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Real-world experience of rituximab therapy in ANCA-associated vasculitis according to renal involvement

ANCA ilişkili vaskülitte renal tutuluma göre rituksimab tedavisi: Gerçek yaşam deneyimi

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Abstract

Objective: To evaluate treatment persistence, efficacy, and safety of rituximab (RTX) in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV), with a specific focus on the impact of renal involvement.

Methods: In this multicenter, retrospective cohort study, 214 AAV patients who received at least one RTX dose between 2012 and 2024 were analyzed. Patients were stratified based on renal involvement. The primary endpoint was RTX retention, defined as the time from the first infusion to permanent discontinuation for any cause. Secondary endpoints included remission, relapse, and infection-related discontinuations. Clinical characteristics, treatment indications (induction or maintenance), cumulative RTX doses, and safety outcomes were compared between renal and non-renal groups using descriptive statistics and survival analyses.

Results: Among the cohort, 132 patients (61.7%) had renal involvement and 82 (38.3%) had non-renal involvement. The median RTX treatment duration was 24 months. RTX was used for maintenance in 72.4% of patients and for induction in 49% of patients. Drug retention did not differ

Özet

Amaç: Bu çalışmada, antinötrofil sitoplazmik antikor ilişkili vaskülit (AAV) hastalarında rituksimab (RTX) tedavisinin sürekliliği, etkililiği ve güvenliliği değerlendirilmiş; özellikle renal tutulumun tedavi sonuçlarına etkisi araştırılmıştır.

Yöntem: 2012-2024 yılları arasında en az bir kür RTX uygulanmış 214 AAV hastasının verileri çok merkezli, retrospektif kohort tasarımında analiz edildi. Hastalar renal tutulum varlığına göre sınıflandırıldı. Birincil sonlanım noktası, herhangi bir nedenle tedavinin kalıcı olarak sonlandırılmasına kadar geçen süre olarak tanımlanan RTX tedavisinde kalımdı. İkincil sonlanım noktaları arasında remisyon, relaps ve enfeksiyon ilişkili tedavi kesilmeleri yer aldı. Klinik özellikler, tedavi endikasyonları (indüksiyon veya idame), kümülatif RTX dozları ve güvenlilik sonuçları renal ve non-renal gruplar arasında tanımlayıcı ve sağkalım analizleriyle karşılaştırıldı.

Bulgular: Kohortun 132'sinde (%61,7) renal, 82'sinde (%38,3) non-renal tutulum mevcuttu. Ortanca RTX tedavi süresi 24 aydı. RTX hastaların %72,4'ünde idame, %49'unda indüksiyon amacıyla kullanıldı. Renal ve non-renal gruplar arasında ilaçta kalım açısından anlamlı fark saptanmadı

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Abstract

significantly between renal and non-renal groups (log-rank p=0.608). Infections were the most frequent cause of RTX discontinuation (38.2% vs. 34.8%). Hypogammaglobulinemia occurred in 17.4% and 15.9% of patients, respectively (p=0.460). Mortality rates were comparable between groups (9.8% vs. 8.5%, p=0.475). Despite higher prior cyclophosphamide exposure in renal patients (12.1% vs. 3.7%, p=0.026), overall treatment outcomes were similar.

Conclusion: RTX demonstrated sustained treatment persistence and an acceptable safety profile across AAV phenotypes, independent of renal involvement. These findings emphasize that RTX can serve as a phenotype-independent long-term therapeutic option, although vigilant infection monitoring remains crucial in all patients.

Keywords: ANCA-associated vasculitis, rituximab, renal involvement, drug retention, real-world data

Özet

(log-rank p=0,608). RTX tedavisinin kesilmesinin en sık nedeni enfeksiyondu (%38,2'ye karşı %34,8). Hipogamaglobulinemi oranları sırasıyla %17,4 ve %15,9 olup gruplar arasında anlamlı farklılık göstermedi (p=0,460). Mortalite oranları da benzerdi (%9,8'e karşı %8,5; p=0,475). Renal grupta siklofosfamid maruziyeti daha yüksek olmasına rağmen (%12,1'e karşı %3,7; p=0,026), genel tedavi sonuçları iki grup arasında benzer bulundu.

Sonuç: RTX, renal tutulumdan bağımsız olarak AAV fenotiplerinde uzun dönemli tedavi sürekliliği ve kabul edilebilir güvenlilik profili sergilemiştir. Bu bulgular, RTX'in fenotipten bağımsız uzun süreli bir tedavi seçeneği olabileceğini, ancak tüm hastalarda enfeksiyonların dikkatle izlenmesinin gerekli olduğunu vurgulamaktadır.

Anahtar Kelimeler: ANCA-ilişkili vaskülit, rituksimab, renal tutulum, ilaçta kalım, gerçek yaşam verisi

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of necrotizing small-vessel vasculitides, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (eGPA).[1,2] These conditions are characterized by diverse clinical presentations that range from renal involvement to severe pulmonary manifestations, necessitating tailored therapeutic strategies.[3]

Historically, combination regimens of cyclophosphamide (CYC) and corticosteroids significantly improved survival by inducing remission in up to 90% of cases.[4] However, the long-term toxicity of CYC, including infertility, malignancy, and opportunistic infections has led to a shift toward less toxic yet effective alternatives.[5]

Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody, has transformed AAV management by enabling selective B-cell depletion and sustained ANCA suppression.[6-9]

Large randomized trials such as RTX in ANCA-AAV (RAVE) and RTX versus CYC in ANCA-AAV (RITUXIVAS) established RTX as non-inferior to CYC for induction therapy, even in patients with severe renal involvement.[7,10] Furthermore, the maintenance of remission using RTX in systemic ANCA-AAV (MAINRITSAN) and RTX versus azathioprine (AZA) for maintenance of remission in ANCA-AAV (RITAZAREM) trials confirmed RTX's superiority over AZA in relapse prevention during maintenance.[11-13]

Despite these advances, how renal involvement influences RTX efficacy and safety remains insufficiently characterized. Renal disease is associated with worse prognosis and typically warrants aggressive immunosuppression to prevent irreversible kidney damage and end-stage renal disease.[14] Conversely, patients without renal involvement, often with upper respiratory tract or pulmonary disease, may both tolerate and require less intensive regimens. Importantly, relapse risk is influenced not only by the extent of organ involvement but also by ANCA subtype, with PR3-ANCA-positive patients (commonly GPA) exhibiting a higher relapse propensity compared to myeloperoxidase (MPO)-ANCA-positive patients (often MPA with renal-limited disease).[15] While several trials have evaluated induction and maintenance strategies in AAV broadly, few have specifically addressed how the presence or absence of renal involvement influences long-term outcomes under RTX maintenance.

Most pivotal trials were not designed to directly compare long-term RTX durability and safety between renal and non-renal AAV phenotypes, e.g. RAVE excluded patients with advanced renal failure and RITUXVAS enrolled exclusively renal disease, while MAINRITSAN and RITAZAREM primarily focused on relapse prevention rather than phenotype-stratified drug survival or cumulative exposure.[4,6,9,16] In real-world cohorts under RTX maintenance, kidney involvement has been associated with longer relapse-free survival and a lower relapse risk, whereas other series suggest kidney involvement may increase the risk of severe hypogammaglobulinaemia leading to RTX discontinuation.[17] Therefore, direct comparative evidence on treatment retention, cumulative dosing, and safety between renal and non-renal AAV remains limited.

Furthermore, the real-world performance of RTX including dosing schedules, drug survival, adverse events, and reasons for discontinuation remains incompletely characterized in stratified populations.[18,19] Additionally, the risk of serious infections remains a key consideration, particularly in patients undergoing long-term maintenance therapy.[20,21] Understanding these distinctions is essential for optimizing personalized treatment pathways in AAV and for refining maintenance strategies to balance efficacy with safety.[22]

This multicenter study aimed to evaluate the real-world outcomes of RTX maintenance therapy in patients with AAV, specifically comparing those with and without renal involvement. We investigated treatment persistence, cumulative dosing, relapse and remission patterns, and adverse events in these

two phenotypes to determine whether renal disease influences the long-term effectiveness and safety of RTX in routine clinical practice.

Materials and Methods

Study Population and Data Collection

This was a multicenter, retrospective, observational cohort study including adult patients (≥18 years) with a diagnosis of AAV; GPA, MPA, or EGPA, according to the 1990 American College of Rheumatology criteria. Patients were recruited from six tertiary rheumatology centers in Türkiye between September 2012 and September 2024.

Patients were eligible if they had a diagnosis of AAV and received at least one course of RTX for either induction or maintenance therapy during the study period. Patients with concomitant autoimmune diseases, active malignancies, insufficient follow-up (<6 months), or missing essential clinical or laboratory data required for outcome assessment were excluded from the analysis. Data were extracted from electronic medical records using standardized case-report forms to ensure uniformity across centers. No statistical imputation was performed, as cases with incomplete essential data were excluded at the time of cohort assembly. In all centers, ANCA was determined by testing for PR3-ANCA and MPO-ANCA using an enzyme-linked immunosorbent assay. Patients with ANCA-negative (double-negative) serology were not excluded if they fulfilled clinical criteria for AAV diagnosis.

Renal involvement was defined as biopsy-proven pauci-immune necrotizing and/or crescentic glomerulonephritis and/or clinical and laboratory findings consistent with active renal vasculitis, including proteinuria >500 mg/day, and/or persistent microscopic hematuria on at least two consecutive assessments, unexplained elevation in serum creatinine attributed to AAV, and/or rapidly progressive renal dysfunction (e.g., rapidly rising serum creatinine levels or dialysis-requiring acute kidney injury) in accordance with established AAV and glomerular disease guidelines.[3,23] Kidney biopsy was performed whenever clinically feasible. In cases where biopsy could not be obtained due to clinical instability or advanced renal failure, classification was based on compatible clinical findings, ANCA positivity, and active urinary sediment. Patients fulfilling any of these criteria were categorized as “renal”, while those without renal manifestations were classified as “non-renal”.

Induction and Maintainance Strategies

In routine clinical practice across participating centers, remission induction was performed with CYC and/or RTX, depending on disease severity and prevailing treatment standards during the study period. In selected severe cases, both agents were used sequentially or in combination at the physician’s discretion. The RTX induction regimen consisted of 1000 mg administered intravenously on days 0 and 15 (total 2000 mg). After achieving remission, patients were transitioned to maintenance therapy tailored according to clinical phenotype, relapse risk, comorbidities, and treatment tolerance. Maintenance options included RTX, AZA, or mycophenolate mofetil. Thus, “induction” and “maintenance” represent sequential treatment phases rather than mutually exclusive patient categories, and reported proportions may overlap.

Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim/sulfamethoxazole was administered to all patients receiving induction therapy unless contraindicated (e.g., by a drug allergy or persistent hyperkalemia). Dosage adjustments were made according to renal function. Prophylaxis was applied in accordance with standard clinical practice guidelines.

Outcomes and Definitions

The primary endpoint was drug retention, defined as the time from the first RTX infusion to permanent discontinuation for any reason. Temporary treatment interruptions lasting less than 6 months were not considered discontinuation events. Censoring occurred at the last clinical visit, upon loss to follow-up, or at death unrelated to RTX discontinuation. Causes of discontinuation were categorized as remission, relapse, adverse event, infection, allergy, physician’s decision, or patient request.

Secondary endpoints included:

- Frequency and causes of discontinuation,
- Occurrence of infections (classified as serious if hospitalization or intravenous antibiotic therapy was required),
- Incidence of hypogammaglobulinemia,
- Mortality during follow-up.

Remission and relapse definitions were adapted from established AAV management guidelines and major clinical trials.[3,4,6] Refractory disease was defined according to European Alliance of Associations for Rheumatology recommendations.[3] Renal dysfunction was defined based on standard laboratory reference ranges in accordance with KDIGO guidelines.[23,24]

Remission was defined as the absence of clinical signs of active vasculitis, as assessed by the treating physician, with no new or worsening organ involvement and stabilization of laboratory parameters. All patients accepted as being in the remission phase had a Birmingham vasculitis activity score of 0. Low-dose glucocorticoid therapy was permitted during remission; however, patients requiring moderate-to-high-dose glucocorticoids due to active disease were not considered in remission. Relapse was defined as new or recurrent organ involvement attributed to AAV. Refractory disease refers to persistent or worsening disease activity despite standard induction therapy. Renal dysfunction

was defined as creatinine levels >1.1 mg/dL in women and >1.3 mg/dL in men.

Serum immunoglobulin G (IgG) levels were routinely measured prior to RTX initiation in all patients. No patient had hypogammaglobulinemia before the first RTX course. Hypogammaglobulinemia observed during follow-up that developed after at least one RTX cycle and was therefore considered treatment-related. Intravenous immunoglobulin (IVIG) replacement therapy was initiated in patients with clinically significant hypogammaglobulinemia, based on serum IgG levels and the presence of recurrent or severe infections. IVIG was administered following formal approval for off-label use by the Turkish Medicines and Medical Devices Agency. Hypogammaglobulinemia was defined as serum IgG <7 g/L. Persistent hypogammaglobulinaemia was defined as the absence of improvement six months after RTX treatment.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (range), while categorical variables were summarized as frequencies and percentages. Differences between renal and non-renal groups were analyzed using the Mann-Whitney U test for continuous data and the chi-square or Fisher's exact test for categorical data. Drug retention was assessed using Kaplan-Meier survival analysis, and survival curves were compared by the log-rank test. All statistical analyses were performed using SPSS version 30.0 (SPSS Inc., Chicago, IL, USA), with a p-value <0.05 considered statistically significant. Given the retrospective, descriptive design, no multivariate adjustment or time-dependent modeling was applied.

Ethical Approval and Funding

The study was approved by the Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (project no. 09.2024.1382, date: 11.03.2025) and conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective design. No external funding was received.

Results

Baseline Characteristics of Study Groups

Baseline Characteristics

A total of 214 patients with AAV were included in the analysis: 132 had renal involvement and 82 did not. The overall cohort comprised 67.3% GPA, 23.4% MPA, and 9.3% EGPA. MPA was significantly more frequent in the renal group than in the non-renal group (32.6% vs. 8.5%, p<0.001), whereas EGPA was more common in the non-renal group (3.5% vs. 18.3%, p=0.004). The distribution of GPA was comparable across groups (Table 1).

Demographic characteristics, including sex, age, and disease duration, were similar across groups. Thirty patients (22.7%) in the renal group required hemodialysis during their disease course. Over a median follow-up of four years, mortality rates were comparable (9.8% vs. 8.5%, p=0.475). Cardiac involvement was more frequent in non-renal patients (7.2% vs. 2.8%, p=0.037), whereas involvement of other organs did not differ significantly (Table 1).

Rituximab Treatment Patterns

RTX was used as maintenance therapy in 72.4% of patients and as induction therapy in 49% of patients. The proportion of refractory cases receiving RTX was higher among renal patients (25.8% vs. 15.6%, p=0.038). CYC exposure was more common in the renal group (12.1% vs. 3.7%, p=0.026), whereas methotrexate (MTX) exposure was more common in the non-renal group (19.5% vs. 4.5%, p<0.001). The frequency of concomitant glucocorticoid or AZA use did not differ significantly between groups.

The median cumulative RTX dose was approximately 7 g in both renal and non-renal patients, with a median treatment duration exceeding 24 months (Table 2). The minimum and maximum cycle doses ranged from 500 mg to 2 g, and the intervals between cycles varied from 4 to 65 months, reflecting wide heterogeneity in real-world regimens. The longest RTX exposure was 144 months in a patient without renal disease. In patients with prolonged treatment, maintenance regimens were frequently de-escalated. Instead of repeated full 2000-mg cycles every 6 months, reduced dosing strategies were applied, including single 500-1000-mg infusions every 6 months or infusions at extended intervals (e.g., 1000-2000 mg annually), according to clinical stability and relapse risk.

Drug Retention and Discontinuation

Kaplan-Meier analysis demonstrated comparable RTX retention rates between renal and non-renal groups, with no statistically significant difference (log-rank p=0.608) (Figure 1). Median drug survival exceeded two years in both cohorts.

The most frequent cause of RTX discontinuation was infection in both renal (38.2%) and non-renal (34.8%) patients, followed by remission (14.7% and 8.7%, respectively) and allergic reactions (14.7% and 8.7%, respectively). Only one patient in the renal group discontinued due to disease relapse. Three patients in the renal group stopped RTX because of hypogammaglobulinemia, and none in the non-renal group did (Table 3).

Safety Outcomes

Infection remained the leading adverse event and the leading cause of treatment discontinuation, but its incidence was similar between groups. Most infections were respiratory or urinary in origin. The rate of serious infection—defined as

requiring hospitalization or intravenous antibiotic therapy—did not differ significantly.

Hypogammaglobulinemia occurred in 17.4% of renal and 15.9% of non-renal patients (p=0.460). Approximately half of these patients received IVIG replacement therapy. Persistent hypogammaglobulinemia, defined as low IgG persisting for six months or more after RTX exposure, was recorded in 23 cases. Despite higher baseline disease severity and cumulative immunosuppressive exposure in the renal group, no increase in severe infections or mortality was observed.

Table 1. Demographic and clinical characteristics of patients based on renal involvement

	Renal (n=132)	Non-renal (n=82)	p-values
Diagnosis (n, %)			
Granulomatosis with polyangiitis	84 (63.6)	60 (73.2)	0.148
Microscopic polyangiitis	43 (32.6)	7 (8.5)	<0.001
Eosinophilic granulomatosis with polyangiitis	5 (3.8)	15 (18.3)	0.004
Gender (male, n, %)	78 (59.1)	39 (47.6)	0.120
Age (mean ± SD, years)	53.49±14.9	50.62±14.1	0.082
Disease duration (median, range, years)	4.0 (0.5-24)	4.0 (0.5-24)	0.391
Death (n, %)	13 (9.8)	7 (8.5)	0.475
Clinical findings (n, %)			
Musculoskeletal	60 (45.5)	43 (52.4)	0.329
Mucocutaneous	35 (26.5)	17 (20.7)	0.413
Eye involvement	9 (6.8)	11 (13.4)	0.146
Upper respiratory	71 (53.8)	54 (65.9)	0.089
Lower respiratory	106 (80.3)	62 (75.6)	0.494
Alveolar hemorrhage	34 (25.8)	13 (15.9)	0.061
Cardiac	2 (2.8)	6 (7.3)	0.037
Central nervous system	6 (4.5)	4 (4.9)	0.994
Peripheral nervous system	19 (14.4)	18 (22)	0.109
Gastrointestinal	7 (5.3)	5 (6.1)	0.771
Hemodialysis	30 (22.7)	0	<0.001
Renal dysfunction	86 (65.2)	0	<0.001
Persistent HGG (n, %)	23 (17.4)	13 (15.9)	0.460
Postponing RTX due to HGG (n, %)	21 (16.0)	9 (11.5)	0.247
Autoantibody positivity (n, %)			
Anti-PR3	80 (60.6)	51 (62.2)	0.886
Anti-MPO	42 (31.8)	18 (22.0)	0.159
Double-negative	10 (7.6)	13 (15.8)	0.059
Indication for RTX use (n, %)			
Induction of remission	59 (44.7)	46 (56.1)	0.069
Relapse	24 (18.2)	17 (20.7)	0.386
Refractory disease	34 (25.8)	12 (14.6)	0.038
Maintenance of remission	97 (73.5)	58 (70.7)	0.753
Concurrent therapies with RTX (n, %)			
Glucocorticoid	128 (97)	77 (93.9)	0.309
Methotrexate	6 (4.5)	16 (19.5)	<0.001
Mycophenolate mophetil	9 (6.8)	11 (13.4)	0.087
Cyclophosphamide	16 (12.1)	3 (3.7)	0.026
Azathioprine	27 (20.5)	21 (25.6)	0.238
Intravenous immunoglobulin	17 (12.9)	11 (13.4)	0.533
Plasmapheresis	14 (10.6)	3 (3.7)	0.054

Anti-PR3: Anti-proteinase 3 antibodies, HGG: Hypogammaglobulinemia, MPO: Myeloperoxidase, RTX: Rituximab, SD: Standard deviation

Table 2. Treatment duration and dose schedule of rituximab in maintenance treatment			
	Renal (n=132)	Non-renal (n=82)	p-value
Treatment duration (median, range, months)	26 (3-141)	31 (6-144)	0.381
Cumulative dose (median, range, g)	7 (1-34)	7.75 (1-36)	0.622
Dose per cycle (median, range, g)			
Minimum	1 (0.5-2)	2 (0.5-2)	0.403
Maximum	2 (0.5-2)	2 (0.5-2)	0.081
Interval between cycles (median, range, months)			
Minimum	6 (4-24)	6 (4-8)	0.597
Maximum	7 (4-65)	7 (4-30)	0.498

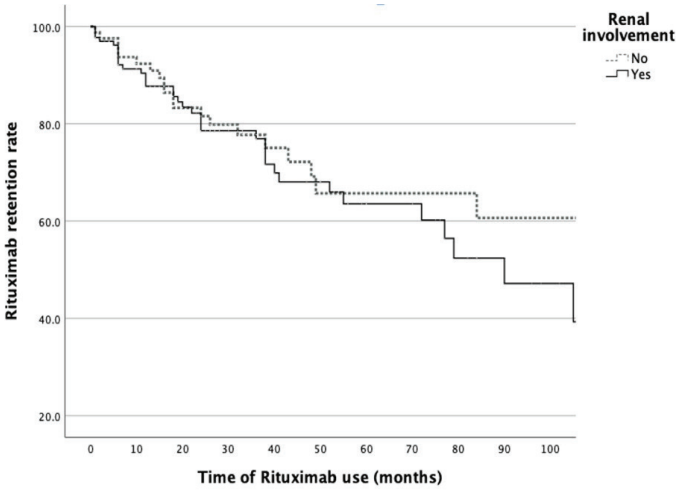

Figure 1. Rituximab retention rates based on renal involvement. The Kaplan-Meier curve shows the rituximab retention rates according to the presence of renal involvement

Table 3. Reasons for discontinuation of rituximab			
Discontinuation reasons n (%)	Renal (n=34)	Non-renal (n=23)	p-values
Infection	13 (38.2)	8 (34.8)	0.929
Remission	5 (14.7)	2 (8.7)	0.689
Rituximab allergy	5 (14.7)	2 (8.7)	0.689
Non-response	3 (8.8)	3 (13.0)	0.677
Physician's decision	1 (2.9)	3 (13.0)	0.292
Hypogammaglobulinemia	3 (8.8)	0	0.265
Flare	1 (2.9)	0	0.980
Other	3 (8.8)	5 (21.7)	0.247

Discussion

This multicenter real-world study compared the long-term outcomes of RTX therapy in patients with AAV, stratified by the presence of renal involvement. Our main finding was that RTX demonstrated comparable drug retention, efficacy, and safety across renal and non-renal disease phenotypes, despite renal patients having higher baseline severity and cumulative immunosuppressive exposure, including CYC. These results suggest that renal involvement does not adversely influence RTX persistence or tolerability in clinical practice.

Our findings are consistent with previous randomized trials demonstrating the efficacy of RTX for remission induction and maintenance in AAV, including patients with renal involvement.[4,6,10,25] However, these studies did not specifically analyze whether renal involvement modifies RTX outcomes. Our study fills this gap by providing dedicated comparative data, indicating that renal involvement does not negatively impact RTX retention, efficacy, or safety in the maintenance phase. Our findings complement this literature by providing phenotype-specific real-world evidence, showing that RTX remains equally effective and safe regardless of renal status.

Although patients with renal involvement had greater prior exposure to CYC and a higher baseline inflammatory burden, rates of drug survival, infection, and hypogammaglobulinemia were comparable to those in patients without renal disease. This indicates that RTX can be used as a phenotype-independent maintenance strategy even in individuals with reduced renal function who may not tolerate other immunosuppressants such as MTX. In contrast to conventional maintenance agents such as AZA or MTX, which may be contraindicated or less effective in patients with impaired renal function, RTX offers a phenotype-independent option with both immunological and clinical durability.[16,26] While MTX is often limited to non-renal disease due to nephrotoxicity, and MMF shows higher relapse rates particularly in PR3-ANCA patients, RTX appears to offer a more balanced efficacy-to-toxicity ratio across subtypes.[13,27]

Based on clinical experience and established practice patterns, the presence of renal involvement in vasculitis is a poor prognostic indicator. Mortality rates in our group with renal involvement and in the non-renal group are similar. One of the most important reasons for this is that non-renal patients with RTX indications are likely to have more severe disease than other non-renal patients. The similarity of retention rates, dosing schedules, and discontinuation rates due to hypogammaglobulinemia and infection in both groups suggests that RTX does not pose an additional risk for patients with renal involvement or those at risk of renal dysfunction. This aligns with findings from registry-based studies and elderly cohorts, where RTX maintained a favorable safety profile even among immunosenescent or comorbid patients.[28,29]

Infections represented the leading cause of RTX discontinuation in both groups, aligning with data from long-term RTX cohorts.[30] Most infections were respiratory or urinary, and the rate of serious infections requiring hospitalization was not elevated among patients with renal disease. Given that almost one in five patients develops persistent hypogammaglobulinemia, these infection rates should be considered in conjunction with

it. Therefore, monitoring immunoglobulin levels and providing IVIG therapy when necessary may improve outcomes. Our study shows that we were able to administer IVIG to only half of the patients with persistent hypogammaglobulinemia. As outlined in the literature, monitoring gamma globulin levels and providing IVIG replacement therapy when necessary are important, particularly for AAV patients receiving RTX, regardless of renal involvement.[26,27,31,32]

In our study, the long-term retention and cumulative dosing patterns suggest clinicians tend to individualize RTX regimens over time, with adjusted intervals and dosages based on relapse history and tolerance, an approach supported by MAINRITSAN2 and newer ANCA-guided re-treatment protocols.[19,33] Maintenance treatment intervals of up to 65 months are a consequence of the chronic nature of the disease. Therefore, individualisation of maintenance treatment protocols is inevitable. Our findings demonstrate equal drug survival and tolerability in renal and non-renal groups and highlight RTX as a reliable first-line treatment not only for refractory disease or induction but also for long-term disease suppression, independent of renal phenotype.

Study Limitations

This study has several limitations. Its retrospective design may introduce selection and information biases. Variability in RTX maintenance protocols across participating centers might affect the generalizability of dose and interval findings. Data on disease activity and more detailed information on the nature and severity of infections could not be provided because insufficient data were available. Nevertheless, the multicenter nature of the study enhances external validity, and the large, well-characterized cohort allows clinically meaningful comparisons. Although the RTX-treated cohort included patients receiving induction, relapse, refractory, and maintenance therapies, such heterogeneity reflects real-world clinical practice. The primary objective of this study was to evaluate outcomes according to renal involvement rather than treatment indication. Therefore, analyses were performed across the entire RTX-exposed cohort.

Conclusion

In conclusion, RTX provided sustained efficacy and safety during long-term maintenance therapy in AAV patients, regardless of renal involvement. Drug retention, hypogammaglobulinemia, and infection rates were similar across phenotypes, suggesting that RTX is a reliable maintenance option for both renal and non-renal disease. These results support individualized RTX strategies, emphasizing infection prevention and immunoglobulin monitoring as key components of long-term care.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Non-Drug and Medical Device Research Ethics Committee (project no. 09.2024.1382, date: 11.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: R.D., N.A.K., Design: R.D., N.A.K.., Data collection and analysis: R.D, P.A.D., A.I., T.O., B.C.E.U., K.U., B.E., M.A.E., E.A., Y.P., N.Ş.Y.B., T.K., F.A.Ö., Ş.E., A.O., H.D., C.B., N.A.K., Literature Search: R.D., N.A.K., Writing: R.D.

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