Real-world outcomes of rituximab- and cyclophosphamide-based induction therapy regimens alone and in combination over 24 months in ANCA-associated vasculitis

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Abstract

Objective

This retrospective cohort study aimed to evaluate real-world data on the efficacy of rituximab (RTX) alone versus combined rituximab/cyclophosphamide (RTX/CYC) induction therapy, followed by RTX maintenance, compared with cyclophosphamide-azathioprine (CYC-AZA) therapy in ANCA-associated vasculitis (AAV).

Methods

Patients with new-onset or relapsing organ- or life-threatening AAV (granulomatosis with polyangiitis [GPA] n=97; microscopic polyangiitis [MPA], n=69) were followed over 24-months. Patients with previous RTX and/or CYC therapy were excluded. Treatment comprised combination of GC with either RTX alone or RTX/CYC combination for remission induction, each followed by RTX maintenance therapy, or CYC-AZA therapy. The primary outcome measure was complete remission defined as absence of vasculitis activity with no concomitant GC therapy after 12 and 24 months.

Results

20% and 35% of the patients in the RTX group and 22% and 33% in the RTX/CYC group achieved complete remission at 12 and 24 months, contrasting with 3% and 9% in the CYC-AZA group (p=0.008 and p=0.003, respectively). The majority of patients achieved remission with concomitant GC therapy at any time during the 24-months observation period (RTX, 88%; RTX/CYC, 87%; CYC-AZA, 81%; p=0.097). RTX alone was associated with a lower relapse rate compared with RTX/CYC in the subgroup of GPA patients (p=0.041). Moreover, RTX alone was comparably effective to RTX/CYC and CYC-AZA in terms of relapse in patients with severe renal disease (p=0.091).

Conclusion

RTX alone was similarly effective to RTX/CYC combination and CYC-AZA therapy in AAV patients, including those with severe renal involvement.

Key words

ANCA-associated vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, cyclophosphamide, rituximab

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterised by a systemic necrotising vasculitis predominantly affecting small and medium-sized vessels. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis are the two major subgroups of AAV (1). AAV is burdened by excess mortality, with renal impairment being the key determinant for unfavourable outcomes (2, 3). For the induction of remission in new-onset or relapsing GPA or MPA with organ- or life-threatening disease, the 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations advise a combination of glucocorticoid (GC) with either rituximab (RTX) or cyclophosphamide (CYC). For relapsing disease, RTX is favoured (4). Due to limited evidence in support of GC and RTX for induction in patients with severe renal impairment, the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a combination of GC with either CYC or a combination of RTX and CYC (RTX/CYC) in those patients (5). For maintenance of remission after RTX or CYC induction, RTX is recommended or, as an alternative, azathioprine (4, 5).

Notably, there is lack of real-world data from observational studies comparing RTX- and CYC-based remission induction regimens, either given alone or in combination, in patients with new-onset or relapsing organ- or life-threatening GPA and MPA. In this open retrospective monocentric cohort study, we therefore assessed the outcomes of AAV patients treated with GC in combination with RTX alone or combined RTX/CYC therapy for the induction of remission, followed by RTX-based maintenance therapy. For comparison, outcomes were determined in patients treated with CYC induction followed by azathioprine (CYC-AZA) maintenance therapy.

Methods

Patients

Study participants were recruited and followed at the Department of Rheumatology and Clinical Immunology and Department of Internal Medicine I, Division of Nephrology and Transplant Centre at Lübeck University Hospital, Germany. Medical records between January 2010 and November 2021 were reviewed. A rheumatologist and/or nephrologist examined each patient. Patients fulfilled the 2012 Chapel Hill Consensus Conference (CHCC) definitions and the American College of Rheumatology (ACR)/EULAR classification criteria for GPA or MPA (1, 6, 7). The study was approved by the regional ethics review board of the University of Lübeck (16-199) and conducted following the principles of the Declaration of Helsinki. All participants gave their informed consent. Clinical data including vasculitis activity and damage scores [Birmingham Vasculitis Activity Score (BVAS) v3 (8), Vasculitis Damage Index (VDI) (9)], inflammatory markers (high sensitivity C-reactive protein (CRP), creatinine, glomerular filtration rate (GFR, MDRD-formula), proteinuria, diagnostic autoantibodies levels (MPO-ANCA, PR3-ANCA), and treatment were assessed at baseline and during follow-up every 3–6 months over 24 months.

Treatment

For the induction of remission, GPA and MPA patients with new-onset or relapsing organ- or life-threatening disease *i.e.*, displaying severe disease according to the EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update (4), were treated with GC, *i.e.*, prednisolone, in combination with RTX alone or combined RTX/CYC therapy based on the RAVE and RITUXVAS trial regimens, respectively (10, 11). Patients with previous RTX and/or CYC therapy were excluded. Treatment decision for one or the other was left at the physician's discretion. Patients treated with RTX alone received intravenous RTX (375 mg/m^2 of body surface area once weekly for 4 weeks), patients treated with combined RTX/CYC therapy received intravenous CYC at a dose of 15 mg per kilogram in addition to the first and third RTX infusion, and in case of progressive

disease a third CYC dose within the first 6 months. CYC induction with subsequent azathioprine maintenance therapy was administered similarly to the CYC-AZA control groups' regimen in the RAVE and RITUXVAS trials (10, 11). After remission induction, patients treated with RTX alone and combined RTX/CYC received RTX-based maintenance therapy according to the MAINRITSAN trial regimen and following EULAR and KDIGO recommendations (4, 5, 12). Patients of the CYC-AZA group received intravenous CYC at a dose of 15mg per kilogram weekly every 2-3 weeks for 3-6 months until remission was achieved, followed by oral azathioprine maintenance therapy (1-2 mg per kilogram per day) (10, 11).

Outcomes

The primary outcome measure was complete remission at month 12 and 24. Complete remission was defined as BVAS of 0 in the absence of concomitant GC therapy as in the RAVE trial definition (10). Secondary outcome measures were remission with concomitant GC therapy [defined as BVAS=0 and GC≤10 mg/d prednisolone as in the RAVE trial (10)] at any time, remission at 6, 12, 18 and 24 months, complete remission at any time, complete remission at 6 and 18 months, relapse rate at 6, 12, 18 and 24 months, mean daily total prednisolone dose at baseline and 6, 12, 18 and 24 months, number of adverse event (AE) including grade of event, and number of serious adverse events (SAE) with regard to events requiring hospitalisation or life-threatening events, cancer and death. In addition, the type of event (non-serious and serious infections, hypogammaglobulinemia) was recorded. Malignant conditions occurring up to month 24 month were recorded and graded according to the National Cancer Institute's Common Terminology (13). Renal involvement was confirmed by a renal biopsy demonstrating necrotizing glomerulonephritis and/or active urine sediment (glomerular haematuria, cellular casts, proteinuria). Severe renal disease was defined as impairment of kidney function with an estimated glomerular filtration rate (eGFR) <30 ml/min (5). Severe adverse events (SAE) were defined as AE requiring hospitalisation or associated with life-threatening events or death (10, 11). Relapse was defined as recurrence of disease activity after a period of remission (4).

Table I. Patient characteristics at baseline.

	RTX n=81	RTX/CYC n=23	CYC-AZA n=62	p-value
Female/Male	36/45	16/7	27/35	*0.082*
Age (years), median (range)	59 (22-85)	59 (44–83)	69 (21–84)	*0.071*
AAV subgroup				
GPA, n (%)	57 (70)	16 (70)	24 (39)	***<0.001***
MPA, n (%)	24 (30)	7 (30)	38 (61)	***<0.001***
New-onset diagnosis, n (%)	49 (60)	18 (78)	58 (94)	***<0.001***
Relapse, n (%)	32 (40)	5 (22)	4 (6)	***<0.001***
Time to previous remission induction treatment (years), median (range)	7 (2-25)	18 (1-21)	8 (8-13)	*0.2341*
BVAS, mean (SD)	12 (5.7)	16 (10.2)	16 (6.9)	***0.001***
VDI, mean (SD)	0 (0.2)	0 (0.7)	0 (0.6)	*0.210*
Clinical manifestations				
Renal involvement*, n (%)	40 (49)	12 (52)	40 (67)	*0.186*
Neurological involvement, n (%)	9 (11)	6 (26)	18 (29)	***0.014***
Cutaneous involvement, n (%)	9 (11)	2 (8)	8 (13)	*0.892*
Ear, nose and throat involvement, n (%)	39 (48)	11 (48)	23 (37)	*0.399*
Lung involvement, n (%)	40 (49)	15 (65)	36 (58)	*0.337*
Mucous membranes / Eyes involvement, n (%)	6 (7)	7 (30)	5 (8)	***0.012***
Cardiovascular involvement, n (%)	3 (4)	6 (23)	6 (10)	***0.005***
Gastrointestinal, n (%)	0 (0)	1 (4)	3 (5)	*0.098*
Organ- /life-threatening manifestations [#]				
Glomerulonephritis, n (%)	40 (49)	12 (52)	40 (67)	*0.186*
Pulmonary haemorrhage, n (%)	18 (22)	3 (13)	12 (19)	*0.692*
Meningeal involvement, n (%)	0 (0)	0 (0)	2 (3)	*0.397*
Central nervous system involvement, n (%)	2 (2)	1 (4)	4 (6)	*0.496*
Retro-orbital disease, n (%)	1 (1)	1 (4)	0 (0)	*0.257*
Cardiac involvement, n (%)	2 (2)	2 (7)	1 (2)	*0.626*
Mesenteric involvement, n (%)	0 (0)	0 (0)	1 (29)	*0.509*
Mononeuritis involvement, n (%)	5 (6)	4 (17)	11 (18)	*0.053*
Laboratory values				
PR3-ANCA (U/ml), median (range)	128.5 (0-4000)	183.5.01 (0-669)	35.3 (3-200)	*0.598*
PR3-ANCA, n (%)	46 (57)	15 (65)	18 (29)	***0.001***
MPO-ANCA (U/ml), median (range)	56.4 (1-100)	18.4 (2-61)	58.9 (1-130)	*0.209*
MPO-ANCA, n (%)	24 (30)	7 (30)	38 (61)	***0.001***
hs-CRP (mg/l), mean (SD)	45.3 (69.4)	62.6 (80.2)	65.71 (84.3)	*0.949*
Creatinine (μmol/l), mean (range)	201.4 (42-1143)	145.8 (54-563)	223.4 (51-984)	*0.272*
eGFR (ml/min/1.73), mean (range)	59.7 (5-128)	62.9 (5-103)	48.0 (6-97)	*0.161*
Severe renal involvement (eGFR <30 ml/min), n (%)	23 (28)	7 (30)	18 (29)	*0.982*
Proteinuria (mg/l), mean (SD)	579.7 (1184)	209.2 (332)	359.8 (493)	*0.282*
Therapy before first infusion of RTX and/or CYC				
Methotrexate, n (%)	20 (25)	2 (9)	3 (5)	***<0.001***
Azathioprine, n (%)	5 (6)	0	1 (2)	*0.356*
Leflunomide, n (%)	6 (7)	0	1 (2)	*0.171*
Mycophenolate mofetil, n (%)	1 (1)	1 (4)	0	*0.259*

RTX: rituximab; RTX/CYC: combination rituximab and cyclophosphamide, each followed by RTX maintenance; CYC-AZA: cyclophosphamide followed by azathioprine; AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; BVAS: Birmingham Vasculitis Activity Score (BVAS) v3; VDI: vasculitis damage index; hs-CRP: high-sensitivity C-reactive protein; eGFR: glomerular filtration rate (MDRD-formula).

*Renal involvement characterised by renal biopsy demonstrating necrotising glomerulonephritis and/or active urine sediment (glomerular haematuria, cellular casts, proteinuria).

[#]Organ- /life-threatening manifestations according to Hellmich *et al*. (4).

Table II. Efficacy outcome. Remission rates at 6, 12, 18, 24 months and at any time stratified by induction therapy.

	RTX *n=81*	RTX/CYC *n=23*	CYC-AZA *n=62*	*p-value*
	Number (percent)			
Complete remission rates (%) *(BVAS = 0, GC = 0mg/d prednisolone)*				
6 months	3/81 (4)	0/23 (0)	1/62 (2)	*0.397*
12 months	15/75 (20)	5/23 (22)	2/58 (3)	***0.008***
18 months	15/62 (24)	6/21 (21)	3/49 (6)	***0.017***
24 months	19/55 (35)	6/18 (33)	4/46 (9)	***0.003***
Remission rates (%) *(BVAS = 0, GC <10mg/d prednisolone)*				
6 months	48/81 (59)	13/23 (57)	28/62 (45)	*0.097*
12 months	53/75 (71)	15/23 (65)	37/58 (64)	*0.396*
18 months	46/62 (74)	15/21 (71)	37/49 (76)	*0.874*
24 months	41/55 (75)	14/18 (78)	36/46 (78)	*0.658*
Complete remission at any time (%) *(BVAS = 0, GC = 0mg/d prednisolone)*	27/81 (33)	9/23 (39)	5/62 (8)	***<0.001***
Remission at any time (%) *(BVAS = 0, GC <10mg/d prednisolone)*	71/81 (88)	20/23 (87)	(50/62) 81	*0.097*

BVAS: Birmingham Vasculitis Activity Score v3.

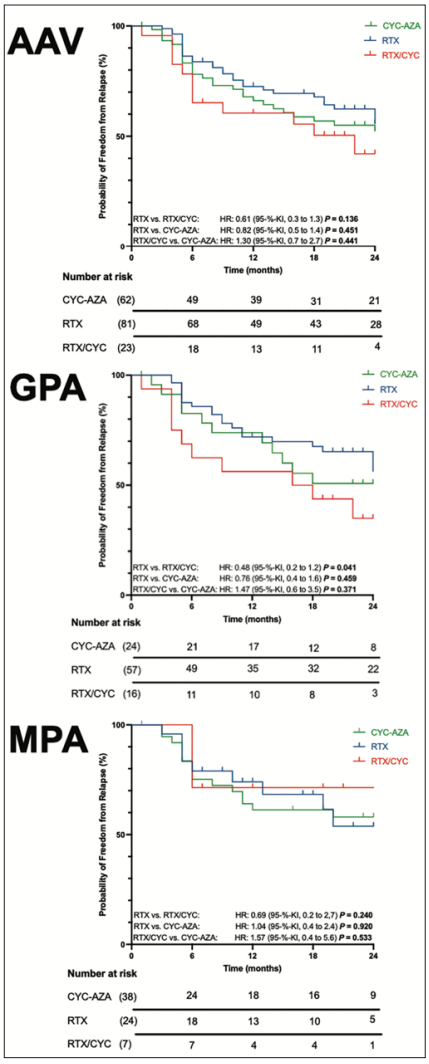

Fig. 1. Kaplan-Meier survival analysis showing relapse-free survival over 24 months observation period.
AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; RTX: rituximab; RTX/CYC: combination rituximab and cyclophosphamide; CYC-AZA: cyclophosphamide followed by azathioprine.

Statistical analysis

Results were visualised and analysed with Prism version 10.3.0 (GraphPad Software). Nonparametric Mann-Whitney U-test and Spearman's rho were used to examine noncategorical, non-normal distributed values. Fisher's exact test or chi-square test was performed to compare categorical values. A one-way ANOVA was performed when two groups of samples were compared for iterating parameters, or more than two groups of samples were compared. Tukey's range test was used as a post hoc analysis of ANOVA. Comparisons of clinical Time-to-event variables between the three groups were calculated using the log-rank test and visualised using the Kaplan-Meier curve. All statistical tests were two-sided. *P* values below 0.05 were considered significant.

Results

Patient characteristics

In this retrospective study, 166 patients with new-onset or relapsing organ- or life-threatening GPA (n=97) or MPA (n=69) treated between January 2010 and November 2021 were included. Patients were treated for remission induction with a combination of GC and either RTX alone (n=81) or combined RTX/CYC (n=23), each followed by RTX maintenance therapy, or CYC-AZA (n=62). Of note, patients with previous RTX and/or CYC therapy were excluded. Our retrospective analysis showed more patients with new-onset disease and MPA in the group of patients treated with CYC-AZA compared to the RTX and RTX/CYC groups. By contrast, the RTX and RTX/CYC groups comprised a higher proportion of patients with relapsing disease. Overall, the creatinine concentration was increased and eGFR decreased in all three treatment groups, with the highest creatinine concentration in the group of patients treated with CYC-AZA. Moreover, CRP and BVAS were higher in the RTX/CYC and CYC-AZA groups compared with the RTX group. Patient characteristics at baseline are summarised in Table I.

Primary outcome measures

Complete remission defined as BVAS of 0 in the absence of concomitant GC therapy was achieved in 20% and 35% of the patients in the RTX group and in 22% and 33% in the RTX/CYC group after 12 and 24 months. By contrast, 3% and 9% of the CYC-AZA group were in complete remission after 12 and 24 months (p=0.008 and p=0.003, respectively) (Table II).

Secondary outcome measures

In all three treatment groups, the majority of patients achieved remission (BVAS=0, GC≤10 mg/d prednisolone) at any time during the 24-months observation period (RTX, 88%; RTX/CYC, 87%; CYC-AZA, 81%; p=0.097) (Table II, Supplementary Fig. S1A). Remissions rates at 6, 12, 18 and 24 months were similar (Table II, Supplementary Fig. S1B). A higher proportion of patients achieved complete remission (BVAS=0, GC=0 mg/d prednisolone) at any time with RTX (33%) and RTX/CYC (39%) compared to CYC-AZA therapy (8%; p=0.001) (Table II, Supplementary Fig. S1C). While there was no difference in complete

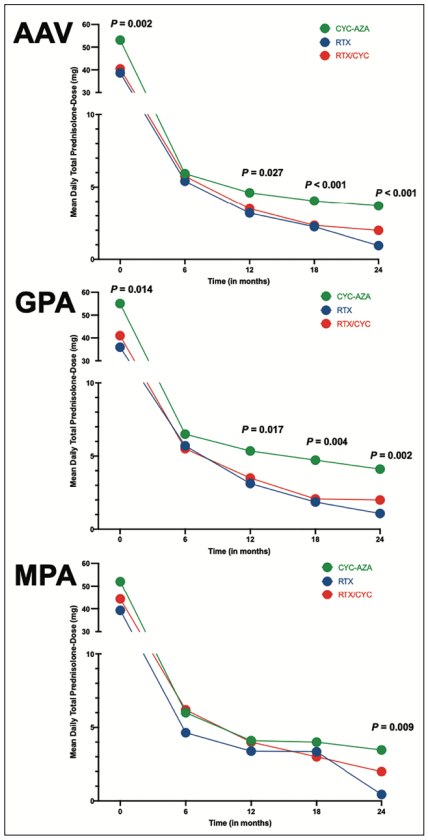

Fig. 2. Mean daily total prednisolone dosage over 24 months observation period.
AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RTX: rituximab; RTX/CYC: combination rituximab and cyclophosphamide; CYC-AZA: cyclophosphamide followed by azathioprine.

remissions rates between the RTX, RTX/CYC and CYC-AZA groups after 6 months, 24% of the patients in the RTX group and 21% in the RTX/CYC group achieved complete remission at 18 months, contrasting with 6% in the CYC-AZA group at 18 months (p=0.017) (Table II, Supplementary Fig. S1D).

Relapse rates were similar across all three treatment groups during the observation period over 24 months (Fig. 1). However, subgroup analysis unveiled a lower risk of relapse in GPA patients treated with RTX alone compared to combined RTX/CYC (HR: 0.48, p=0.041) (Fig. 1), which was not observed in MPA patients (HR: 0.69, p=0.240) (Fig. 1). The relapse rate in patients with glomerulonephritis and with an eGFR<30 ml/min (severe renal involvement) receiving RTX therapy alone did not differ from that observed with RTX/CYC and CYC-AZA therapy (Supplementary Fig. S2, S3).

At baseline, the mean daily total prednisolone dosage was higher in patients treated with CYC-AZA compared to RTX alone and combined RTX/CYC (p=0.002) (Fig. 2). Subgroup analysis showed that this was true for the group of GPA patients (p=0.014), while there was no difference in mean daily total prednisolone dosage between the three treatment groups at baseline in the MPA group (Fig. 2). Over the 24 months observation period, the mean daily total prednisolone dosage was efficiently reduced in all three treatment groups, with greater prednisolone dose reduction in the RTX and RTX/CYC treatment groups compared to the CYC-AZA group at 12, 18 and 24 months (p=0.027, p<0.001, p<0.001) (Fig. 2). Subgroup analysis showed a greater reduction in mean daily total prednisolone dosage in GPA patients treated with RTX or RTX/CYC compared to CYC-AZA at 12, 18 and 24 months (p=0.017, p<0.004, p<0.002) (Fig. 2). By contrast, greater reduction in mean daily total prednisolone dosage in MPA patients treated with RTX or RTX/CYC compared to CYC-AZA was not observed before month 24 (p<0.009) (Fig. 2).

The number of AE did not differ between the three treatment groups, nor did the type event with respect to non-serious and serious infections and hypogammaglobulinemia (Table III).

Table III. Adverse events according to treatment regimen.

Events	RTX *n=81*	RTX/CYC *n=23*	CYC-AZA *n=62*	*p-value*
Grade 1-5 events				
Grade 1 or 2, n (%)	27 (32)	9 (39)	26 (42)	*0.288*
Grade 3,4, or 5, n (%)	28 (35)	9 (39)	21 (34)	*0.173*
All, n (%)	55 (68)	18 (78)	47 (76)	*0.280*
Serious events				
Events requiring hospitalisation or life-threatening events, n (%)	25 (31)	10 (43)	29 (48)	***0.029***
Cancer, n (%)	4 (5)	3 (13)	6 (10)	*0.274*
Death, n (%)	2 (2)	0	3 (5)	*0.438*
Types of events				
Non-serious infections, n (%)	27 (34)	0 (39)	26 (45)	*0.315*
Serious infections, n (%)	16 (20)	7 (30)	17 (29)	*0.272*
Hypogammaglobulinemia, n (%)	6 (8)	3 (15)	6 (16)	*0.614*

RTX: rituximab; RTX/CYC: combination rituximab and cyclophosphamide, each followed by RTX maintenance; CYC-AZA: cyclophosphamide followed by azathioprine.

However, SAE due to life-threatening events or necessitating hospitalisation were more frequent in the group of patients treated with CYC-AZA compared to patients treated with RTX alone and combined RTX/CYC (CYC-AZA 48%, RTX 31%, RTX/CYC 43%; p=0.029) (Table III). Cancer was observed at similar rates with RTX, RTX/CYC and CYA-AZA therapy during the observation period (5%, 13%, 10%, p=0.272) (Table III) Fatal outcomes were rare during that time (RTX 2%, RTX/CYC 0%, CYC-AZA 5%, p=0.438) (Table III).

Discussion

In this retrospective observational cohort study, induction therapy in patients with new-onset or relapsing organ- or life-threatening AAV with a combination of GC and either RTX alone or combined RTX/CYC, each followed by RTX maintenance therapy, or CYC-AZA was similarly effective in terms of achieving remission with concomitant GC therapy (GC ≤10 mg/d prednisolone) and the relapse rate. However, as primary outcome measure, complete remission defined as the absence of vasculitis activity with a BVAS of 0 and being off GC therapy was more often achieved with RTX alone and combined RTX/CYC therapy compared with CYC-AZA therapy after 12 and 24 months. RTX therapy alone was associated with a lower relapse rate compared to combined RTX/

CYC in the subgroup of GPA patients. Moreover, RTX therapy alone was comparably effective to combined RTX/CYC and CYC-AZA therapy in terms of relapse in patients with severe renal disease (eGFR <30 ml/min; renal biopsy demonstrating necrotizing glomerulonephritis and/or active urine sediment with glomerular haematuria, cellular casts, and proteinuria). Disease-specific pathomechanisms may thus be more consistently addressed by RTX through B cell depletion without additional benefit of CYC and in comparison, to CYC-AZA therapy.

Our real-world data are consistent with the so-far largest randomised controlled trial which showed non-inferiority of a combination of GC and RTX alone compared to CYC-AZA for remission induction in AAV (RAVE trial) (10). A *post-hoc* analysis of the RAVE trial data also suggests similar efficacy of RTX and CYC-AZA for remission induction in the subgroup of AAV patients with renal involvement (14). However, patients with severe renal disease (creatinine >354 μmol/l) were excluded from the RAVE trial (10). The smaller RITUXVAS trial included such patients and showed similar efficacy of GC and combined RTX/CYC or CYC-AZA therapy in AAV with renal involvement (11). Contrasting with the real-world treatment approach presented herein, RTX-based induction therapy was not followed by RTX maintenance in both of those landmark trials (10, 11). In our cohort, patients were assigned to recommended induction therapies at the physician's discretion. Preference for induction therapy changed over the observational period (2010-2019), with RTX-based induction therapy (RTX alone or combined RTX/CYC) followed by RTX maintenance becoming increasingly preferred over CYC-AZA therapy. This trend may have influenced treatment group composition. Whereas a larger proportion of MPA patients and patients with new-onset disease was found in the CYC-AZA treatment group, more patients with GPA and relapsing disease were found in the RTX alone and combined RTX/CYC therapy groups. Higher BVAS in the group of patients treated with combined RTX/CYC compared with those treated with RTX alone suggests selection bias, with patients with more severe disease being preferentially assigned to combined RTX/CYC therapy. Yet, creatinine concentrations were similar in both RTX-based induction therapy groups and comparable to those of the CYC-AZA treatment group.

Outcomes for overall- and kidney survival are largely driven by renal involvement in AVV, with patients displaying severe renal impairment having the worst prognosis (3). While uncontrolled cohort studies suggest improved responses and low relapse rates with combined RTX/CYC induction therapy followed by AZA maintenance therapy, randomised controlled studies comparing combined RTX/CYC therapy with RTX alone for the induction of remission in AAV, including patients with severe renal involvement, have not been published so far (4). Currently, combined RTX/CYC therapy versus RTX alone for remission induction, followed by tailored RTX maintenance therapy, is investigated in an open-label phase 3 study (ENDURRANCE trial, NCT03942887). Our real-world retrospective observational cohort study suggests comparable efficacy of induction therapy with RTX alone compared with combined RTX/CYC and CYC-AZA therapy with respect to remission induction and relapse rates in AAV, including patients with severe renal disease with an eGFR lower than 30ml/min. Complete remission was even more often achieved with RTX alone and combined RTX/CYC therapy compared with CYC-AZA therapy after 12 and 24 months. In support of our observation of a lack of benefit from the addition of CYC to RTX compared to RTX therapy alone, efficacy of RTX alone induction therapy was shown in the ADVOCATE trial in AAV patients, including patients with severe renal disease (eGFR ³15 ml/min) (15). The ADVOCATE trial demonstrated superiority of the oral C5a receptor antagonist avacopan in comparison to GC with respect to sustained remission at week 52 in AAV treated with either RTX or CYC-AZA for the induction of remission. Moreover, avacopan improved the renal outcome (15). Of note, the observation period of our retrospective study did not extend beyond the date of EU-approval of avacopan for the treatment of severe AAV (January 2022). Thus, data on avacopan treatment are not included in this study.

Overall, the rate of AE was comparable in the three treatment groups in our study. Similar AE and SAE rates were reported for RTX-based therapies versus CYA-AZA therapy in the above mentioned randomized controlled trials (10, 11). In our study, fewer relapses occurred with RTX alone compared with combined RTX/CYC therapy in the subgroup of GPA patients during the observation period. SAE requiring hospitalization or due to life-threatening events were found more frequently in the CYC-AZA therapy group possibly due to a higher cumulative CYC dose compared with the RTX-based therapy regimen. Moreover, a greater reduction in the mean daily total prednisolone dose was shown for the patient groups treated with RTX alone or RTX/CYC compared with those treated with CYC-AZA. However, this may be due to a general tendency aiming at reducing GC-doses during the observation period of this study. Moreover, we hypothesize that the reduced dose of GC can be a cumulative effect of sustained remission following induction by RTX-based therapies.

Furthermore, RTX maintenance therapy may have contributed to improved GC-reduction and achieving complete remission more often following RTX alone and RTX/CYC induction therapy compared to CYC-AZA treatment, as RTX therapy has been shown to be superior to AZA therapy for remission maintenance in AAV (4). Intriguingly, despite higher concomitant mean daily prednisolone dosage with CYC-AZA therapy over the 24-months period, complete remission rates were higher in the groups of patients treated with RTX alone or combined RTX/CYC therapy after 12, 18 and 24 months.

The strength of our study lies in the comparatively large size of the AAV cohort, non-preselected patient population (unlike patients in randomised

controlled trials) and length of the longitudinal observation period. Our study provides real-world evidence on induction (RTX, RTX/CYC, CYC-AZA) and maintenance (RTX) therapy with respect to safety and effectiveness over 24 months in patients with new-onset or relapsing organ- or life-threatening AAV. Limitations of our study are its retrospective observational design, monocentric character, and selection bias with non-random assignment of patients to RTX-based therapy, *i.e.*, either RTX alone or combined RTX/CYC, by the treating physician, and thus, unbalanced group sizes. Moreover, preference for induction therapy regimen changed over the observational period, as outlined above, as did recommendations for GC-dosing (4, 5).

In conclusion, the present retrospective study suggests comparable efficacy of GC in combination with RTX alone and combined RTX/CYC therapy, followed by RTX maintenance therapy, and CYC-AZA treatment for the induction and maintenance of remission over 24 months in patients with AAV, including those with severe renal disease. Indirect evidence from the ADVOCATE trial (15) suggests added value of avacopan for GC-taper in combination with RTX alone, thus further challenging the rationale of adding CYC to RTX for induction therapy in patients with severe AAV.

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References

1. JENNETTE JC, FALK RJ, BACON PA *et al.*: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; 65(1): 1-11. https://doi.org/10.1002/art.37715
2. SÁNCHEZ ÁLAMO B, MOI L, BAJEMA I *et al.*: EUVAS. Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 2023; 38(7): 1655-65. https://doi.org/10.1093/ndt/gfac320
3. GISSLANDER K, WHITE A, ASLETT L *et al.*: Data-driven subclassification of ANCA-associated vasculitis: model-based clustering of a federated international cohort. *Lancet Rheumatol* 2024; 6(11): e762-e770. https://doi.org/10.1016/S2665-9913(24)00187-5
4. HELLMICH B, SANCHEZ-ALAMO B, SCHIRMER JH *et al.*: EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis* 2024; 83(1): 30-47. https://doi.org/10.1136/ard-2022-223764
5. KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES (KDIGO) ANCA VASCULITIS WORK GROUP: KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis. *Kidney Int* 2024; 105(3S): S71-S116. https://doi.org/10.1016/j.kint.2023.10.008
6. ROBSON JC, GRAYSON PC, PONTE C *et al.*: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Granulomatosis with Polyangiitis. *Arthritis Rheumatol* 2022; 74(3): 393-9. https://doi.org/10.1002/art.41986
7. SUPPIAH R, ROBSON JC, GRAYSON PC *et al.*: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis. *Arthritis Rheumatol* 2022; 74(3): 400-6. https://doi.org/10.1002/art.41983
8. MUKHTYAR C, LEE R, BROWN D *et al.*: Modification and validation of the Birmingham Vasculitis Activity Score (version 3). *Ann Rheum Dis* 2009; 68(12): 1827-32. https://doi.org/10.1136/ard.2008.101279
9. EXLEY AR, BACON PA, LUQMANI RA *et al.*: Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. *Arthritis Rheum* 1997; 40(2): 371-80. https://doi.org/10.1002/art.1780400222
10. SPECKS U, MERKEL PA, SEO P *et al.*: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369(5): 417-27. https://doi.org/10.1056/NEJMoa1213277
11. JONES RB, FURUTA S, COHEN TERVAERT JW *et al.*: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis* 2015; 74(6): 1178-82 https://doi.org/10.1136/annrheumdis-2014-206404
12. TERRIER B, PAGNOUX C, PERRODEAU É *et al.*: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 2018; 77(8): 1150-6. https://doi.org/10.1136/annrheumdis-2017-212768
13. National Cancer Institute. Common terminology criteria for adverse events v5.0 (CTCAE). (Accessed April 4, 2024) https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf)
14. GEETHA D, SPECKS U, STONE JH *et al.*: Rituximab for ANCA-Associated Vasculitis Immune Tolerance Network Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* 2015; 26(4): 976-85. https://doi.org/10.1681/ASN.2014010046
15. JAYNE DRW, MERKEL PA, SCHALL TJ *et al.*: Avacopan for the Treatment of ANCA-Associated Vasculitis. *N Engl J Med* 2021; 384(7): 599-609. https://doi.org/10.1056/NEJMoa2023386
16. VON ALLWÖRDEN K, KLAPA S, WERTH SC *et al.*: POS1161 Rituximab vs. combination of rituximab and cyclophosphamide induction therapy for ANCA-associated vasculitis: a retrospective study. *Ann Rheum Dis* 2023; 82: 912-3. https://doi.org/10.1136/annrheumdis-2023-eular.3867