonmelanoma skin cancer]), deaths, causes of death, pregnancies, and severe flares, defined as worsening of GPA or MPA as evidenced by ≥1 new or worsening abnormality over the preceding 28 days and/or disease activity prompting treatment with high-dose glucocorticoids, rituximab, and/or cyclophosphamide (15). The Vasculitis Damage Index (VDI) (16) score was recorded for patients at baseline and every 6 months that they remained under observation.

Statistical analysis. Descriptive statistics were used to characterize baseline characteristics and treatment during the study period. The IR and percentage of patients with each type of safety event were estimated with 95% confidence intervals (95% CIs) under the assumption that the number of events followed a Poisson distribution and that distribution of the log-transformed event rate could be approximated by a normal distribution with a sufficiently large sample size. IRs of outcomes expressed as events per 100 patient-years (PYs) were calculated as the total number of events that occurred during the study period divided by the sum of PY follow-up in the safety-evaluable population. All data collected prior to patient discontinuation were included in the analysis.

RESULTS

Patient disposition and baseline characteristics. Of 100 patients enrolled, 97 received rituximab and were included in the long-term safety population (Figure 1); 3 patients were excluded because of unverifiable data. The mean ± SD age was 56.3 ± 16.5 years, and the majority of patients were female (58.8%) and White (90.7%) (Table 1). Overall, 72 patients (74.2%) had GPA, and 25 (25.8%) had MPA, with a mean and median disease duration of 3.5 and 0.44 years, respectively (range 0–29.7 years). In total, 71

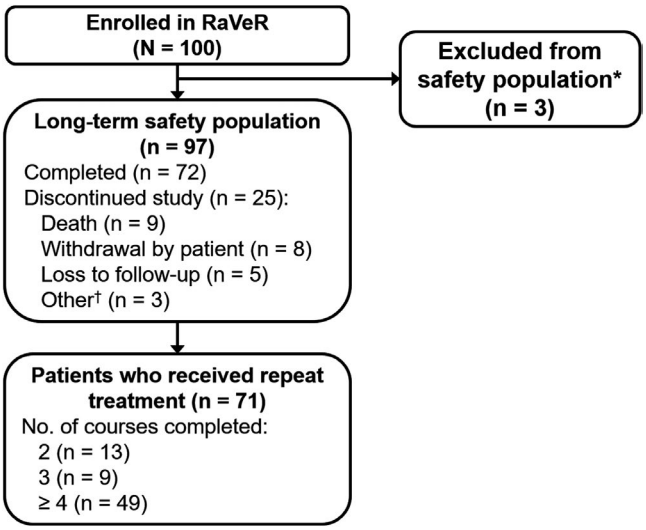

Figure 1. Study patient disposition. RaVeR = Rituximab in ANCA-Associated Vasculitis registry; * = 3 patients from an unresponsive study site were excluded because the data could not be verified; † = 3 patients had unspecified reasons for discontinuation.

patients (73.2%) received additional courses of rituximab for maintenance of remission (follow-up) after the initial course of treatment to induce remission and were included in the repeat treatment population. Most patients who discontinued participation in the study did so for non-safety reasons, including study withdrawal by patient (8 [8.2%]), loss to follow-up (5 [5.2%]), and other (3 [3.1%]).

For the 60 patients with VDI scores at baseline, the median score was 2.0 with a range from 0 to 14. Seventeen patients (17.5%) had a prior history of plasmapheresis and/or dialysis, and 19 (19.6%) were receiving concomitant cyclophosphamide on day 1 of study treatment.

Exposure to rituximab. The median duration on study was 3.94 years (range 0.05–4.32 years), and 79 patients (81.4%) were followed up for ≥3 years. Patients received a median of 8 (range 1–28) infusions of rituximab, for a total of 337.66 PYs of exposure. During the study, 38.2% of patients received ≥10 infusions of rituximab, and 3.1% received just 1 infusion (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24332/abstract). The median total cumulative dose of rituximab was 7,336 mg (range 844–19,725 mg).

Safety. *AEs.* A total of 194 AEs were reported in 61 patients (62.9%) during the study. The most common AEs reported were infections (53 events in 24 patients [24.7%]), primarily pneumonia, which occurred in 6 patients (6.2%) (Table 2). No cases of reactivation of hepatitis B were reported. One opportunistic infection, cryptococcal pneumonia, was reported as a nonserious AE; the dose of rituximab was not reduced, no treatment for the infection was reported, and the patient recovered. No cases of pneumocystis pneumonia, progressive multifocal leukoencephalopathy, or other opportunistic infections were reported. No pregnancies were reported during the study.

Nineteen patients (19.6%) had 23 AEs that were considered by the treating physician to be related to study treatment. The most common treatment-related AEs were respiratory, thoracic, and mediastinal disorders (7 events in 7 patients [7.2%]: throat irritation, dyspnea at rest in 1 patient, and throat tightening in 1 patient) and infections (6 events in 6 patients [6.2%]) and are consistent with the known side effects of rituximab.

Fourteen AEs in 11 patients (11.3%) led to dose modification or interruption of rituximab. Three of these AEs were serious and resulted in dose modification; all patients recovered. The majority of the events that led to modification of the dose or interruption of rituximab were reported in the system organ class of respiratory, thoracic, and mediastinal disorders (8 events in 8 patients [8.2%]).

Table 1. Patient demographic and baseline characteristics*

Characteristic	Safety population (n = 97)
Age, mean ± SD years	56.3 ± 16.5
Female sex	57 (58.8)
Race	
White	88 (90.7)
Black	5 (5.2)
Asian	2 (2.1)
Other	2 (2.1)
Ethnicity	
Hispanic/Latino	7 (7.2)
Not Hispanic/Latino	89 (91.8)
Unstated	1 (1.0)
GPA	72 (74.2)
MPA	25 (25.8)
Disease duration, median (range) years	0.44 (0–29.7)
ANCA antigen type (n = 87)	
Myeloperoxidase	36 (41.4)
Proteinase 3	50 (57.5)
Other	1 (1.1)
Baseline VDI score, median (range)	2.0 (0–14)
Baseline no. of severe flares (n = 74)†	
1	71 (95.9)
2	3 (4.1)
Concomitant treatment at baseline	
Dialysis	5 (5.2)
Plasmapheresis	6 (6.2)
Cyclophosphamide	19 (19.6)
Previous treatment for GPA or MPA	
Dialysis	7 (7.2)
Plasmapheresis	11 (11.3)

* Values are the number (%) unless indicated otherwise. ANCA = antineutrophil cytoplasmic autoantibody; GPA = granulomatosis with polyangiitis; MPA = microscopic polyangiitis; VDI = Vasculitis Damage Index.
† Defined as worsening disease as evidenced by ≥1 new or worsening abnormality over the preceding 28 days (ref. 15) possibly up to 4 weeks prior to baseline.

Table 2. Adverse events reported in ≥3 patients*

Adverse event	Patients with ≥1 adverse event
Pneumonia	6 (6.2)
Atrial fibrillation	5 (5.2)
Deep vein thrombosis	5 (5.2)
Throat irritation	5 (5.2)
Urinary tract infection	4 (4.1)
Death, cause not specified	4 (4.1)
Hemoptysis	3 (3.1)
Hypoxia	3 (3.1)
Influenza	3 (3.1)

* Values are the number (%).

The only event that led to dose modification or interruption in >1 patient was throat irritation (4 patients [4.1%]).

SAEs. The IRs of overall SAEs in the total safety population and the population of patients who received repeat rituximab treatment are shown in Figure 2. Overall, a total of 94 SAEs were observed in 38 patients (39.2%) during the study, with an IR of 27.8 per 100 PYs (95% CI 22.5–34.1). Among the 71 patients who received repeat treatment with rituximab, a total of 63 SAEs were reported, with an IR of 23.9 per 100 PYs (95% CI 18.4–30.6). The rate of SAEs was not increased among patients who received 6–10 or >10 infusions of rituximab (see Supplementary Figure 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24332/abstract). The most frequently occurring SAEs were atrial fibrillation and deep vein thrombosis (5 patients each [5.2%]); other SAEs included atrial flutter, chest pain, gastroenteritis, herpes zoster, hemoptysis, hypoxia, influenza, laryngeal stenosis, pneumonia, staphylococcal bacteremia, and urinary tract infection (2 patients each [2.1%]) (Table 3). None of the SAEs occurred during or within 24 hours of an infusion of rituximab.

Twenty-four serious infections were reported in 14 patients (14.4%), with an IR of 7.11 per 100 PYs (95% CI 4.55–10.58) (Figure 3). One patient died from a serious infection (septic shock). This event was considered by the treating physician to be unrelated to treatment with rituximab. In the 71 patients who received repeat treatment with rituximab, 16 serious infections were reported, with an IR of 6.07 per 100 PYs (95% CI 3.47–9.86).

A total of 17 serious cardiac events occurred in 10 patients (10.3%), with an IR of 5.03 per 100 PYs (95% CI 2.93–8.06) (Figure 3). The majority of cardiac events were arrhythmias, occurring in 7 of 10 patients: atrial fibrillation in 5 patients (5.2%), atrial flutter in 2 (2.1%), and atrial tachycardia and supraventricular tachycardia in 1 each (1.0%). With the exception of 1 SAE of supraventricular tachycardia, which occurred in a patient with a medical history of mitral regurgitation and unspecified cardiovascular events, the serious cardiac events were not considered by the investigator to be related to study treatment, nor did they occur during or within 24 hours of infusion of the rituximab. All but 1 of the patients who experienced cardiovascular AEs had significant risk factors for cardiovascular disease, such as prior cardiovascular events, renal disorders, obesity, hypertension, tobacco use, or concomitant use of medications known to induce cardiovascular events (such as cyclophosphamide and prednisone).

Eight serious vascular events were reported in 6 patients (6.2%), with an IR of 2.37 per 100 PYs (95% CI 1.02–4.67) (Figure 3): deep vein thrombosis in 5 patients [5.2%]), followed by 1 event each of hematoma and orthostatic hypotension (1.0%). All of the vascular SAEs resolved, except in 1 patient who had 2 events of deep vein thrombosis. The patient recovered from the first event; the second event (grade 3) occurred along with staphylococcal bacteremia and was ongoing when the patient died due to septic shock. This event was considered by the investigator to be unrelated to study treatment. Most of the vascular SAEs resolved, and no patients withdrew from the study or had dose decreases or interruptions due to vascular SAEs.

Three patients (3.1%) experienced 3 malignancies (adenocarcinoma, lung adenocarcinoma, and intraductal proliferative breast lesion), with an IR of 0.89 per 100 PYs (95% CI 0.18–2.60) (Figure 3). None of these events were considered by the treating physician to be related to study treatment.

A post hoc subgroup analysis revealed that 21 patients (21.6%) received concomitant cyclophosphamide during the study. Of these 21 patients, 7 (33.3%) experienced a total of 15 SAEs, with an IR of 17.82 per 100 PYs (95% CI 9.97–29.39). Of the 76 patients (78.4%) who did not receive cyclophosphamide during the study, 31 patients (40.8%) experienced a total of 79 SAEs, with an IR of 31.17 per 100 PYs (95% CI 24.67–38.84). Low patient numbers in the cyclophosphamide group and overlapping confidence intervals should be taken into consideration when interpreting these data.

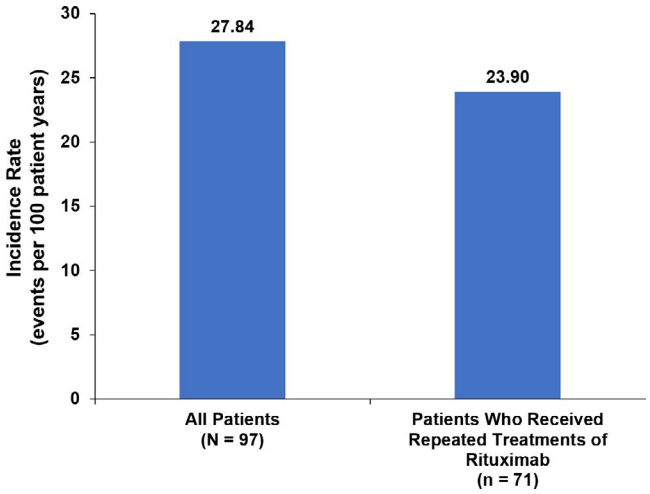

Figure 2. Overall incidence rates of serious adverse events among patients in the study.

Table 3. Serious adverse events reported in ≥2 patients*

Serious adverse event	Patients with ≥1 serious adverse event
Atrial fibrillation	5 (5.2)
Deep vein thrombosis	5 (5.2)
Death	4 (4.1)
Atrial flutter	2 (2.1)
Chest pain	2 (2.1)
Gastroenteritis	2 (2.1)
Hemoptysis	2 (2.1)
Herpes zoster	2 (2.1)
Hypoxia	2 (2.1)
Influenza	2 (2.1)
Laryngeal stenosis	2 (2.1)
Pneumonia	2 (2.1)
Staphylococcal bacteremia	2 (2.1)
Urinary tract infection	2 (2.1)

* Values are the number (%).

Deaths. Nine patients (9.3%) died during the study, for a crude mortality rate of 2.67 per 100 PYs (95% CI 1.22–5.06). One patient each died from interstitial lung disease, congestive cardiac failure, lung adenocarcinoma, cardio-respiratory arrest, and septic shock; 4 patients died from unknown causes. None of the deaths were considered by the treating physician to be related to rituximab.

Severe disease flares. During the study, a total of 15 severe flares of GPA or MPA were reported, with an IR of 4.44 per 100 PYs (95% CI 2.49–7.33). The median VDI score ranged from 2.0 to 3.0 over the course of the study.

DISCUSSION

This study reports long-term safety data following treatment with rituximab in 97 patients with GPA or MPA in a prospective observational manner outside of a controlled clinical trial and in a real-world setting. The primary safety outcome in this analysis was the incidence of serious infections, an identified risk with rituximab (9). Overall, 14.4% of patients experienced a serious infection, with an IR of 7.11 per 100 PYs. No patients withdrew from the study or had dose modifications due to infections, suggesting that, in general, such infections were medically manageable and resolved with standard treatment. These results are consistent with those in patients with GPA or MPA treated with 1 course (≤1 month) of rituximab for induction of remission of vasculitis (3). Despite the difference in indication, these data are also consistent with results from the Sunstone registry (IR of 7.6 per 100 PYs), in which 989 patients with moderate-to-severe rheumatoid arthritis (RA) were followed up for up to 5 years (total of 3,844 PYs) in a real-world setting (17). The incidence of serious infections in the current analysis did not increase over time or with an increasing number of infusions of rituximab, suggesting that long-term, repeated treatment does not increase the risk of serious infections.

The prevalence of concurrent serious cardiac disorders in patients with vasculitis is highly variable and has been reported to range between 3.3% and 24% (18,19). In the current study, 10 patients (10.3%) had serious cardiac events (5.03 per 100 PYs); most of these were arrhythmias, which are currently characterized in the existing label for rituximab (9). All but 1 of the patients who experienced cardiovascular AEs had significant risk factors for cardiac events. With the exception of 1 event of supraventricular tachycardia reported in a patient with a history of cardiovascular events, no serious cardiac events were considered by the treating physician to be related to study treatment.

Patients with GPA or MPA have an increased risk of thromboembolic events (20,21). In this study, 6 patients (6.2%) developed serious vascular disorders, with an overall IR of 2.37 per 100 PYs. This rate is comparable to that in published reports of the occurrence of venous thrombotic events in patients with GPA or MPA receiving short-term rituximab (6.1%) or cyclophosphamide (9.2%) (3). Most of the thromboembolic events in the RaVeR study resolved, and no patients withdrew from the study or required dose modification of rituximab due to serious vascular disorders, suggesting that, in general, such events were medically manageable.

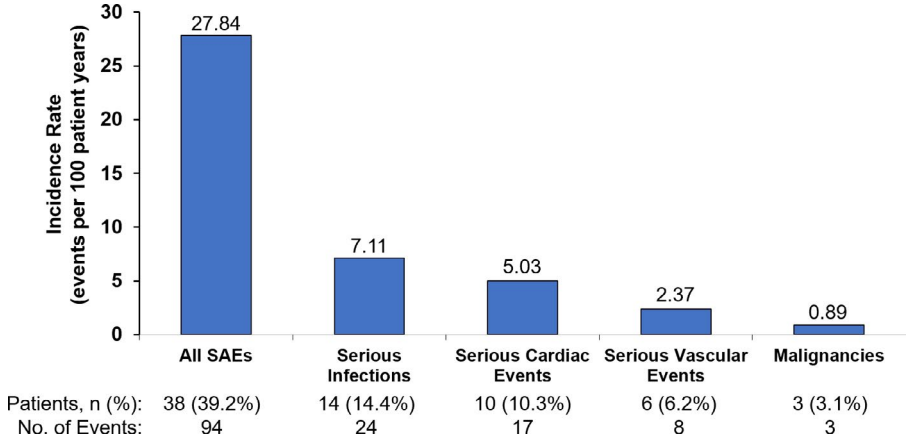

Figure 3. Incidence rates of specific serious adverse events (SAEs).

Patients with GPA or MPA may also be at an increased risk of de novo cancers compared with the general population (22). Of the 3 malignancy events (3.1%; 0.89 per 100 PYs) reported in this study, none were considered by the investigators to be related to study treatment. The prevalence of malignancy has similarly been observed in 2% to 6% of patients with GPA or MPA in clinical trials investigating the safety of short-term rituximab (3–5). In patients with RA receiving long-term treatment with rituximab as part of the RA clinical trial program and the Sunstone RA registry, the reported IRs of malignancy were 0.7422 and 0.44 per 100 PYs (17), respectively, although it should be noted that the recommended dosage and dosing frequency of rituximab for RA differs from that recommended for GPA or MPA.

SAEs were reported in 39.2% of patients, with an overall IR of 27.84 per 100 PYs. The distribution and type of SAEs were consistent with the known safety profile of rituximab in GPA and MPA and in other autoimmune indications. The incidence of SAEs among patients who had received repeat treatment was slightly lower (23.90 per 100 PYs), suggesting that additional infusions of rituximab and increasing exposure to rituximab over time were not associated with an increased risk of SAEs. These data are also consistent with the rate of SAEs over 18 months reported in patients with ANCA-associated vasculitis who were treated with rituximab for induction of remission (42%) in a controlled clinical trial (5). However, the proportion of patients with SAEs in the current study was numerically higher than that observed in patients with RA in the Sunstone registry (29.7%) (17). Because the majority of SAEs in RaVeR were single events, the rate of SAEs is likely not the result of SAEs of a particular type or pattern.

This study has some limitations to consider. This study excluded patients <18 years old; therefore, these results are not generalizable to children with GPA or MPA. Given the observational and open-label nature of RaVeR, the rituximab dose and regimen were administered at the treating physicians' discretion, leading to inevitable variability in dose, intervals, frequency, and duration of treatment. In addition, concomitant medications were managed without restriction by the treating physicians. It is possible that AEs may have resulted from the use of concomitant medications, but causality is difficult to determine due to the absence of a comparator arm. AEs may have also resulted from underlying GPA or MPA or other preexisting concurrent medical conditions because patients with preexisting conditions were not excluded from the study in order to reflect a real-world setting more accurately. Finally, data on immunoglobulin levels were not collected, preventing the assessment of hypogammaglobulinemia in this population.

In this study, no new safety concerns were identified for the use of rituximab to treat GPA or MPA. The safety profile of long-term (up to 4 years) follow-up treatment with rituximab in patients with GPA or MPA was consistent with the known overall safety profile of rituximab in patients with GPA or MPA treated for shorter periods. Safety data were also consistent with the known safety profile of rituximab in other autoimmune diseases in which it is approved for use (23). These findings provide clinicians with long-term, practice-level safety data for rituximab in the treatment of GPA or MPA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Merkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Merkel, Niles, Mertz.
Acquisition of data. Merkel, Niles, Mertz, Lehane.
Analysis and interpretation of data. Merkel, Niles, Mertz, Lehane, Pordeli, Erblang.

ROLE OF THE STUDY SPONSOR

Genentech had roles in the study design and in the collection, analysis, interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication. Publication of this article was contingent upon approval by Genentech.

ADDITIONAL DISCLOSURES

Authors Lehane, Pordeli, and Erblang are employees of Roche.

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APPENDIX A: STUDY COLLABORATORS

The following colleagues and investigators contributed to this study: Nancy Allen, Joel A. Block, Rodrigo Cartin-Ceba, Curry Koening, Carol Langford, Paul Monach, Larry W. Moreland, Patrick Nachman, and Daniel Wallace.