Renal involvement at baseline can predict major renal relapse in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

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ABSTRACT

Objective. *In ANCA-associated vasculitis (AAV), renal relapses are cause of concern as they are unpredictable and predictors of end-stage renal disease (ESRD). We aimed to assess the frequency of major renal (MR) relapses in AAV and to identify independent baseline predictors.*

Methods. *We performed a retrospective monocentric observational cohort study of patients affected by granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and renal limited vasculitis (RLV), diagnosed from 2000 to 2019, and who achieved clinical remission defined as Birmingham Vasculitis Activity Index version 3 (BVASv3)=0 and/or clinical judgment. MR relapse was defined as the occurrence of major items of renal BVASv3. Univariate and multivariable analysis was performed with competitive risk analysis.*

Results. *We included 96 patients: 73 GPA, 21 MPA and 2 RLV. Eighty-five (90%) patients were ANCA-positive: 56 c-ANCA/PR3, 28 p-ANCA/MPO and 1 double positive. During the follow-up, 17/96 patients developed at least one MR relapse, 2/96 progressed to ESRD and 3/96 died without events; 74 did not develop MR relapse. Patients with MR relapse were all ANCA positive and had higher frequency of skin (p=0.034), kidney (p=0.004) and nervous system (p=0.024) involvement and lower frequency of ear, nose and throat (ENT) manifestations (p=0.043). At multivariable analysis, renal involvement at baseline (sHR 20.4, 95% confidence interval (95% CI) 2.6-158.2, p=0.004) and remission-induction treatment without cyclophosphamide and/or rituximab (sHR 4.2, 95% CI 1.5-12.0, p=0.007) were independent predictors of MR relapses.*

Conclusion. *Baseline renal involvement predicts MR relapse in AAV while intense initial treatment seems to be protective.*

Introduction

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and renal limited vasculitis (RLV) are anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) (1). Renal involvement occurs in a percentage ranging between 50% in GPA and 100% in RLV (2, 3) and it is usually associated with older age at AAV onset, positive ANCA serology, MPO specificity and less frequent ear, nose and throat (ENT) involvement (4, 5). Renal manifestations are mostly due to crescentic glomerulonephritis and tubulo-interstitial vasculitis leading to a spectrum of clinical manifestations ranging from urinary casts and proteinuria with preserved renal function to acute kidney failure requiring dialysis within few days (1, 6).

Kidney involvement is critical since it affects disease prognosis in terms of relapse rate, renal and patients' survival (7, 8). Patients with renal manifestation at AAV onset are widely recognised as a subgroup with higher mortality and lower relapse rate, though relapse rate differs according to ANCA specificity (7, 9).

During the follow-up, the occurrence of renal relapses has proven to be an independent predictor of end-stage renal disease (ESRD) (8). However, only few studies focused on predictors of renal relapses. Some authors reported a higher risk of renal relapse in remitted patients with persistent haematuria, but not proteinuria (10). Göçeroğlu *et al.* observed a significantly higher risk of renal relapse in patients with interstitial infil-

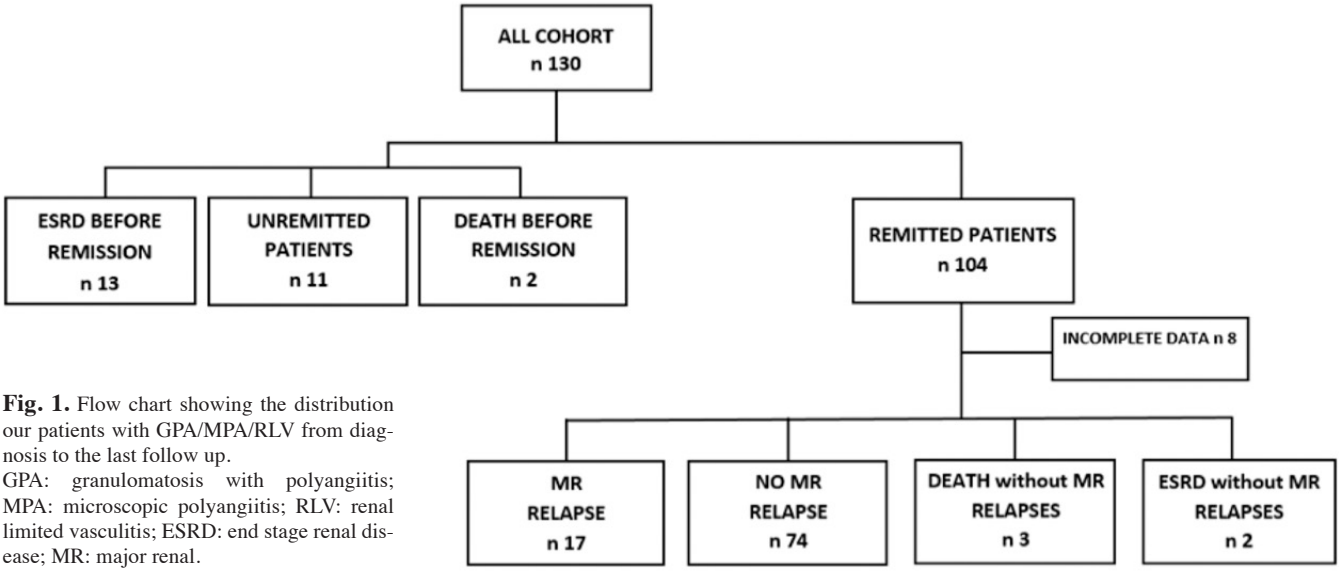

Fig. 1. Flow chart showing the distribution our patients with GPA/MPA/RLV from diagnosis to the last follow up.
GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal limited vasculitis; ESRD: end stage renal disease; MR: major renal.

trates and sclerotic class at first renal biopsy (11). A recent study conducted on the AAV cohort of the European vasculitis study group randomised controlled trials (EUVAS RCTs) failed to identify any independent predictors of renal relapse (8). It should be noted that all these studies were performed in cohorts where the prevalence of MPA and renal AAV at disease onset was much higher than that reported in observational cohorts (2, 3): thus, they might not closely resemble a typical clinical setting.

Some authors observed that AAV relapses are more likely to occur in the same organ involved at disease onset (12), while a recent paper showed that 46% of patients with relapsing AAV experienced manifestations in a new organ during the disease relapse (13).

Our aim was to assess the clinical features and frequency of major renal (MR) relapses in GPA, MPA and RLV patients and to identify independent predictors of MR relapses. In addition, we evaluated whether having a specific organ involvement at AAV onset, *i.e.* kidney disease, could be a risk factor for MR relapse, irrespective of the ANCA subset.

Methods

We performed a retrospective monocentric observational study where we analysed the data of all GPA, MPA and RLV patients regularly seen in the Vasculitis Clinic of Rheumatology Unit, Padova University Hospital, Italy from January 2000 to July 2019. We considered the following inclusion criteria:

GPA, MPA or RLV diagnosis fulfilling EMA algorithm criteria (14).

Achievement of remission was defined as the absence of vasculitis manifestations according to Birmingham Vasculitis Activity Score version 3 (BVASv3)=0 and/or clinical judgement (performed by AAV expert physicians).

We excluded all remitted patients who developed ESRD before remission. ESRD was defined as estimated glomerular filtration rate (eGFR) calculated with CKD-EPI formula (15) <15 ml/min or requiring continuative dialysis.

Major renal (MR) relapse was defined as the occurrence of at least one major item of renal Birmingham Vasculitis Activity Score version 3 (BVASv3) ("New/worse haematuria≥10 RBCs/hpf" and/or "New/worse rise in serum creatinine >30% or fall in creatinine clearance >25%". According to BVASv3 "New/worse" should be applied if "the features have started or deteriorated in the past month or if the manifestations is new for definition as serum creatinine >30% or fall in creatinine clearance >25%") (16). Other causes of haematuria and renal function decrease than vasculitis relapse were ruled out.

This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles and was approved by the local Institutional Review Board.

Patients' assessment

We collected the following data at the time of diagnosis (baseline) in all patients: demographic and clinical data, including updated Charlson comorbidity index (uCCI) (17); laboratory variables: haemoglobin (Hb), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), creatinine, eGFR calculated with CKD-EPI formula (15), presence of urinary casts, proteinuria >1+ and proteinuria >0.5 g/daily, ANCA serology and specificity; organ involvement, disease activity assessed by BVASv3 and damage accrual assessed by Vasculitis Damage Index (VDI) (18).

We also recorded all immunosuppressants (IS) administered from baseline until treatment withdrawal or last follow-up (LFU), glucocorticoid pulses (GC pulses), plasma exchange (PEX), the date of first remission, the date of first MR relapse, the date of ESRD and death. Minor renal relapses were not considered because deemed less reliable in a retrospective data collection.

Statistical analysis

All remitted patients were allocated in two subgroups: patients without MR relapses and patients with MR relapses during the follow-up.

Shapiro-Wilk test was performed to test normality. Continuous variable were expressed as mean and standard deviation (SD) or median, minimum (min) and maximum (max) or median and I-III quartiles (Q1-Q3), as appro-

priate. Categorical data were express as numbers and percentages.

Comparisons between the two groups were performed with Mann-Whitney test or t-test for independent samples, while for categorical variables we applied Fisher test or Chi square test as appropriate.

Univariate and multivariable Fine and Gray (F&G) sub distribution hazard (sHR) model was applied to identify the baseline predictors of first MR relapse with ESRD and death as competing risks. Each sHR was reported with its specific 95% confidence interval (95% CI). Due to the relatively low frequency of events and the risk of overfitting, we performed several multivariable models with three variables, as recommended by Peduzzi *et al*. and reported in other papers (11, 19, 20). We performed two sets of multivariable analysis. All models included remission-induction treatment, categorised as cyclophosphamide (CYC) or/and rituximab (RTX) *versus* others, because associated to significantly different relapse rate (21-25), while the second covariate was different in the two sets. In the first set we included age [a predictor of lower relapse rate in one our previous study (4)], and in the second set PR3-ANCA specificity, a well known predictor of relapse (7, 9). In all models, the third variable was selected based on literature data or variables with $p<0.10$ at univariate analysis. Complete renal histopathology at baseline was retrieved in only a minority of patients, so it was not included in the analysis. The best multivariable model was selected according to the Akaike information criterion (AIC) (the lowest AIC identified the best model and a model was considered superior if ΔAIC was greater than 2).

Fine and Gray sub proportional sub distribution hazard models were performed with SAS software, Version 9.4, while all other analysis was performed with IBM SPSS Statistics for Windows, v. 25.0.

Results

Among the 130 GPA, MPA and RLV patients followed in our Unit from January 2000 to July 2019, 104 met the inclusion criteria. Out of them, 8 patients

Table I. Demographics and clinical features at baseline and treatment during the follow up in all patients and according to whether or not they developed MR relapse.

	OVERALL No. 96	Patients with MR relapse n=17	Patients without MR relapse n=79	*p*
Age, median (Q1-Q3)	54 (44-64)	53 (48-64)	54 (39-65)	0.558
Female, n. (%)	51 (53)	6 (35)	45 (57)	0.104
GPA, n. (%)	73 (76)	12 (71)	61 (77)	
MPA/RLV, n. (%)	23 (24)	5 (29)	18 (23)	0.545
Diagnosis decade				
2000-2010, n. (%)	22 (23)	5 (29)	17 (21)	
2011-2019, n. (%)	74 (77)	12 (71)	62 (79)	0.529
ANCA negative, n. (%)	9/94 (9.6)	0/16 (0.0)	9/78 (11.5)	
c-ANCA/PR3, n. (%)	56/94 (59.6)	11/16 (68.8)	45/78 (57.7)	
p-ANCA/MPO, n. (%)	28/94 (29.8)	5/16 (31.2)	23/78 (29.5)	
Double positivity, n. (%)	1/94 (1.0)	0/16 (0.0)	1/78 (1.3)	0.347[a]
uCCI, median (Q1-Q3), n. 89	0 (0-1)	0 (0-1)	0 (0-1)	0.498
Diagnostic latency, months, median (min-max), n. 95	4 (0-84)	2 (0-7)	4 (0-84)	*0.065*
Histologically confirmed diagnosis, n. (%), n. 94	63 (66)	6 (38)	57 (72)	**0.007**
Hospitalisation, n. (%)	84 (88)	16 (94)	68 (86)	0.686
WBC cellx10^3/uL, median (Q1-Q3), n. 78	10.3 (8.2-12.5)	12.2 (9.5-13.7)	10.1 (8.2-12.3)	0.115
Hb, g/dl, median (Q1-Q3), n. 84	10.7 (8.7-12.4)	9.7 (8.4-11.2)	10.9 (8.8-12.4)	0.255
PTLs, elx10^6/uL, median (Q1-Q3), n. 75	336 (268-472)	399 (269-530)	325 (266-469)	0.410
ESR, mm/h, mean (SD), n. 71	64.8 (31.2)	77.8 (21.7)	62.1 (32.3)	0.113
CRP, mg/L, median (Q1-Q3), n. 80	79 (21-142)	118 (34-195)	54 (19-140)	*0.072*
Creatinine, mg/dl median (Q1-Q3), n. 89	1.5 (0.8-3.5)	1.9 (1.0-2.9)	1.4 (0.8-3.6)	0.266
eGFR, median (Q1-Q3), n. 89	37.2 (18.0-90.8)	34.7 (21.0-82.2)	56.2 (17.2-96.6)	0.369
eGFR<60 ml/min, n. (%), n. 95	16 (48.4)	11 (68.8)	35 (44.3)	*0.074*
Organ involvement:				
Systemic symptoms, n. (%)	77 (80.2)	16 (94.1)	61 (77.2)	0.180
ENT involvement, n. (%)	55 (57.3)	6 (35.3)	49 (62.0)	**0.043**
Lung involvement, n. (%)	66 (68.8)	15 (88.2)	51 (64.6)	*0.056*
Skin involvement, n. (%)	21 (21.9)	7 (41.2)	14 (17.7)	**0.034**
Eye involvement, n. (%) n. 95	11 (11.5)	2 (11.8)	9 (11.4)	1.000
CV involvement, n. (%) n. 95	3 (3.2)	0	3 (3.8)	1.000
GI involvement, n. (%) n. 95	4 (4.2)	0	4 (5.1)	1.000
Renal involvement, n. (%)	61 (63.5)	16 (94.1)	45 (57.0)	**0.004**
Neurological manifestations, n. (%)	29 (30.2)	9 (52.9)	20 (25.3)	**0.024**
BVASv3, mean (DS)	19.1 (8.1)	24.1 (6.2)	18.1 (8.1)	**0.007**
VDI, median (min-max), n. 92	0 (0-4)	0 (0-3)	0 (0-4)	**0.049**
PEX, n. (%), n. 93	11 (12)	1 (6)	10 (13)	0.682
GC pulses, n. (%), n. 89	37 (42)	8 (57)	29 (39)	0.198
Remission induction IS				
None, n. (%)	7 (7)	0 (0)	7 (9)	
CYC, n. (%)	46 (48)	10 (60)	36 (46)	
RTX, n. (%)	13 (14)	0 (0)	13 (17)	
MTX, n. (%)	12 (13)	1 (6)	11 (14)	
MMF, n. (%)	4 (4)	1 (6)	11 (14)	
AZA, n. (%)	12 (13)	5 (29)	7 (9)	
Others, n. (%)	2 (2)	0 (0)	2 (3)	*0.093*
Remission induction treatment duration, months, median (Q1-Q3), n. 92	5.5 (3-6)	6 (3.25-6)	5 (3-6)	0.485
Time to remission, months, median (Q1-Q3), n. 93	6 (3-8)	6 (3-8.5)	6 (4-8)	0.938
GC withdrawal, n. (%)	64 (67)	11 (65)	53 (68)	0.796
Length of GC treatment, months, median (Q1-Q3), n. 91	27 (16-50)	45.5 (25.5-61.5)	26 (14-47)	**0.009**
FU time, months, median (Q1-Q3)	54.5 (29.3-96.5)	90 (53-126)	50 (26-94)	**0.008**

***p*<0.05**, *p 0.10-0.05*, [a]not considered double positivity.

MR: major renal; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal limited vasculitis; ANCA: anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; MPO: myeloperoxidase; uCCI: updated Charlson comorbidity index; WBC: white blood count; Hb: haemoglobin; PTLs: platelets; ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ENT: ear, nose and throat; CV: cardiovascular; GI: gastrointestinal; eGFR: estimated glomerular filtration rate; BVASv3: Birmingham vasculitis activity score (version 3); VDI: vasculitis damage index; PEX: plasma exchange; CYC: cyclophosphamide; RTX: rituximab; MTX: methotrexate; MMF: mycophenolate; AZA: azathioprine; GC: glucocorticoid; FU: follow up.

were excluded due to incomplete data (all clinical features of excluded patients were reported in Supplementary Table S1). Our patients were mostly Caucasian (98%) and were classified as follows: 73 GPA, 21 MPA and 2 RLV. The diagnosis was histologically confirmed in 66% of cases. Median follow up time was 54.5 months (29.3-96.5), significantly longer in MR relapse group [90 months (53-126)] than in MR relapse free group [50 months (26-94), p=0.008].

Results of ANCA testing were available in 94 patients; 85 (90%) were ANCA positive: 56 (59.6%) c-ANCA/PR3, 28 (29.8%) p-ANCA/MPO and 1 double positive.

During the follow up, 17 (17.7%) had at least one MR relapse, while 74 remained in stable renal remission until LFU. In 2 patients renal function worsened to ESRD without clear evidence of active vasculitis and 3 patients died without ESRD or MR relapse (Fig. 1).

GC and IS treatment was available in 15/17 patients: 8/15 (53.3%) patients were on GC and 10/15 (66.7%) were on IS treatment when the MR relapse occurred; *i.e.* 5 azathioprine (AZA) and 5 mycophenolate (MMF).

In the MR relapse group, one patient developed ESRD after MR relapse and and one died three years after the MR relapse.

In Table I we listed the demographics and clinical features at baseline in all patients, and according to whether or not they developed MR relapse.

MR relapses were found only in ANCA positive patients; however, no differences were observed in the ANCA specificity (c-ANCA/PR3 *vs.* p-ANCA/MPO) between patients with or without MR relapse (100% *vs.* 88%, p=0.349). The subgroup analysis showed that patients with MR relapse had higher rate of c-ANCA/PR3 specificity compared to p-ANCA/MPO specificity (68.8% *vs.* 31.2%, p=0.038).

MR relapse group had a higher frequency of skin (p=0.034), renal (p=0.004) and neurological (p=0.024) involvement and a lower frequency of ear, nose and throat (ENT) involvement (p=0.043).

Renal involvement at baseline was observed in 16/17 patients who later developed MR relapses. By contrast, only 1 (5.6%) patient without renal involvement at baseline experienced a MR relapse during the follow up. BVASv3 score was significantly higher in MR relapse group [24.1(6.2) *vs.* 18.1(8.1), p=0.007].

Univariate and multivariable analysis were performed in 94 patients (16 events) who had complete records. The results are reported in Table II.

Univariate analysis showed a significant association between MR relapses and skin, renal and neurological involvement at baseline (sHR 3.1, 95%CI 1.2–8.3, p=0.025; 8.9, 95% CI 1.2–69.0, p=0.036; 2.7, 95% CI 1.1–7.1, p=0.039, respectively). BVASv3 was also associated with MR relapses (sHR 1.1, 95% CI 1.1–1.2, p<0.001). Male sex, ENT involvement and eGFR<60 ml/min were not associated to MR relapse, but they had p<0.10 and were included in the multivariable models (male sex: sHR 2.5 95% CI 0.9–6.6, p=0.061; ENT involvement: sHR 0.4, 95% CI 0.1–1.1, p=0.083 and eGFR<60 ml/min: sHR 2.8, 95% CI 1.0–8.1, p=0.052).

In multivariable analysis, higher risk of MR relapse was in patients with observed renal involvement at baseline (sHR 20.4 95% CI 2.6–158.2, p=0.004) and in those treated without CYC or/and RTX (sHR 4.2, 95% CI 1.5–12.0, p=0.007). C-ANCA/PR3 specificity showed a trend to higher MR relapse risk (sHR 2.5 95% CI 0.9–7.1, p=0.091) (Table II).

In Supplementary Tables S2 and S3 we reported all multivariable models with the model fitness coefficients (AIC/SBC and ΔAIC/ΔSBC *vs.* the best model).

Table II. Baseline predictors of MR relapse. Results of univariate and multivariable (best model) analysis.

Variables	Univariate analysis*		Multivariable analysis*	
	sHR (IC95%)	p	sHR (IC95%)	p
Age	1.0 (0.9-1.0)	0.306	-	-
Sex (male *vs.* female)	2.5 (0.9-6.6)	0.061	-	-
c-ANCA/PR3 specificity	1.5 (0.5-4.2)	0.437	2.5 (0.9-7.1)	0.091
Systemic symptoms	3.9 (0.5-29.5)	0.187	-	-
ENT involvement	0.4 (0.1-1.1)	0.083	-	-
Lung involvement	3.1 (0.8-13.2)	0.114	-	-
Skin involvement	3.1 (1.2-8.3)	0.025	-	-
Eye involvement	0.8 (0.2-3.3)	0.707	-	-
Renal involvement	8.9 (1.2-69.0)	0.036	20.4 (2.6-158.2)	0.004
eGFR<60	2.8 (1.0-8.1)	0.052	-	-
Nerve involvement	2.7 (1.1-7.1)	0.039	-	-
BVASv3	1.1 (1.1-1.2)	<0.001	-	-
Remission induction treatment (others vs CYC/RTX)	1.5 (0.6-4.1)	0.402	4.2 (1.5-12.0)	0.007

*analysis was performed on 94/96 patients.
MR: major renal; sHR: subdistributional hazard ratios; c-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody; PR3: proteinase 3; ENT: ear, nose and throat; eGFR: estimated glomerular filtration rate; BVASv3: Birmingham vasculitis activity score (version 3); CYC/RTX: cyclophosphamide and/or rituximab.

Discussion

The results of our study showed low MR relapse rate in our cohort (about 18%) that was significantly higher in patients with renal involvement at baseline and not treated with CYC and/or RTX. In ANCA-negative patients we did not observe any MR relapses and only one of the 17 patients who experienced MR relapses had no renal involvement at baseline.

Our results indirectly confirm, also in clinical practice setting, that remission-induction IS regimes based on CYC and/or RTX could result in a significantly prolonged remission and lower relapse rate, as previously demonstrated in some RCTs (21, 23).

The significantly higher MR relapse rate in patients with renal involvement at baseline was an interesting finding of our study since few studies have evaluated the organ involvement at the time of diagnosis and during MR relapse

so far. In 1993, some Authors found that the severity of disease manifestations during relapses was similar or greater than at disease onset in limited GPA and they reported the occurrence of new onset renal involvement during disease relapses. By contrast, the frequency of renal involvement during disease relapses in MPA and non-limited GPA was reported to be lower than that observed at baseline (26). However, those data might not reflect the current AAV course since the management of AAV has improved in the meanwhile (27-29). Cartin-Ceba *et al*. reported that subsequent relapses in RTX-treated GPA were similar to the first relapse in terms of severity, but the specific organ involvement observed at disease onset and during relapses was not reported (30). Two studies in the last decade specifically focused on organ involvement at disease onset and during relapses with contrasting results. Chen *et al*. found that up to 70% of relapses occurred in the same organ initially affected (12), while Outh *et al*. observed a consistent frequency of relapses involving new organs (46%) (13). Notably, ANCA specificity identifies AAV subsets with specific organ involvement at baseline (9, 31), thus it is expected that the same organ involvement may occur during relapse, as well.

Our findings are in contrast with the study of Wester Trejo *et al*. who found a significant rate of renal relapses (18%) in patients without any evidence of renal involvement at baseline and did not find any predictors of renal relapse (8). However, the Wester Trejo's study was a pooled analysis of randomised controlled trials which considered patients with clinical features different from those enrolled in our cohort (8).

Although we were unable to confirm previous findings of c-ANCA specificity as an independent predictor of relapse, we found a trend of higher MR relapse rate in c-ANCA PR3 positive patients. The lack of significance may be due to the relative small sample size of our cohort and the low frequency of events.

There are some limitations in our study. First, we restricted our analysis to MR relapses as we deemed this outcome more consistent with the retrospective design of our study. Patients with MR relapse usually entail a fast referral to the vasculitis centre, so they have a low probability of being overlooked or missed. The second limitation of our study is that patients with specific manifestations at baseline such as kidney vasculitis might have been more closely monitored, resulting in a more reliable detection of renal vasculitis recurrence. This bias, however, was minimised by the aforementioned choice of a consistent outcome, and by the monocentric design of our study that ensured a uniform follow-up in our cohort. In our centre we routinely test creatinine and urinalysis at each follow-up visit, irrespective of disease severity or organ involvement at baseline, and remitted patients are visited at least twice a year. Finally, we did not evaluate the role of remission-maintenance treatment with IS and GC at the time of relapses, despite evidence that they could significantly affect AAV course. Some RCTs showed that RTX was superior to AZA and cost-effective in relapse prevention (32-34), while MMF was inferior to AZA (35). GC withdrawal was also associated with a higher risk of AAV relapses (36). Although we did not analyse the role of maintenance therapy, our data seem to be in line with the current evidence. Indeed, during vasculitis recurrence, the majority of patients were on IS treatment, mainly AZA or MMF, but none was on RTX and about half of them were off GC treatment.

Being our study carried out in one of the larger monocentric AAV Italian cohort and spanning over almost 20 years of follow-up, it thus reports long-term data about AAV management in a real-life clinical setting. Therefore, our data are extremely informative for physicians, also keeping into account that RCTs are focused on "selected" patients and thus they could poorly reflect the heterogeneity and complexity of the AAV patients observed in everyday clinical practice. Notably, RCTs on GPA and MPA tend to skew the evidence towards a patients' subset characterised by higher severity and higher rate of renal vasculitis compared with those enrolled in observational cohorts (3).

Conclusion

In our cohort, GPA, MPA and RLV patients with renal involvement at the time of diagnosis had higher risk of MR relapse, while initial treatment regimen based on CYC and/or RTX seems to be protective. However, the absence of renal involvement at disease onset does not completely rule out the occurrence of a MR relapse, especially in ANCA positive patients.

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