



Asthma control in eosinophilic granulomatosis with polyangiitis treated with rituximab

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Abstract

Objectives Rituximab (RTX) treatment is used for antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, but its benefits in eosinophilic granulomatosis with polyangiitis (EGPA) are unclear. Our aim was to characterize asthma control and glucocorticoid (GC) sparing after RTX treatment.

Methods A retrospective, computer-assisted search was performed to identify patients with EGPA and GC-dependent asthma diagnosed between 2000 and 2017 who received RTX for remission induction. Demographic and clinical features were analyzed.

Results Of the 17 patients included, the majority were myeloperoxidase-ANCA positive ($n = 13$, 76.5%). Uncontrolled asthma symptoms and atopy were present in 13 patients (76.5%). RTX was used for initial remission induction in patients with new onset of severe disease ($n = 5$, 29.4%) and after failed remission induction with other immunosuppression ($n = 12$, 70.6%). It was used for remission maintenance in nine patients (52.9%). GCs were used for maintenance at a median dose of 25 mg/day (interquartile range, 16.25–37.5). At the end of follow-up, 13 patients (76.5%) had non-severe or controlled asthma, and remission was achieved in 12 (70.6%). Median serum eosinophil and C-reactive protein values decreased (1.06 vs $0.10 \times 10^9/L$ [$P = .012$] and 27.0 vs 5.0 mg/dL [$P = .001$], respectively), whereas pulmonary function test results remained unchanged. Median GC dose was significantly reduced at 6, 12, 18, and 24 months ($P < .0001$). Patients receiving RTX for maintenance required less than 10 mg of GCs for asthma control.

Conclusion RTX seems to be safe and have GC-sparing efficacy for asthma control in EGPA. Randomized controlled trials are needed for detailed study of RTX for treating EGPA.

Key Points

- In this retrospective study we have concluded that rituximab (RTX) might be considered for the control of severe corticosteroid-dependent asthma in eosinophilic granulomatosis polyangiitis (EGPA) patients especially when myeloperoxidase antibodies are positive.
- Rituximab has not been studied particularly for asthma control in EGPA patients.
- The most noticeable effect of RTX was the decrease in the use of corticosteroids for the control of asthma.

Keywords Autoantibodies · Churg-Strauss syndrome · Epidemiology · Eosinophilic granulomatosis with polyangiitis · Observational studies · Vasculitis

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Abbreviations

ANCA	Antineutrophil cytoplasmic antibody
BVAS/WG	Birmingham Vasculitis Activity Score for Wegener Granulomatosis
EGPA	Eosinophilic granulomatosis with polyangiitis
FEV ₁	Forced expiratory volume in the first second
FVC	Forced vital capacity
GC	Glucocorticoid
IQR	Interquartile range
RTX	Rituximab

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic small-vessel necrotizing vasculitis presenting

with allergic manifestations, asthma, and eosinophilia [1]. Therapeutic clinical trials in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis did not include patients with EGPA. Its eosinophilic-driven pathogenesis and a higher proportion of ANCA-negative patients differentiate EGPA from other ANCA-associated vasculitides [2–4]. Therefore, therapeutic recommendations have been mainly based on expert opinion rather than on reported research findings in the patients with EGPA [5].

In the other ANCA-associated vasculitides, namely, granulomatosis with polyangiitis and microscopic polyangiitis, rituximab (RTX) has been approved for remission-induction and maintenance-remission treatment [2–4]. RTX is a chimeric monoclonal anti-CD20 antibody with immunosuppressant activity resulting from B cell depletion. The pathogenic role of ANCA in EGPA has been suggested by the high prevalence of patients who are positive for ANCA in some series [6]. The efficacy of treatment with RTX in EGPA has been noted in case reports and series, one small formal pilot trial, and one multicenter retrospective review [7–10]. The most important benefit was found in patients who had positive results of myeloperoxidase-ANCA tests [9, 10].

Patients with EGPA present with increased levels of interleukin-5, responsible for eosinophil proliferation, maturation, and differentiation [11]. An anti-interleukin-5 receptor monoclonal antibody, mepolizumab, was tested in the MIRRA study (mepolizumab in the treatment of EGPA) [12]. The study showed a consistent reduction in the absolute eosinophil count and improvement in the clinical manifestations of EGPA, such as severe eosinophilic asthma. However, only half of the patients achieved protocol-defined remission, and less than one-third achieved the primary outcome. Therefore, conceivably, suppression of B cell-mediated immune response may provide an additional benefit to the control of EGPA disease activity. In fact, B cell depletion with RTX has been proposed to have a suppressive effect on T cell function [8].

Glucocorticoid (GC)-dependent severe or uncontrolled asthma remains the most serious long-term management challenge in EGPA [13]. Recent data clearly suggest that asthma severity is independent of the vasculitic disease manifestations, both at presentation and during the subsequent course of the disease [14]. In some studies, persistence of moderate to severe asthma in patients with EGPA did not allow the withdrawal of oral GC therapy [7]. Yet, RTX facilitated GC sparing when used for induction and maintenance of remission in patients with granulomatosis with polyangiitis [3].

Therefore, the objectives of this retrospective study were to (1) characterize asthma control in patients with EGPA treated with RTX and (2) understand the impact of RTX on GC sparing in the treatment of symptomatic asthma.

Methods

Study design

We conducted a single-center retrospective cohort study of all consecutive patients with EGPA who presented with severe uncontrolled or GC-dependent asthma and who received RTX for remission-induction treatment at Mayo Clinic between January 1, 2000, and December 31, 2017. The study population was identified by using an internal search engine (Advanced Cohort Explorer) to search clinical notes for the following keywords: “Churg-Strauss,” “eosinophilic granulomatosis with polyangiitis” or “EGPA,” and “rituximab,” “Rituxan,” or “RTX.” To better understand the effects of RTX, we required that patients have a minimum of 1 year of follow-up at our institution. This study was approved by the Mayo Clinic Institutional Review Board, and all patients who did not allow their medical records to be used for research purposes were excluded from the study.

Definitions of patient characteristics

EGPA was defined according to the criteria of the American College of Rheumatology [15], which require the presence of at least four of six criteria: (1) asthma (wheezing, expiratory rhonchi), (2) more than 10% eosinophils in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates (transient included), (5) histologic proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex or polyneuropathy in patients with signs of vasculitis.

Severe asthma was defined according to joint guidelines from the European Respiratory Society and the American Thoracic Society [16]: asthma requiring treatment during the previous year with medications listed in steps 4 and 5 by the Global Initiative for Asthma (high-dose inhaled corticosteroids and long-acting β_2 -agonists or leukotriene modifier or theophylline) or with systemic GCs for 50% of the previous year to prevent symptoms from becoming uncontrolled or remaining uncontrolled despite therapy. Uncontrolled asthma was defined as having at least one of the following features: (1) poor symptom control—asthma control questionnaire score consistently 1.5 or more or Asthma Control Test (QualityMetric, Inc) score less than 20; (2) frequent severe exacerbations—two or more bursts of systemic corticosteroid (3 days each) in the previous year; (3) serious exacerbations—at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year; (4) airflow limitation—after withholding the appropriate bronchodilator, forced expiratory volume in the first second (FEV₁) of less than 80% predicted (in addition to a reduced Tiffeneau index, FEV₁/FVC [forced vital capacity], defined as less than the lower limit of normal); and (5) controlled asthma that worsens

on tapering of high doses of inhaled corticosteroid or systemic GC therapy (or additional biological agents) [16].

Treatment with rituximab

The use of RTX was categorized as follows: (1) used for initial remission induction or for remission induction in patients who had previous treatment with other immunosuppressants or (2) for maintenance of remission after induction. The decision to start RTX therapy was at the discretion of the treating physician. Patients received intravenous RTX at a dose of 375 mg/m² of body surface area once weekly for 4 weeks for induction or two 1000-mg doses 2 weeks apart for maintenance. Peripheral blood B cells were measured at 3-month intervals. Re-treatment with RTX was considered at the time of reconstitution of B cells.

Variables registered and outcomes assessment

Standard demographic variables were collected. The Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) instrument was used to characterize disease activity by the presence of symptoms by organ system [17]. The Vasculitis Damage Index was used for clinical assessment of damage induced by systemic vasculitis or its treatment [18]. The Five-Factor Score was applied to assess EGPA severity and prognosis [19].

ANCA status was determined with enzyme-linked immunosorbent assay at the time of EGPA diagnosis and at the start of therapy with RTX. Other important laboratory variables related to disease activity and inflammatory status, pulmonary function test results, and radiologic evaluations were documented at the time of diagnosis of EGPA, at the start of RTX therapy, and at the end of follow-up. Data were also collected about previous immunosuppressant therapies, treatments for symptomatic asthma control received before and after EGPA diagnosis or RTX therapy, and concomitant GC doses.

Remission was defined as a BVAS/WG score of 0 with a prednisone dose of less than 10 mg/day or its equivalent (defined as low-dose GC). Nonresponse was defined as the inability to reach a BVAS/WG score of 0 and a prednisone dose of less than 10 mg/day or its equivalent at 18 months. Relapse was defined as a BVAS/WG score of one or more resulting in a change of immunosuppressive therapy after initially reaching remission. At relapse, organ involvement, BVAS/WG score, and laboratory studies were obtained.

Statistical analysis

Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range [IQR]) if they were not normally distributed. For

comparisons between groups, the χ^2 test was used for categorical variables; for continuous variables, an unpaired Student *t* test for independent samples and the Mann-Whitney *U* test were used for normally distributed data and for skewed distributions, respectively. The analyses were conducted with SPSS Statistics for MacOS, version 25 (IBM).

Results

Patient characteristics and clinical outcomes

Initial screening identified 117 patients with EGPA who were treated at our institution during the study period. After careful electronic chart review, 100 patients were excluded: (1) 41 patients did not meet the stringent EGPA classification criteria, (2) in 49 patients RTX treatment was considered but was not prescribed, (3) in eight patients, the duration of follow-up was less than 12 months, (4) one patient did not fulfill criteria for severe asthma at any point in time, and (5) one patient did not consent to the use of data for research. Inclusion criteria were fulfilled by 17 patients. Baseline demographic characteristics and clinical presentation are summarized in Table 1.

Vasculitis characteristics at remission induction with rituximab

Of the 14 patients (82.4%) who had positive ANCA test results, 13 (93%) had positive myeloperoxidase-ANCA results. The median BVAS/WG score was ten points at EGPA diagnosis (IQR, 7.5–11.5) and at the start of RTX therapy (IQR, 6.5–11.0). The predominantly affected systems were the respiratory tract (94.1%); the nervous system (88.2%); and the ears, nose, and throat (82.4%). The median Vasculitis Damage Index score at the time of remission induction with RTX was 6.0 points (IQR, 3.5–7.0). As determined by the Five-Factor Score, severe manifestations due to renal and central nervous system involvement were documented in five patients (23.5%). Peripheral eosinophilia (eosinophils, > 10%) was present in ten patients (58.8%) at the start of RTX therapy, and the median serum C-reactive protein value was 27.0 mg/dL (IQR, 8.0–71.0; normal, < 8.0). The median duration of follow-up after EGPA diagnosis for all patients was 38 months (IQR, 17.0–107.0).

Asthma characteristics at remission induction with rituximab

Severe asthma was present in all patients and was considered uncontrolled in 13 (76.5%). Atopy was present in 13 patients (76.5%), and immunoglobulin E levels were increased in 11 patients (64.7%). The radiologic findings were compatible

Table 1 Baseline characteristics and clinical presentations in 17 patients with EGPA and severe asthma treated with rituximab

Variable	Value ^a
Median age at remission-induction treatment with RTX, y	53 (49–69)
Male	9 (52.9)
Smoker	3 (17.6)
BMI, kg/m ²	25.0 (22.25–31.50)
Atopy	13 (76.5)
ANCA test (ELISA) positive at diagnosis	14 (82.4)
MPO-ANCA positivity (ELISA) at diagnosis	13 (76.5)
BVAS/WG	
At diagnosis	10 (7.5–11.5)
At RTX treatment start	10 (6.5–11.0)
BVAS/WG subscores	
1. General	6 (35.3)
2. Cutaneous	8 (47.1)
3. Mucous membranes, eyes	0 (0.0)
4. Ears, nose, throat	14 (82.4)
5. Chest	16 (94.1)
6. Cardiovascular	1 (5.9)
7. Gastrointestinal	0 (0.0)
8. Renal	4 (23.5)
9. Nervous system	15 (88.2)
VDI score	6 (3.5–7.0)
FFS subscores	
1. Severe gastrointestinal involvement	0 (0.0)
2. Serum creatinine > 1.58 mg/dL	1 (5.9)
3. Proteinuria in 24 h > 1 g	4 (23.5)
4. Cardiac involvement	3 (17.6)
5. CNS involvement	4 (23.5)
Duration of follow-up, mo	38 (17.0–107.0)

Abbreviations: ANCA antineutrophil cytoplasmic antibody, BMI body mass index, BVAS/WG Birmingham Vasculitis Activity Score for Wegener Granulomatosis, CNS central nervous system, EGPA eosinophilic granulomatosis with polyangiitis, ELISA enzyme-linked immunosorbent assay, FFS Five-Factor Score, MPO myeloperoxidase, RTX rituximab, VDI vasculitis damage index

^a Categorical variables are presented as number (percentage), and continuous variables are presented as median (interquartile range)

with asthma in eight patients (47.1%) who presented with bronchial wall thickening or hyperinsufflation seen on computed tomography in the absence of other radiologic findings. The median absolute FEV₁ was 1.88 L (IQR, 1.24–2.56); the median percentage predicted FEV₁ was 54% (IQR, 43%–73%); the median percent predicted FEV₁/FVC was 62.8% (IQR, 44.1%–67.8%); and the median fractional oral exhaled nitric oxide was 43.3 parts per billion (IQR, 17.39–80.38) (upper limit of normal, 40).

The median dose of GCs for symptomatic asthma control before RTX treatment was 40 mg/day (IQR, 27.5–70.0). In 15 patients (88.2%), specific pharmacologic asthma therapy was considered maximal. The treatments included inhaled corticosteroids in 14 patients (82.4%), short-acting β_2 -agonist inhalers in 11 (64.7%), long-acting β -agonist inhalers in 10

(58.8%), anticholinergic medication in 3 (17.6%), and leukotriene receptor antagonists in 2 (11.8%). The median duration of asthma in our cohort was 10 years (IQR, 2–14), and the median duration between asthma diagnosis and EGPA diagnosis was 4 years (IQR, 0–8).

Treatment with rituximab

All patients received RTX for induction of remission. It was used as initial remission-induction therapy in five patients (29.4%) because of severe new disease at onset (BVAS/WG score, > 3) (Table 2). In the remaining 12 patients (70.6%), RTX was used after other induction-remission therapies: 6 (35.3%) had refractory disease, 3 (17.6%) had relapsing disease, 2 (11.8%) had a contraindication to cyclophosphamide,

and 1 (5.9%) had refractory eosinophilia. Before treatment with RTX, cyclophosphamide was the most frequent immunosuppressant used for remission induction (9 patients, 52.9%), and azathioprine was the most frequent immunosuppressant used for maintenance of remission (6 patients, 35.3%).

RTX was used for maintenance of remission in 9 patients (52.9%) (Table 3). GCs were not administered at the time of the RTX infusion used for maintenance of remission, but they were included in all maintenance regimens (median dose, 25 mg/day [IQR, 16.25–37.5]). The timing of maintenance treatment with RTX was mainly guided by B cell reconstitution after the RTX induction effect had subsided (7 patients, 41.2%). Only 4 patients (23.5%) had positive myeloperoxidase-ANCA results at the start of maintenance treatment with RTX. The median duration of follow-up after treatment with RTX was 34 months (IQR, 13.0–77.5).

Outcomes

After remission-induction therapy with RTX, during 12 months of follow-up, 12 patients (70.5%) had vasculitis remission, 2 (11.8%) had a BVAS/WG score of 0 but a GC

dose of less than 10 mg could not be confirmed, and 3 (17.6%) had relapse (Table 4).

At the end of the 12-month follow-up, 13 patients (76.5%) had non-severe or controlled asthma: 8 of the 9 (88.9%) who received RTX for maintenance remission and 5 of the 8 (62.5%) who did not. The therapeutic inhaler regimen used was similar to that used before the treatment with RTX in most patients: 16 patients (94.1%) continued to receive inhaled corticosteroids, high dose in 10 (58.8%); 13 patients (76.5%) received long-acting β -agonists; and 12 patients (70.6%) used short-acting β_2 -agonists for asthma control. In response to RTX treatment, pulmonary function test variables did not improve, but the serum eosinophil count decreased (1.06 vs $0.10 \times 10^9/L$, $P = .012$), as did the C-reactive protein level (27.0 vs 5.0 mg/dL, $P = .001$).

After treatment with RTX, a predictable GC tapering was favored. The median GC dose decreased until 12 months and remained lower than 10 mg until 24 months. This pattern was in marked contrast to that before the use of RTX (Fig. 1A). The median GC dose (milligrams per day) needed in the first month after RTX was given was significantly reduced at months 3 (40.0 vs 15.0), 6 (40.0 vs 8.75), 12 (40.0 vs 5.0), 18 (40.0 vs 7.5), and 24 (40.0 vs 5.0) ($P < .0001$ for all comparisons). The 9 patients who received RTX for maintenance remission received low-dose GCs for asthma control between 12 and 24 months after remission induction with RTX. In contrast, the 8 patients who did not receive RTX for maintenance, because they had predominantly neurologic or renal manifestations as a result of previous damage from vasculitis, tended to require higher doses of GCs for asthma control between 12 and 24 months (mean dose, 12.4 vs 5.5 mg/day), but the median GC doses were not significantly different ($P = .59$) (Fig. 1B).

Hypogammaglobulinemia was present in four patients (23.5%). Severe or opportunistic infections due to an immunocompromised state did not occur. Infusion-related adverse events, cancer, or death did not occur in association with or during the 24 months of follow-up after RTX treatment.

Discussion

This retrospective study of the effect of RTX on asthma severity and control in patients with EGPA had several findings. First, the majority of patients had improvement (76.5% had non-severe or controlled asthma) at 12 months after remission-induction treatment with RTX. Second, RTX seems to be effective and safe for remission induction: remission was achieved in 12 patients (70.6%), including 6 (35.3%) who were refractory to the previous immunosuppressive treatment. No serious adverse events were noted. Third, a GC-sparing effect in our EGPA cohort may be attributable to the reduction of GC doses required solely for asthma control in EGPA.

Table 2 Treatment in 17 patients with EGPA and severe asthma

Variable	Value ^a
Treatment	
Induction	
Bolus methylprednisolone	11 (64.7)
Increased oral prednisone dose	3 (17.6)
Maintained oral prednisone dose	3 (17.6)
RTX	17 (100)
Induction treatment received before RTX	
CYC	9 (52.9)
MTX	1 (5.9)
PLEX	1 (5.9)
IVIg	1 (5.9)
Maintenance	
Prednisone	17 (100)
Prednisone dose, mg/day	25 (16.25–37.50)
RTX	9 (52.9)
Maintenance treatment received before RTX	
AZA	6 (35.3)
MTX	5 (29.4)
MMF	3 (17.6)

Abbreviations: AZA azathioprine, CYC cyclophosphamide, EGPA eosinophilic granulomatosis with polyangiitis, IVIg intravenous immunoglobulin, MMF mycophenolate mofetil, MTX methotrexate, PLEX plasma exchange, RTX rituximab

^a Categorical variables are presented as number (percentage), and continuous variables are presented as median (interquartile range)

Table 3 Rituximab treatment in 17 patients with EGPA and severe asthma^a

Variable	Maintenance			P value
	EGPA (n = 17)	RTX (n = 9)	No RTX (n = 8)	
Induction treatment dosage				.37
375 mg/m ² BSA once/week for 4 weeks	10 (58.8)	4 (44.4)	6 (75.0)	
1 g IV, twice (2 weeks apart)	6 (35.3)	4 (44.4)	2 (25.0)	
Other	1 (5.9)	1 (11.1)	0 (0.0)	
Maintenance treatment				
MAINRITSAN scheme	NA	2 (11.8)	NA	NA
Guided by B cell reconstitution	NA	7 (41.2)	NA	NA
Corticosteroid dose at RTX start, mg	40 (27.5–70.0)	40 (33.0–60.0)	60 (17.5–80.0)	.61
MPO-ANCA positivity (ELISA)				
At RTX induction	13 (76.5)	7 (77.8)	6 (75.0)	.89
At RTX maintenance	4 (11.8)	0	0	NA
Months of follow-up after RTX start	34 (13.0–77.5)	29 (12.5–77.5)	46 (22.0–92.5)	.42
Adverse reaction (hypogammaglobulinemia)	4 (11.8)	3 (33.3)	1 (12.5)	.31

Abbreviations: ANCA antineutrophil cytoplasmic antibody, BAS body surface area, EGPA eosinophilic granulomatosis with polyangiitis, ELISA enzyme-linked immunosorbent assay, IV intravenously, MAINRITSAN Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis, MPO myeloperoxidase, NA not applicable, RTX rituximab

^a Categorical variables are presented as number (percentage), and continuous variables are presented as median (interquartile range)

Fourth, the use of RTX as a maintenance remission agent after remission induction also seems to be a safe option and might be chosen using the same decision criteria as for other ANCA-associated vasculitis syndromes (especially in ANCA-positive patients).

Some studies have found that about 40% of patients have severe asthma at the time of EGPA diagnosis [20]. In our study, all 17 patients with EGPA received off-label RTX and had asthma as the main clinical manifestation. Increased doses of GCs were used without adequate control of asthma before RTX therapy in these patients. GC sparing was the main outcome after RTX therapy was started. The GC dose tended to

be tapered to less than 10 mg/day by 12 months in patients treated with RTX for maintenance of remission. For vasculitis manifestations, studies suggest that the GC dose is decreased after remission-induction treatment with RTX [10, 21]. The effect of RTX for remission induction and for maintenance of remission was not addressed specifically in previous studies [10, 21]. Thiel et al. [21] found that GC doses, after treatment with cyclophosphamide or RTX, were rapidly tapered but that all patients continued to receive low-dose GC maintenance therapy. Other investigators [10, 22] reported that the GC-sparing effect subsequent to RTX remission-induction therapy was short-lived; GC use was stopped in only 6% of the patients, in contrast to patients who had granulomatosis with polyangiitis or microscopic polyangiitis. In the patients who also received RTX for maintenance remission, the GC-sparing effect is more sustained. Importantly, symptomatic asthma improvement is thought to be independent of systemic disease treatment [7]. Moreover, uncontrolled asthma and ears, nose, and throat manifestations are generally the main reasons to continue treatment with GCs [23, 24]. Most recently, Teixeira et al. [24] described 69 patients with EGPA that were treated with RTX, 35% of whom were ANCA-positive. They had favorable disease activity outcomes, including a more sustained response of isolated asthma or otorhinolaryngologic exacerbations, a shorter time to remission, and longer relapse-free survival, especially in the ANCA-positive subset. Unlike

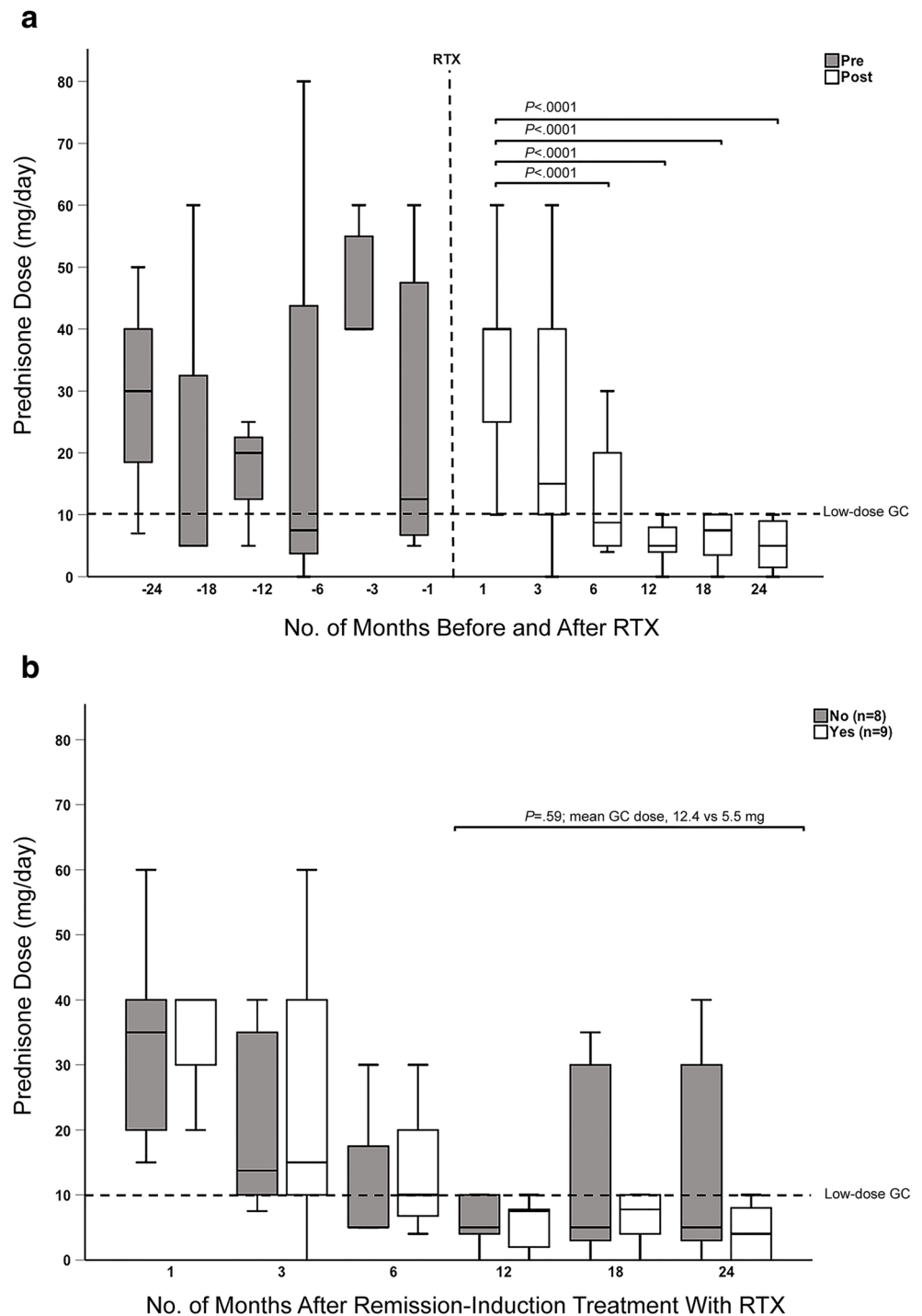
Table 4 Outcomes of 17 Patients with EGPA and severe asthma

Variable	Value ^a
Outcomes after treatment with RTX	
Remission	12 (70.5)
Relapses	3 (17.6)
Outcomes before treatment with RTX	
Relapse (history or main reason for treatment)	9 (52.9)
Refractory	6 (35.3)

Abbreviations: EGPA eosinophilic granulomatosis with polyangiitis, RTX rituximab

^a Categorical variables are presented as number (percentage)

Fig. 1 Median doses of prednisone (milligrams per day) prescribed for asthma symptom control in 17 patients with eosinophilic granulomatosis with polyangiitis treated with rituximab (RTX). **a**, Before (pre) and after (post) receiving remission-induction treatment with RTX. The median dose of glucocorticoid (GC) decreased after treatment with RTX and was significantly reduced at months 6, 12, 18, and 24 compared with the first month of treatment ($P < .0001$). **b**, Median prednisone dose after remission-induction treatment with RTX, stratified by status of maintenance remission treatment with RTX. The median dose of GC decreased faster in patients who did not receive RTX and at a slower but constant pace in patients who received RTX until 12 months. After 12 months, the median dose of GC was lower than 10 mg for a longer duration in patients who received RTX for maintenance remission treatment than in patients who did not receive RTX for maintenance. The mean dose of GC was higher in patients who did not receive RTX (12.4 vs 5.5 mg/day), but the median doses were similar ($P = .59$)



our study, the primary focus of that study was not asthma control. Nevertheless, both studies suggest an effect of RTX on the non-vasculitic disease manifestations of EGPA.

Our study suggests a beneficial GC-sparing effect when patients receive RTX for both remission induction and maintenance remission. Even though this effect was most prominent for the GC doses required for asthma management, the subjective symptomatic improvement of asthma was not associated with measurable improvements in pulmonary

function. The symptomatic improvement of asthma may be related to control of the inflammatory response and decreased eosinophil counts. The effect of treatment with RTX on control of the inflammatory response has not been shown consistently in previous studies in diverse EGPA populations [11, 13]. The fact that the majority of our patients were ANCA-positive at the time of remission-induction with RTX might explain this difference in inflammatory response. The underlying inflammatory response, especially mediated by

profibrotic cytokines from eosinophils, is responsible for processes of remodeling in the airways, which result in permanent damage [25]. Patients with long-term severe or uncontrolled asthma in EGPA have a higher proportion of bronchial obstruction and have more severe airway resistance [14, 25]. Moreover, pulmonary function does not improve during follow-up, even when vasculitis is under control [14, 25]. Superimposed chronic damage or airway remodeling from asthma or vasculitis seems to persist even after improvement in clinical manifestations and inflammation, and they seem to be hallmarks of severe or uncontrolled asthma in EGPA [26].

Because the effect of RTX on granulomatosis with polyangiitis and microscopic polyangiitis has been established in randomized controlled trials [2, 3], we hypothesized that effects on the control of vasculitis in EGPA might be comparable. Of note, anti-interleukin-5 therapy with mepolizumab was not available or approved for asthma or EGPA treatment during the majority of the time from which data were collected [12]. RTX was shown to be safe and successful for controlling renal disease activity in three patients with EGPA [9]. The benefits of RTX in EGPA were shown in retrospective cohort studies suggesting efficacy for maintenance of remission, reduced relapse rates, and GC sparing [21, 27]. Although the majority of our patients who received RTX were ANCA-positive (as in other cohorts [6, 18]), other retrospective cohort studies have also shown benefit of RTX in ANCA-negative patients with EGPA [14]. In our cohort, 50% of patients who received RTX for maintenance of remission were ANCA-negative. These observations suggest that RTX may be beneficial in EGPA regardless of the ANCA status. Additionally, in another study [28], all patients with EGPA who were in remission had B cell depletion after receiving RTX, a finding that supports a pathogenic role for B cells in EGPA. Our study findings also support this observation. Furthermore, in another study [29], RTX was effective for asthma control in other autoimmune diseases in which asthma plays a central role in the clinical presentation. Asthma associated with orbital immunoglobulin G4-related disease manifested generally as adult-onset bronchial wall thickening on computed tomography and increased serum immunoglobulin G4 levels. In that cohort study, patients received prednisone therapy followed by RTX, and asthma was controlled in the majority of patients.

The use of other immunosuppressants in addition to GC for remission induction of non-severe presentations in EGPA was not beneficial in one study [30]. Long-term outcomes, namely, vasculitis relapse or isolated asthma or rhinosinusitis exacerbation rates, are not improved when azathioprine is used with GC for remission induction [31]. Additionally, maintenance treatment strategy in EGPA, apart from GC therapy, is not established. For these reasons, alternative pathways need to be explored. B cell depletion therapies are conceptually attractive. Importantly, B cell depletion during remission of EGPA has a suppressive effect on T cell function [28]. This

suppression may interfere in Th2-mediated processes, promoting, perhaps, asthma control in EGPA [32].

The limitations of this study are its retrospective nature, the rarity of EGPA, and the fact that asthma is not treated with RTX: thus, a non-EGPA control group matched for asthma severity is unavailable. The majority of patients being ANCA-positive in this case series reflects selection bias caused by the clinical practice of preferential use of RTX in ANCA-positive patients. Because 14 of our 17 patients were ANCA-positive, we could not perform a meaningful comparison of outcomes in subsets defined by ANCA status. Because the patients were not treated in a protocol-determined fashion and the asthma control questionnaire was not performed systematically at all time points, we could not quantitate objectively the improvement on asthma control. The duration of follow-up was also limited. Therefore, definite conclusions cannot be drawn from our data regarding a long-term GC-sparing effect for symptomatic asthma control after treatment with RTX.

Despite the limitations, our study (1) is the largest population of patients with EGPA and GC-dependent asthma treated with RTX for symptomatic asthma control from a single center, (2) characterized asthma control after treatment with RTX, (3) determined that use of RTX as remission induction and also a maintenance agent is safe, and (4) provides evidence to support that treatment with RTX might be an alternative in GC-resistant asthma in patients with EGPA when mepolizumab treatment is not available.

Prospective randomized clinical trials evaluating RTX as an option for remission induction and maintenance of remission in EGPA are under way [33]. Overall, our data indicate that patients with EGPA and GC-dependent asthma treated with RTX for both remission induction and maintenance of remission required lower GC doses for symptomatic asthma treatment after 12 months.

Compliance with ethical standards

Disclosures None.

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