

Phase IIa Global Study Evaluating Rituximab for the Treatment of Pediatric Patients With Granulomatosis With Polyangiitis or Microscopic Polyangiitis

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Objective. To assess the safety, tolerability, pharmacokinetics, and efficacy of rituximab (RTX) in pediatric patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA).

Methods. The Pediatric Polyangiitis Rituximab Study was a phase IIa, international, open-label, single-arm study. During the initial 6-month remission-induction phase, patients received intravenous infusions of RTX (375 mg/m² body surface area) and glucocorticoids once per week for 4 weeks. During the follow-up period, patients could receive further treatment, including RTX, for GPA or MPA. The safety, pharmacokinetics, pharmacodynamics, and exploratory efficacy outcomes with RTX were evaluated.

Results. Twenty-five pediatric patients with new-onset or relapsing disease were enrolled at 11 centers (19 with GPA [76%] and 6 with MPA [24%]). The median age was 14 years (range 6–17 years). All patients completed the remission-induction phase. During the overall study period (≤4.5 years), patients received between 4 and 28 infusions of RTX. All patients experienced ≥1 adverse event (AE), mostly grade 1 or grade 2 primarily infusion-related reactions. Seven patients experienced 10 serious AEs, and 17 patients experienced 31 infection-related AEs. No deaths were reported. RTX clearance correlated with body surface area. The body surface area–adjusted RTX dosing regimen resulted in similar exposure in both pediatric and adult patients with GPA or MPA. Remission, according to the Pediatric Vasculitis Activity Score, was achieved in 56%, 92%, and 100% of patients by months 6, 12, and 18, respectively.

Conclusion. In pediatric patients with GPA or MPA, RTX is well tolerated and effective, with an overall safety profile comparable to that observed in adult patients with GPA or MPA who receive treatment with RTX. RTX is associated with a positive risk/benefit profile in pediatric patients with active GPA or MPA.

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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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INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are rare, potentially organ- and life-threatening, systemic autoimmune small vessel vasculitides. GPA and MPA are associated with the presence of ANCAs against proteinase 3 (PR3) or myeloperoxidase (MPO) (1). Pediatric patients with GPA or MPA share many signs and symptoms of these diseases with adult patients (2). Childhood-onset disease carries considerable disease-related morbidity and mortality, mainly as a result of progressive renal failure or aggressive respiratory involvement (2).

The conventional treatment for severe GPA or MPA in patients is remission induction with cyclophosphamide (CYC) (3) or mycophenolate mofetil (MMF) (4) in combination with glucocorticoids (GCs), usually followed by maintenance with azathioprine (AZA) or methotrexate (5). CYC in combination with GCs does not prevent frequent relapses in the majority of children with GPA or MPA, and this treatment is associated with a significant toxicity risk (2). Relapses may occur more frequently in pediatric patients treated with MMF than in those treated with CYC (4). Pediatric patients with GPA or MPA therefore have major unmet needs, including the lack of improvement in remission rates as well as inability to prevent flares and reduce the toxic effects of GCs and immunosuppressive therapies. Because children and adolescents require treatment during critical periods of growth and development and require treatment for a longer duration than adult patients, it is important to have alternatives to GCs and toxic immunosuppressants.

There is strong evidence to indicate that B cells play a crucial role in the pathogenesis of GPA and MPA (6,7). B cells may contribute to GPA and MPA pathogenesis by acting as antigen-presenting cells, through the production of various cytokines or through ANCA autoantibody production by their progenitor cells (7). Rituximab (RTX) is an anti-CD20 monoclonal antibody that targets and depletes CD20+ B cells. Thus, RTX may disrupt the critical functions of B cells in the pathogenesis and progression of AAVs. The efficacy and safety of RTX as remission-induction treatment in adult patients with severe GPA or MPA were demonstrated in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial (8). RTX, in combination with GCs, was approved worldwide for the treatment of GPA and MPA in adult patients. Recently, the Rituximab versus Azathioprine in ANCA-Associated Vasculitis trial (9) demonstrated the efficacy of RTX for remission maintenance in adult patients with GPA or MPA, leading to regulatory approvals in the US and European Union.

Due to the rare nature of AAVs, controlled clinical trials in pediatric patients with GPA or MPA are difficult to conduct (2). RTX is increasingly being used as a first-line remission-induction treatment in children with AAVs, instead of CYC (10); however, limited data are available regarding pediatric RTX use. Since the

pathogenesis of GPA and MPA is similar in adult and pediatric patients, efficacy can be extrapolated from the outcomes data obtained in adult patients in the RAVE trial (8).

The objective of this first company-sponsored global clinical study was to evaluate the safety, pharmacodynamics (PD), and pharmacokinetics (PK) of RTX in pediatric patients with GPA or MPA. Exploratory efficacy outcomes were also evaluated. Our study led to the US Food and Drug Administration and European Medicines Agency approving RTX for the treatment of GPA and MPA in pediatric patients ≥ 2 years of age in September 2019 and March 2020, respectively (11,12).

PATIENTS AND METHODS

Patient population. Eligibility criteria included being between age 2 years and age 18 years at the time of screening, having received a diagnosis of either GPA (13) or MPA (14), and having newly diagnosed or relapsing disease, defined as the recurrence or new onset of potentially organ- or life-threatening disease (≥ 1 major Birmingham Vasculitis Activity Score [BVAS] for GPA [15]) or disease activity severe enough to require treatment with CYC or immunosuppressive therapy. Exclusion criteria included having received a diagnosis of eosinophilic GPA, having severe disease requiring mechanical ventilation due to alveolar hemorrhage, requiring plasmapheresis or dialysis at the time of screening, or receiving prior treatment with RTX or other B cell-targeted therapy within 6 months prior to the baseline visit.

Written informed consent was obtained from all pediatric patients or from patients' parents or legal guardians, with assent provided by the patient as appropriate, depending on the patient's age and level of understanding. The trial was conducted in accordance with the Declaration of Helsinki. Ethics approval for this study was obtained from the respective institutional review boards or ethics committees (see the Supplementary Methods, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

Study design. The Pediatric Polyangiitis and Rituximab Study (PePRS) (clinical study no. WA25615; ClinicalTrials.gov identifier: NCT01750697; European Clinical Trials database no. 2012-002062-13) (see Appendix A for a list of members of the PePRS Study Group) is a phase IIa, international, multicenter, open-label, single-arm uncontrolled study consisting of a screening period of ≤ 28 days and an initial 6-month remission-induction phase followed by a minimum additional 12-month follow-up phase (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

During the remission-induction phase, RTX was administered as an intravenous (IV) infusion of 375 mg/m² (≤ 1 gm/dose) once a week for 4 consecutive weeks, at baseline (day 1) and on

days 8, 15, and 22. The RTX dose was calculated according to the body surface area of each patient assessed at the screening visit and remained the same for all 4 infusions. Pediatric patients received acetaminophen and an antihistamine prior to each RTX infusion. Before the first RTX infusion, patients received 3 separate IV infusions of methylprednisolone (MP) (each at a dosage of 30 mg/kg/day; maximum dosage of 1 gm/day) at any time after the screening visit, up to and including day 1. If clinically indicated and at the investigator's discretion, up to 3 additional IV infusions of MP could be administered prior to the first RTX infusion. All patients received concomitant oral prednisolone or prednisone (1 mg/kg/day, up to a maximum dosage of 60 mg/day) tapering to ≤ 0.2 mg/kg/day by month 6 (maximum dosage 10 mg/day) and mandatory prophylactic treatment for *Pneumocystis jirovecii* infection. During the remission-induction phase, concomitant use of immunosuppressive agents for GPA or MPA was not permitted. However, patients who experienced a disease flare that could not be controlled using glucocorticoids prior to month 6 could receive standard of care treatment and remain in the study.

During the follow-up phase, further RTX infusions were administered at the discretion of the investigator according to local practice to maintain remission or to treat disease activity. After month 6, other immunosuppressive treatments for GPA or MPA were permitted in accordance with the clinical judgment of the investigator (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). After month 18, pediatric patients continued to be followed up at study visits every 3 months until the common closeout date, May 10, 2018, 18 months after the last patient was enrolled.

Outcomes and assessments. The safety and tolerability of RTX were evaluated based on an assessment of all adverse events (AEs) and serious AEs (SAEs), vital signs, and routine laboratory test results. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Infusion-related reactions were defined as AEs that occurred during or within 24 hours of an RTX infusion and were classified within the Roche standard AE definition of infusion-related reactions with hypersensitivity (Medical Dictionary for Regulatory Activities [MedDRA] version 20.1; available online at <http://www.meddrasso.com/>). Total serum Ig, IgG, and IgM levels were regularly measured every 8–12 weeks throughout the treatment period and follow-up period. Abnormal laboratory test results indicating prolonged low levels of IgG or IgM were defined as IgG or IgM levels less than the lower limit of normal (LLN) for a ≥ 4 -month period. Antidrug antibody positivity and titers were monitored throughout the study.

During the remission-induction phase, serum samples were collected for a population PK analysis prior to the first, second,

third, and fourth infusions; after the completion of the first and fourth infusions; and subsequently at months 1, 2, 4, and 6. The PK parameters that we assessed included RTX clearance, volume of distribution, and exposure (measured as area under the curve [AUC]). The influence of several covariates, such as demographic characteristics (e.g., body surface area, sex, and the presence of antidrug antibodies), on PK parameters was tested. The relationship between RTX exposure and efficacy, B cell counts, and safety parameters was also assessed. In an exploratory analysis, the PD effects of RTX were evaluated using a longitudinal assessment of circulating CD19+ B cell counts.

All efficacy end points were exploratory in nature. Achievement of remission by months 6, 12, and 18 was assessed, with remission defined based on the Pediatric Vasculitis Activity Score (PVAS) (16), according to either of 2 different definitions: 1) a PVAS score of 0 and achievement of an oral prednisone dose (or prednisolone equivalent dose) of ≤ 0.2 mg/kg/day (maximum dosage of 10 mg/day); or 2) a PVAS score of 0 on 2 consecutive visits ≥ 4 weeks apart, irrespective of the dose of GC being received. Other exploratory efficacy end points included BVAS, physician global assessment of disease activity (evaluated using a 0–100-mm visual analog scale, with 0 defined as no disease activity and 100 defined as maximum disease activity), Pediatric Vasculitis Damage Index (PVDI) (17,18), and cumulative GC dose.

Statistical analysis. We did not conduct formal statistical hypothesis testing for any of the study end points. Nonlinear mixed-effects modeling (NONMEM 7.4.1; ICON Development Solutions) (19) was used to analyze PK data from pediatric and adult patients with GPA and MPA enrolled in this study and the RAVE study (8), respectively, and nonlinear mixed-effects modeling was also used to characterize the sources contributing to variability in the frequency of exposure to RTX.

Exploratory analyses. For the exposure-efficacy analysis, cumulative exposure over the remission-induction phase for each pediatric patient (AUC of cumulative exposure to RTX over 180 days [baseline to month 6] [AUC_{0–180}]) was computed using the individual pediatric patient's dosing history and the individual PK parameters from the final population PK model. Logistic regression models were used to assess the association between the probability of disease being in PVAS-based remission by 6 months and RTX exposure (AUC_{0–180}). A logistic regression model was fitted to these remission data, and a confidence interval (CI) was defined around the regression line. For each exposure value, a 90% CI was defined as the 5th and 95th percentiles of the predictions among 1,000 bootstrap data sets. Logistic regression models were used to assess any correlation between probability of the occurrence of selected AEs and RTX exposure in pediatric patients. The selected AEs included SAEs,

grade ≥ 3 AEs, infusion-related reactions, serious infections, and hypogammaglobulinemia.

For the exploratory efficacy analyses, all data were summarized using descriptive statistics. For binary end points, the number and percentage of patients are presented by visit. At key time points (months 6, 12, and 18), 2-sided 95% CIs were calculated for the percentage of pediatric patients who achieved PVAS-based remission. For continuous end points, the median and interquartile range (IQR) are presented.

RESULTS

Characteristics of the patients at baseline. Between May 23, 2013 and Nov 16, 2016, the study enrolled 25 patients from 11 investigational sites across 6 countries, of whom 17 (68%) were from Europe and 8 (32%) were from North America. Most patients were female (80%), White (68%), and between 12 and 17 years of age (76.0%) (Table 1). A total of 19 patients (76%) had GPA and 6 patients (24%) had MPA. A total of 18 patients (72.0%) had newly diagnosed disease at baseline and 7 patients (28%) had relapsing disease. Two patients (8%) with relapsing disease had received prior CYC therapy, but not within the 4 months prior to the baseline visit. A total of 22 patients (88%) were positive for ANCA at baseline. Of the 3 patients who were negative for ANCA at baseline, 2 patients with relapsing disease were perinuclear ANCA (pANCA)-positive and/or MPO-positive at initial diagnosis, and 1 was a patient with newly diagnosed disease who was positive for pANCA 51 days before the baseline visit. At baseline, the most common disease manifestations were arthralgia/arthritis, nasal crusts/ulcers, hematuria/proteinuria, and purpura (Table 1). A total of 15 patients (60%) experienced renal involvement, 4 patients (16%) experienced major renal disease, and 11 patients (44%) experienced vasculitis-related pulmonary involvement (Table 1).

Treatment regimens. All 25 patients completed the per-protocol RTX regimen (infusions of 375 mg/m² once per week for 4 weeks) and also completed the 6-month remission-induction phase (Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). A total of 24 patients completed ≥ 18 months of follow-up; 1 patient withdrew from the study around month 16 due to either an administrative reason or another reason, and was transferred back to a local hospital for care. Eight patients discontinued participation between month 18 and the common closeout date, primarily due to either an administrative reason or some other reason, such as a physician or family decision or transfer to adult care services for their GPA or MPA. There were no withdrawals due to AEs. During the overall study period, patients received 4–28 infusions of RTX. The mean number of infusions per patient was 8. The majority of patients

Table 1. Demographic and baseline clinical characteristics of the patients treated with rituximab (N = 25)*

Sex, female	20 (80.0)
Age, median (range) years	14.0 (6.0–17.0)
Age group	
<12 years	6 (24.0)
≥ 12 years	19 (76.0)
Race	
Asian	4 (16.0)
Black or African American	1 (4.0)
White	17 (68.0)
Other or multiple	3 (12.0)
Height, median (range) cm	154.9 (120.0–175.2)
Weight, median (range) kg	50.9 (23.0–80.8)
Diagnosis	
Newly diagnosed GPA	13 (52.0)
Newly diagnosed MPA	5 (20.0)
Relapsing GPA	6 (24.0)
Relapsing MPA	1 (4.0)
Disease duration, median (range) months	0.5 (0.2–72.1)
ANCA positivity†	22 (88.0)
MPO-ANCA positivity	8 (32.0)
PR3-ANCA positivity	14 (56.0)
Estimated GFR, median (IQR) ml/minute/1.73 m ²	138.0 (120.0–157.0)
PVAS, median (IQR) score (scale 0–63)	8.0 (5.0–15.0)
PhGA, median (IQR) score	46.0 (29.0–71.0)
PVDI, median (IQR) score (scale 0–72)	0.0 (0.0–3.0)
IgG, median (IQR) gm/liter	9.24 (8.5–12.6)
IgM, median (IQR) gm/liter	1.36 (0.8–1.7)
Previous CYC therapy	2 (8.0)
Disease manifestations at baseline	
Arthralgia/arthritis	16 (64.0)
Nasal crusts/ulcers	14 (56.0)
Hematuria	13 (52.0)
Proteinuria	7 (28.0)
Purpura	10 (40.0)
Renal involvement‡	15 (60.0)
Major renal disease§	4 (16.0)
Pulmonary involvement	11 (44.0)

* Except where indicated otherwise, values are the number (%) of patients. MPA = microscopic polyangiitis; MPO = myeloperoxidase; PR3 = proteinase 3; GFR = glomerular filtration rate; IQR = interquartile range; PhGA = physician global assessment of disease activity; PVDI = Pediatric Vasculitis Damage Index; CYC = cyclophosphamide.

† Three patients with relapsing disease were negative for antineutrophil cytoplasmic antibodies (ANCA) at screening but positive for ANCA at the time of the original diagnosis.

‡ According to the Pediatric Vasculitis Activity Score (PVAS) criteria.

§ Based on the definitions in the Birmingham Vasculitis Activity Score for granulomatosis with polyangiitis (GPA), with presence of either red blood cell casts or a significant decline in renal function (rise in creatinine levels $\geq 30\%$ above baseline values or $>25\%$ reduction in creatinine clearance).

(68%) were followed up for 18 months to 3 years, and 6 patients (24%) were followed up for 3–4.5 years. Overall, the total duration of observation was 61.1 patient-years of follow-up.

In total, 17 patients (68%) received additional RTX treatment at or after month 6 until the common closeout date, the dosing of which was variable and determined at the discretion of the treating physician. Among these 17 patients, 5 received infusions of RTX (375 mg/m²) approximately every 6 months administered

once weekly for 4 weeks, and 5 received 1 infusion of RTX (375 mg/m²) every 6 months; a further 7 patients received other, varied doses of RTX within individualized regimens. A total of 9 patients (36%) received ≥ 1 additional immunosuppressive therapy for GPA or MPA between months 6 and 18 (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

Safety based on AEs and SAEs. During the 6-month remission-induction phase, all 25 patients (100%) experienced ≥ 1 AE; 158 AEs were reported, 10 of which were SAEs that occurred in 7 patients (28%) (Table 2). Most AEs (147 [93%], which occurred in 18 patients [72%]), were CTCAE grade 1 or 2 (mild to moderate). A total of 11 grade 3 AEs were reported in 7 patients (28%). No grade 4 or 5 AEs were reported. The most common AEs by MedDRA System Organ Class (SOC) were infections and infestations (31 AEs that occurred in 17 patients [68%]). The most common AEs by MedDRA Preferred Term (PT) were infusion-related reactions, reported in 15 patients (60%), followed by headache, upper respiratory tract infection, and nausea, reported in 4 patients (16%) each (Table 2). The most frequently reported SAEs classified by MedDRA SOC were infections and infestations (3 that occurred in 3 patients [12%]) and vascular disorders (4 that occurred in 3 patients [12%]). The SAEs classified by MedDRA PT that occurred most frequently were related to

Table 2. AEs and SAEs reported during the remission-induction phase in patients treated with rituximab (N = 25)

	No. (%) of patients	No. of events
AEs*		
Infusion-related reaction	15 (60.0)	29
Headache	4 (16.0)	4
Upper respiratory tract infection	4 (16.0)	4
Nausea	4 (16.0)	5
Upper abdominal pain	3 (12.0)	3
Constipation	3 (12.0)	3
Arthralgia	3 (12.0)	3
Back pain	3 (12.0)	3
Cough	3 (12.0)	3
Epistaxis	3 (12.0)	3
SAEs		
GPA worsening†	3 (12.0)	4
Influenza	1 (4.0)	1
Lower respiratory tract infection	1 (4.0)	1
Viral gastroenteritis	1 (4.0)	1
Infusion-related reaction‡	1 (4.0)	1
Myopathy	1 (4.0)	1
Bronchial stenosis	1 (4.0)	1

* Only adverse events (AEs) reported in $\geq 10\%$ of patients are shown.
 † Includes 4 serious AEs (SAEs) of worsening vasculitis in 3 patients, reported with the Medical Dictionary for Regulatory Activities Preferred Terms granulomatosis with polyangiitis (GPA) (3 events) and vasculitis (1 event).

‡ The event was generalized edema that occurred after the fourth rituximab infusion.

worsening GPA (disease flare); these flares were reported to occur in 3 patients (12%) with either GPA (n = 3 events) or vasculitis (n = 1 event) (Table 2).

During the overall study period (6-month remission-induction and follow-up phases), the safety profile of RTX was consistent with what was reported during the remission-induction phase (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). Due to the longer data collection period (up to 4.5 years compared to 6 months), the total number of AEs that were reported was greater (404 AEs were reported to have occurred in 25 patients [100%], 27 of which were SAEs that occurred in 12 patients [48%]). The majority of AEs (370 [92%]) were either grade 1 or 2 in intensity, 32 AEs were grade 3, and 2 AEs were grade 4. No AEs led to discontinuation of study treatment. No deaths, malignancies, progressive multifocal leukoencephalopathy (PML), or other opportunistic infections were reported. During the overall study period, the majority of AEs that resulted in dose modification or treatment interruption were infusion-related reactions (21 AEs that occurred in 10 patients [40%]). The most frequently reported SAEs were consistent with those reported during the remission-induction phase.

Among the SAEs classified by MedDRA SOC, most of them were infections and infestations (9 SAEs that occurred in 7 patients [28%]) and vascular disorders (7 SAEs that occurred in 5 patients [20%]). The SAEs that occurred most frequently by PT were related to worsening GPA and were reported to occur in a total of 6 patients (24%) in conjunction with GPA (n = 6 events), ANCA-positive vasculitis (n = 1 event), or vasculitis (n = 1 event) (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

Infusion-related reactions. Infusion-related reactions predominantly occurred after the first infusion (8 of 25 patients [32%]). The most frequently reported symptoms of infusion-related reactions during the remission-induction phase were rash (n = 3 events), headache (n = 2 events), rhinorrhea (n = 2 events), and pyrexia (n = 2 events), occurring in 2 patients each. The incidence of infusion-related reactions decreased with repeated RTX infusions over time (Supplementary Figure 3, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). One serious infusion-related reaction (generalized edema) was reported and was suspected to be attributable to the concomitant use of GCs. The majority of infusion-related reactions that were reported during the study were grade 1 or 2; 2 nonserious grade 3 infusion-related reactions were reported to occur in 1 patient. No grade 4 or 5 infusion-related reactions were reported.

Infections. During the remission-induction phase, a total of 31 infection-related AEs (serious and nonserious) were reported

to occur in 17 patients (68%), the most frequent being upper respiratory tract infections (occurring in 4 patients [16%]) (Table 2). The majority of infections (90%) were either grade 1 or 2 and were nonserious, resolving without sequelae. In the overall study period, 105 infection-related AEs, of which the majority (91%) were considered to be nonserious, were reported, occurring in 23 patients (92%). Similar to that observed during the remission-induction phase, the most frequent infections that occurred during the overall study period were upper respiratory tract infections.

A total of 3 serious infections in 3 patients (12%) were reported during the remission-induction phase (Table 2): influenza, lower respiratory tract infection, and gastroenteritis. During the overall study period, 9 serious infections were reported to have occurred in 7 patients (28%), including influenza (occurring in 2 patients [8%]) and lower respiratory tract infection (occurring in 2 patients [8%]) as the most frequently occurring events (Supplementary Table 2, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). Overall, the majority of serious infections resolved without sequelae.

During the overall study period, 6 of the 18 patients in whom prolonged low serum levels of IgG were observed subsequently experienced a total of 7 serious infections, and 6 of the 19 patients in whom prolonged low serum levels of IgM were observed subsequently experienced a total of 8 serious infections. Most of the infections were reported as being unrelated to study treatment.

Laboratory test results. IgG, IgM, and total Ig serum concentrations decreased from baseline values over the course of the study. Median IgG levels decreased below the LLN within the first month and returned to within-normal limits between months 9 and 12, with a subsequent slight decrease below the LLN observed through month 18 (Figure 1). Median IgM levels fell below the LLN by month 2 and remained below the LLN through month 18 (Figure 1). The proportions of patients with low levels of IgG and IgM at key study points are shown in Supplementary Table 3 (available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). A total of 3 patients experienced hypogammaglobulinemia AEs, for which they received treatment with intravenous immunoglobulin. All of these patients had previous and concomitant use of steroids and immunosuppressive medications. During the study, no clinically significant changes or abnormalities were observed in other laboratory analyses (e.g., chemistry, hematology, urinalysis) and other safety tests (e.g., vital signs, chest radiographs, electrocardiogram).

Immunogenicity. Of 21 evaluable patients, 4 (19%) developed treatment-induced antidrug antibodies during the overall study period. One patient tested antidrug antibody-positive at month 4 and subsequently at each study visit until month 18. This patient achieved PVAS-based remission by month 6, which was maintained through month 18. The 3 other patients tested positive for antidrug antibodies at month 18, and all were in PVAS-

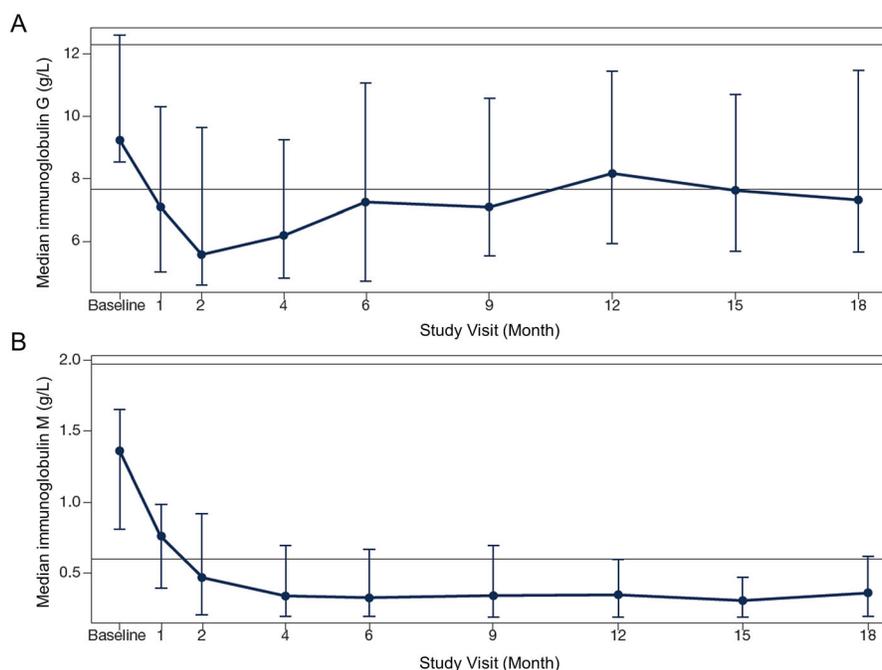


Figure 1. Levels of IgG (A) and IgM (B) at each study visit in the serum of 25 pediatric patients with granulomatosis with polyangiitis or microscopic polyangiitis. Bars show the median with interquartile range. Top and bottom horizontal lines show the lowest upper limit of normal and the highest lower limit of normal (in A, 12.29 gm/liter and 7.68 gm/liter, respectively; in B, 1.97 gm/liter and 0.6 gm/liter, respectively).

based remission at month 18. No serious infusion-related reactions or increases in the occurrence of nonserious infusion-related reactions were observed after the development of antidrug antibodies, and no trends or differences were observed in the type of AEs reported in antidrug antibody-positive patients compared to antibody-negative patients. Two of the patients received repeat RTX treatment after the development of antidrug antibodies, and, as expected, depletion of CD19 B cells occurred following repeated exposure to RTX.

PK analysis. A population PK analysis of the RTX treatment populations was conducted, using 204 serum samples from the 25 pediatric patients in the present study and 487 serum samples from the 97 adult patients with AAVs in the RAVE trial (8). Model parameters for a typical patient (body surface area 1.9 m² and absence of antidrug antibodies), such as RTX clearance (258 ml/day), RTX intercompartmental clearance (317 ml/day), central volume (3,070 ml), peripheral volume (4,160 ml), and terminal half-life (25.6 days), were in the typical range for monoclonal antibodies and were consistent with the known PK of RTX in other autoimmune diseases. The 2 covariates impacting RTX PK were body surface area and the presence of antidrug antibodies. As is typical for monoclonal antibodies, RTX clearance and the volume of distribution parameters increased with body surface area. Because of the effect of body surface area on RTX PK parameters, RTX clearance was lower in pediatric patients compared to adult patients, but RTX exposure (AUC₀₋₁₈₀) was similar between adult patients and pediatric patients because dosages were based on body surface area (Figure 2). As a result, the body surface area-adjusted RTX dosing regimen ensured similar exposure across the whole range of body surface area in pediatric patients with GPA or MPA. Patients with detected antidrug antibodies had 38.2% higher clearance, resulting in a 27.6% lower AUC.

The efficacy-exposure analysis did not show any relationship between RTX exposure variability (in terms of dosing regimens) and achievement of PVAS-based remission (Supplementary Figure 4, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). Moreover, the exposure-safety analysis did not reveal a relationship between RTX exposure and the occurrence of SAEs grade ≥ 3 , infusion-related reactions, serious infections, or laboratory abnormalities, indicating prolonged low serum levels of IgG, during the remission-induction phase (each $P > 0.05$).

PD analysis. Consistent with its mode of action, RTX treatment resulted in sustained CD19+ peripheral B cell depletion that persisted until at least month 6 (Supplementary Figure 5, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). By month 18, B cell levels had increased slightly but still remained low (median 58 cells/ μ l), which is consistent with levels in patients receiving repeat RTX treatment. Among the pediatric patients from the

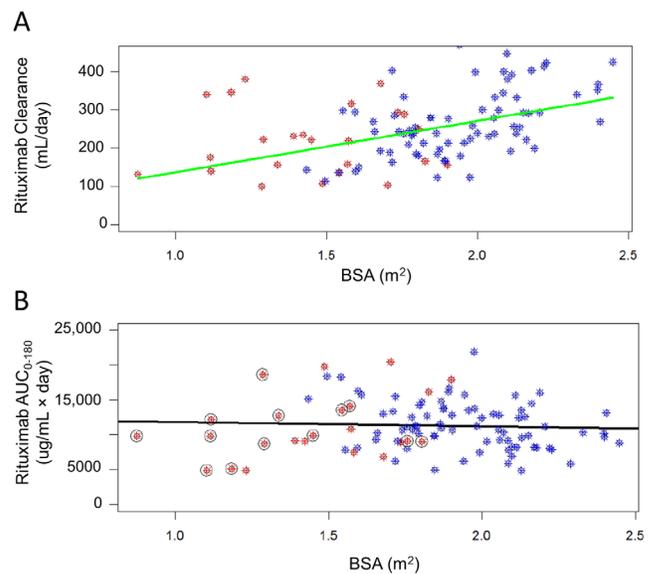


Figure 2. Relationship between the rate of rituximab clearance and body surface area (BSA) (A) and between the cumulative exposure to rituximab over the remission-induction phase (measured as the area under the curve over the first 180 days [AUC₀₋₁₈₀]) and body surface area (B) in antidrug antibody-negative adult and pediatric patients with granulomatosis with polyangiitis or microscopic polyangiitis. Relationships were assessed by linear regression analyses. Red symbols represent predicted individual rituximab clearance (A) and AUC₀₋₁₈₀ values (B) in pediatric patients in the Pediatric Polyangiitis and Rituximab Study. Blue symbols represent the respective predicted individual values in adult patients in the Rituximab in ANCA-Associated Vasculitis trial (8). Circled red symbols in B denote pediatric patients in remission by month 6.

current PePRS study and the adult patients from the RAVE trial, B cell depletion lasted longer in patients with higher levels of exposure (Supplementary Figure 6, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

Exploratory efficacy. Disease activity was primarily assessed using PVAS as an exploratory efficacy outcome measure. PVAS was adapted from BVAS for use in childhood vasculitis. PVAS-based remission was achieved in 14 patients (56.0%), 23 patients (92.0%), and 25 patients (100.0%) by months 6, 12, and 18, respectively (Table 3). Of the 25 patients who achieved PVAS-based remission by month 18, remission was achieved in 24 patients according to the criteria of either the first definition of remission or both the first and second definitions of remission, and in 1 patient, only the criteria of the second definition of remission were met. The mean \pm SD duration of remission during the study was 71.7 \pm 50.9 weeks. The shortest duration of remission was 6.9 weeks, and the longest was 193.4 weeks (\sim 3.5 years). The rate of remission achievement at key study visits is shown in Supplementary Table 4 (available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

Table 3. Efficacy outcomes in patients treated with rituximab (N = 25) by each follow-up time point*

Achievement of PVAS-based remission, no. (% [95% CI])	
Month 6	14 (56.0 [34.9–75.6])
Month 12	23 (92.0 [74.0–99.0])
Month 18	25 (100.0 [86.3–100.0])
Change in PhGA score from baseline, median (IQR)	
Month 6	–39.0 (64.5–16.0)
Month 12	–39.0 (64.0–16.0)
Month 18	–46.0 (72.0–17.0)

* Seventeen pediatric patients received additional rituximab treatment at or after month 6 until the common closeout date. PVAS = Pediatric Vasculitis Activity Score; 95% CI = 95% confidence interval; PhGA = physician global assessment of disease activity; IQR = interquartile range.

Median PVAS scores decreased through month 18 (Supplementary Figure 7, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>). There was no obvious impact of PR3-ANCA or MPO-ANCA status on remission achievement. A decrease in median physician global assessment of disease activity scores from baseline was reported at months 6, 12, and 18 (Table 3), indicating a reduction in disease activity over the course of the study. The median PVDI was 0 at baseline and 2.0 at months 6, 12, and 18. Thus, after an initial increase in the median PVDI from baseline to month 6 (PVDI score of 0 at baseline to 2.0 at 6 months), no further damage was accrued between months 6 and 18.

During the administration of protocol-defined oral steroids in tapering doses, a clinically meaningful decline in the overall dose of oral GCs was observed from week 1 to month 6 (median prednisolone equivalent dose 45 mg [IQR 35–60] at week 1 to 7.5 mg [IQR 4–10] at month 6). This dose tapering of oral GCs was subsequently maintained at month 12 (median prednisolone equivalent dose 5 mg [IQR 2–10]) and month 18 (median prednisolone equivalent dose 5 mg [IQR 1–5]) (Figure 3).

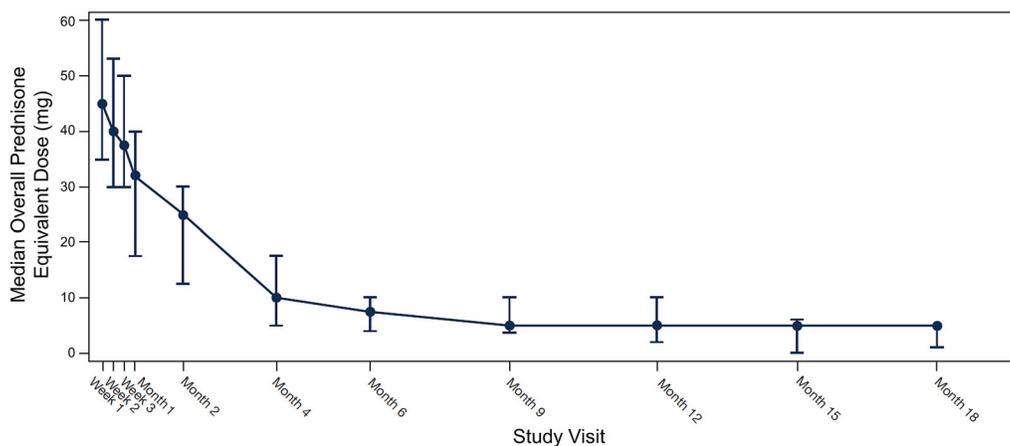


Figure 3. Oral glucocorticoid use over time in 25 pediatric patients with granulomatosis with polyangiitis or microscopic polyangiitis. Bars show the median with interquartile range.

A post hoc sensitivity analysis of the exploratory efficacy outcome (i.e., achievement of PVAS-based remission) was conducted in which 2 patients were excluded who had been continuously receiving additional immunosuppressive therapies (both receiving MMF) between the baseline visit and month 6 and who were considered to be RTX nonresponders. The results of the sensitivity analysis did not change the overall results with regard to the exploratory efficacy outcome at month 6 (data available upon request from the corresponding author). Of the 9 patients who received additional immunosuppressive therapy between months 6 and 18, 5 patients were nonresponders at each of the efficacy time points. Two of these patients received AZA for a short duration (<1 month), which was determined to not have affected whether a patient achieved PVAS-based remission through month 18. Among the 2 patients who received CYC as well as maintenance doses of RTX, efficacy outcomes were variable: PVAS-based remission was achieved at month 12 and month 18 in 1 of the 2 patients, while the other patient was a nonresponder at both time points (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at <http://onlinelibrary.wiley.com/doi/10.1002/art.41901/abstract>).

DISCUSSION

In the PePRS single-arm, open-label clinical study, RTX was evaluated as an alternative treatment option for pediatric patients with GPA or MPA. In the study, safety data regarding RTX use in pediatric patients was consistent with data from adult patients with GPA or MPA, in whom the efficacy and safety profile of RTX is well established. This is the first company-sponsored global clinical trial investigating the use of RTX in pediatric patients with active GPA or MPA. In our study, RTX, administered as 4 weekly IV infusions of 375 mg/m² for remission induction followed by repeat treatment as determined by the treating physician, was

generally safe and well tolerated (for up to 4.5 years). Furthermore, findings from the exploratory efficacy analyses demonstrated a clinical benefit with RTX for achieving PVAS-based remission.

There were no new or unexpected safety findings. The safety profile of RTX in pediatric patients was consistent with the safety profile previously observed in adult patients with GPA or MPA (8) and was consistent with the well-characterized safety profile of RTX for approved autoimmune indications (11,12). Over the course of the study, no patients died or experienced AEs leading to withdrawal, and no malignancies, PML, or other opportunistic infections were reported.

Safety events were associated with confounding/contributory risk factors (e.g., past or concomitant medication use, such as oral GC use), were associated with underlying conditions (GPA or MPA), or were events that were expected with RTX treatment (adverse drug reactions including infusion-related reactions and infections). The most common AEs were infusion-related reactions, which decreased in frequency throughout the study and with repeated treatment. Pretreatment with MP can reduce the incidence and severity of infusion-related reactions (20); however, because patients received high doses of MP prior to the baseline visit, up to day 1, IV MP premedication was optional. The overall incidence and type of infections were characteristic of the general population and pediatric population of AAV patients receiving oral GCs and immunosuppressive therapy.

Low serum levels of IgG or IgM have also been observed in adult patients with autoimmune diseases treated with RTX, which may have no clinical consequence and often do not require specific medical management (21,22). In this study, no consistent pattern in IgG or IgM levels over time was observed, and the majority of patients with prolonged low levels of IgG or IgM did not experience any serious infections. The incidence of antidrug antibodies in pediatric patients (19%) was similar to the incidence observed in adult patients (23% in the RAVE study). In both populations, the presence of antidrug antibodies had no apparent effect on the efficacy, safety, or PD of RTX.

Since RTX dose was based on body surface area, the dosing regimen used in this trial (375 mg/m²) resulted in similar levels of RTX exposure in pediatric patients compared to those observed in adult patients in the RAVE study, in whom a positive benefit/risk profile of RTX was demonstrated (8). Furthermore, the PD effects on CD19 peripheral B cells were similar between pediatric and adult patients, further supporting the idea that efficacy observed in the adult patients could be extrapolated to the pediatric population. There was no relationship between exposure variability and achievement of efficacy outcomes. In addition, findings from the exposure-safety analysis suggested a lack of a relationship between the occurrence of AEs in the safety analysis and RTX exposure.

Clinical disease remission findings from the exploratory efficacy analyses indicated that RTX had an important

clinical benefit, with PVAS-based remission of GPA or MPA achieved in 56%, 92%, and 100% of patients by months 6, 12, and 18, respectively. In a post hoc sensitivity analysis, excluding 2 patients who had received additional immunosuppressive therapies during the remission-induction period did not change the overall exploratory efficacy outcome conclusions at month 6. Despite the important role of GCs in the treatment and control of GPA and MPA, RTX treatment allowed for a clinically meaningful rapid reduction in the tapering dose of oral GCs from the baseline visit to month 6, which was subsequently maintained at months 12 and 18.

This study was not without limitations. Our small sample size limits the generalizability of the findings to all pediatric patients with GPA or MPA. The inclusion of predominantly female patients is consistent with published reports indicating that AAV is more common in female pediatric patients than in male pediatric patients (23). The PePRS study was designed as an open-label, single-arm, uncontrolled study. The lack of a comparator arm prevents direct comparison of the treatment outcomes with conventional standard of care treatments, such as GCs or CYC. However, given the rarity of the disease and alternative treatment options for pediatric patients newly diagnosed as having GPA or MPA or those who were diagnosed as having relapsing GPA or MPA, an open-label design was considered to be the most appropriate and acceptable study design by global ethics and regulatory agencies. Since other induction regimens (i.e., combining RTX with low-dose CYC) were not studied, the question of whether other approaches could induce remission faster and/or improve overall remission rates with acceptable levels of safety could not be answered in this study.

In summary, treatment with 4 weekly infusions of RTX in combination with a tapering dose of oral GCs was demonstrated to have a clinically important effect on remission induction in pediatric patients who were newly diagnosed as having GPA or MPA or in those with relapsing active GPA or MPA. RTX was well tolerated, with an overall safety profile comparable to that observed in adult patients with GPA or MPA who were treated with RTX, and was an effective long-term approach for disease maintenance or for treating relapsing disease through ≥18 months of follow-up.

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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 published. Dr. Brogan 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. Brogan, Brunetta, Lehane.

Acquisition of data. Brogan, Yeung, Cleary, Rangaraj, Kasapcopur, Hersh, Li, Paripovic, Schikler, Zeft, Bracaglia, Eleftheriou, Brunetta, Cooper, Lehane.

Analysis and interpretation of data. Brogan, Yeung, Cleary, Rangaraj, Kasapcopur, Hersh, Li, Paripovic, Schikler, Zeft, Bracaglia, Eleftheriou, Pordeli, Melega, Jamois, Gaudreault, Michalska, Brunetta, Cooper, Lehane.

ROLE OF THE STUDY SPONSOR

Hoffmann-La Roche had a role in the study design and in the collection, analysis, and interpretation of the data, and the writing of the manuscript. Authors Pordeli, Melega, Jamois, and Lehane are employees of Hoffmann-La Roche.

ADDITIONAL DISCLOSURES

Author Gaudreault is an employee of JJG Pharma Consulting. Authors Michalska and Brunetta are employees of Genentech.

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APPENDIX A: MEMBERS OF THE PePRS STUDY GROUP

Members of the PePRS Study Group include Kishore Warrior, Samundeeswari Deepak, the NIHR Team at Nottingham University Hospital, Jennifer Weiss, Liza McCann, Clare Pain, Rebecca Nicolai, Susanna Livadiotti, Nur Canpolat, Kenan Barut, Damien Noone, and Diane Hebert.