CLINICAL COURSE AND OUTCOME PREDICTORS IN PAUCI-IMMUNE ANCA-POSITIVE RENAL-LIMITED VASCULITIS

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SUMMARY – Our aim was to assess the clinical course and outcome of ANCA-positive, pauci-immune renal limited vasculitis, their correlation with laboratory and histopathologic parameters recorded at initial and follow up testing, and to identify the possible outcome predictors. The study included 17 patients with renal biopsy, clinical, serologic and histopathologic parameters meeting the criteria for pauci-immune ANCA-positive glomerulonephritis without extrarenal manifestations of the disease. Creatinine clearance, 24-hour proteinuria and ANCA titer by ELISA method were determined at disease onset, during treatment and at the end of follow up. In 15 patients, the diagnosis was verified by kidney biopsy. Data were processed by Spearman correlation coefficient and Mann-Whitney test, and survival by Kaplan-Meier test. Lower percentage of glomeruli affected with vasculitis, better initial renal function as measured by serum creatinine or creatinine clearance, and lower chronicity on biopsy were identified as favorable indicators of kidney function outcome. Therapy responders had highest initial and lowest final 24-h proteinuria. The highest level of final 24-h proteinuria was recorded in dialysis dependent patients. The cumulative one-year and two-year patient and kidney survival rate was 64% and 50%, and 64% and 38%, respectively.

Key words: *Antibodies, antineutrophil cytoplasmic; Anti-neutrophil cytoplasmic antibody-associated vasculitis; Kidney diseases; Glomerulonephritis*

Introduction

Vasculitis is an inflammation of the vascular wall as an immune response to a number of antigens that are very rarely detected. Based on Chapel-Hill's consensus definition, vasculitides are classified into three groups according to the size of blood vessels involved[1]. Vasculitides with the presence of antineutrophil cytoplasmic antibodies (ANCA) have subsequently been singled out from group 3 vasculitides. This group includes microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome, and a variant of ANCA renal vasculitis, named ANCA-associated vasculitis[2-4]. Renal involvement is frequently observed.

The annual incidence of ANCA-associated vasculitis is 20 *per* million population[2-4]. The prognosis was very poor before the advent of immunosuppressant therapy; 80% of patients died in the first year. With the introduction of immunosuppressants, this fatal disease has turned to a relapsing disease with 60%-80% 5-year patient survival[2-7]. Renal involvement develops with time in 50%-85% of patients[3,8]. The rate of two-year kidney survival is only 64%-75%[9].

Some ANCA-associated vasculitides are exclusively limited to the kidneys. At the time of biopsy, some grade of extracapillary proliferation is seen in more than 50% of these patients. The presence of both acute and chronic glomerular and renal interstitial le-

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sions is quite frequently observed, indicating numerous exacerbations[2,7,9,10].

To our knowledge, there is no literature report on the study of prognostic factors in pauci-immune glomerulonephritis without extrarenal manifestations[7]. The aim of the present study performed in a relatively small group of patients was to assess the clinical course and outcome of ANCA-positive renal vasculitis, and correlation between the disease outcome and initial parameters of this type of vasculitis, including ANCA-antibodies, serum creatinine, creatinine clearance, 24-hour proteinuria and renal biopsy histology, with the same treatment protocol.

Patients and Methods

The study included 17 patients with pauci-immune ANCA-positive renal vasculitis. None of the patients had any extrarenal manifestations. Clinical diagnosis was based on the finding of nephritic urinary sediment and progressing renal failure. The diagnosis was verified by the finding of elevated ANCA titer (negative ANCA finding did not rule the disease out when it was demonstrated on renal biopsy[11]) and renal biopsy. The titer of ANCA antibodies was determined by ELISA at three time points (initially, t_1; during immunosuppressant therapy, t_2; and at the end of follow up, t_3). Serum creatinine and creatinine clearance were also determined at these time points, whereas 24-hour proteinuria was measured immediately before therapy initiation and at the end of follow up. Renal biopsy was performed in 15 of 17 study patients. Patients were divided into three groups according to the percentage of vasculitis-affected glomeruli detected on microscopy: 25%-50%, 50%-75% and >75% of glomeruli involved. Histologic features were used to assess the disease activity (fibrinoid necrosis, cellular and fibrocellular extracapillary and intracapillary proliferates, interstitial edema, cellular infiltration of renal interstitium, and tubular necrosis) and chronicity (glomerular sclerosis, fibrous crescents, Bowman capsule adhesions, interstitial fibrosis and tubular atrophy). Disease activity and chronicity were expressed as mild (+), moderate (++) or pronounced (+++).

All patients except one (dropout from follow up) were treated with prednisolone and cyclophosphamide. They were initially administered methyl-prednisolone as bolus infusion, 15 mg/kg body weight (b.w.) over three days, then oral prednisolone, 1 mg/kg b.w. daily, tapered to 0.4 mg/kg b.w. daily at the end of the first month and to 0.25 mg/kg b.w. daily at the end of the second month of treatment. Cyclophosphamide was administered as intravenous (i.v.) infusion in a single dose of 500 mg/m^2 body surface area every four weeks (n=12), or as a continuous oral dose of 2 mg/kg b.w. daily until remission (n=4). In patients older than 65, the dose was reduced by 20%, and in those with creatinine clearance below 10 mL/min by 50%. Upon remission, the treatment was continued with corticosteroids in a dose of 5 mg/day, in combination with azathioprine or mycophenolate mofetil, or with cyclophosphamide until completion of 12-month period. Plasmapheresis was performed instead of methyl-prednisolone boluses when the patient presented with serum creatinine higher than 500 μmol/L or was dependent on dialysis and without significant chronicity on renal biopsy, expecting better renal survival[12,13]. We had four patients treated with plasmapheresis. None of them recovered renal function (sample too small for statistical analysis). There was no between-group difference in patient survival and rate of severe adverse events.

According to therapeutic response, patients were classified into four groups: group 1, patients that achieved remission (R), i.e. significant improvement of renal function with significant reduction of 24-hour proteinuria and erythrocyturia; group 2, patients with partial remission, i.e. further deterioration of renal function was prevented, however, without its improvement; group 3, patients that failed to respond to therapy (no remission), i.e. initially dialysis dependent patients in which therapy failed to improve their renal function; and group 4, patients with or without disease relapse that developed end-stage renal disease (ESRD). Disease relapse was determined by serum creatinine increase by more than 30% between two consecutive measurements.

Immunosuppressant side effects were classified into five categories: 0, no side effects; 1, mild side effects; 2, moderate side effects; 3, serious side effects; and 4, death due to side effects.

Spearman correlation coefficient was used to determine correlations among selected variables, whereas between-group distribution differences were assessed

Table 1. Patient laboratory data

Variable	n	Mean	±SD	Minimum	Maximum
Serum creatinine$_0$ (μmol/L)	17	349.5	320.2	94.0	1112.0
Serum creatinine$_1$ (μmol/L)	17	513.0	315.6	155.0	1100.0
Serum creatinine$_2$ (μmol/L)	16	406.8	303.6	110.0	1110.0
Creatinine clearance$_0$ (mL/s)	17	0.5	0.4	0.1	1.1
Creatinine clearance$_1$ (mL/s)	16	0.4	0.3	0.1	0.9
Creatinine clearance$_2$ (mL/s)	16	0.5	0.3	0.1	1.0
Proteinuria$_1$ (mg/24 h)	17	2533.2	1893.8	800.0	6926.0
Proteinuria$_2$ (mg/24 h)	16	1406.4	1919.2	227.5	8015.0
MPO-ANCA titer$_1$ (U/mL)	13	68.0	44.9	10.1	158.0
MPO-ANCA titer$_2$ (U/mL)	8	22.6	18.5	4.5	51.0
MPO-ANCA titer$_3$ (U/mL)	11	12.2	10.6	1.1	27.4

$_0$ = initial value; $_1$ = value measured at therapy initiation; $_2$ = value measured at the end of follow up

by Mann-Whitney exact test. As the study population was rather small, statistical analysis was not performed, only tables of contingency were employed. Patient and kidney survival was assessed by Kaplan-Meier test. Statistical significance was set at 1% and 5% (P<0.01 and P<0.05)[14,15].

Results

The study included 17 patients (nine female and eight male) with ANCA-positive renal vasculitis, mean age at study entry 67.10±9.58 years, mean follow up 7.50±8.95 months, and mean duration of prodromal symptoms 6.00±9.58 months as assessed from their history data. The mean serum creatinine level was 350±320 μmol/L at disease onset, 513±316 μmol/L at initiation of immunosuppressant therapy, and 407±304 μmol/L at the end of follow up. The mean daily proteinuria was 2533±1894 mg at therapy introduction and 1406±1919 mg at the end of follow up.

Elevated ANCA antibody titer as determined by ELISA was recorded in 13 (76.47%) patients (MPO-ANCA), with the following mean values recorded at three time points: t_1=68±45 U/L, t_2=23±19 U/L and t_3=12±11 U/L (Table 1).

Renal biopsy was performed in 15 of 17 study patients; 25%-50% glomerular involvement with vasculitis was recorded in three (20%), 50%-75% involvement in five (33.33%) and >75% involvement in seven (46.67%) patients, i.e. almost half of patients undergoing renal biopsy (Table 2).

Disease activity as assessed from renal biopsy histology was mild in six, moderate in five and severe in four patients with renal biopsy. The signs of mild, moderate and serious disease chronicity were recorded in three, four and eight patients, respectively (Table 2).

Five patients treated with corticosteroids and cyclophosphamide died, four of them due to complications of immunosuppressant therapy (most frequently

Table 2. Results of renal biopsy

Variable	n	Percentage
Percentage of affected glomeruli		
25%-50%	3	17.7
51%-75%	5	29.4
>75%	7	41.2
Missing	2	11.8
Activity		
Mild	6	35.3
Moderate	5	29.4
Severe	4	23.5
Missing	2	11.8
Chronicity		
Mild	3	17.7
Moderate	4	23.5
Severe	8	47.1
Missing	2	11.8

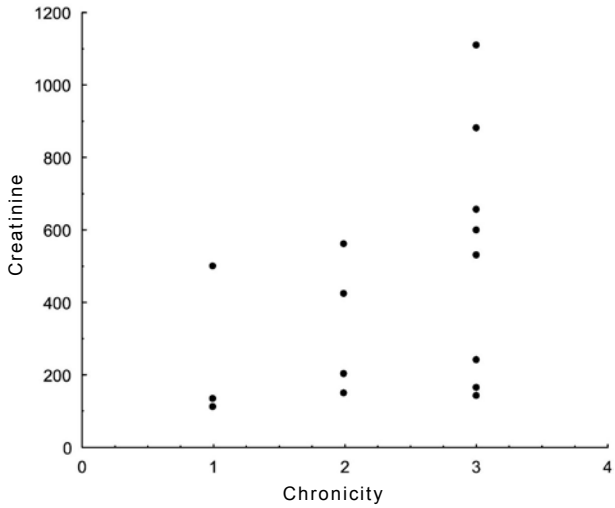

Fig. 1. Correlation between the degree of chronicity on renal biopsy and final values of serum creatinine. Chronicity is expressed semiquantitatively according to degree 1-3. Testing was performed using Spearman coefficient correlation.

from respiratory infection and respiratory failure). Another five patients developed ESRD. Two of these patients were dialysis dependent at study entry and none recovered renal function in spite of treatment. Remission was observed in only three patients and partial remission in four patients. Spearman correlation coefficient showed negative correlation between older age and creatinine clearance at the beginning (R=0.605, *P*=0.012) but not at the end of follow up (Table 3). As expected, these patients received lower doses of cyclophosphamide, ANCA titer showed negative correlation with cyclophosphamide dosage during (R=0.761, *P*=0.027) and at the end (R=0.646, *P*=0.043) of treatment. A positive, statistically significant correlation was found between final ANCA titer and percentage of vasculitis affected glomeruli (R=0.684, *P*=0.029), between initial and final serum creatinine levels (R=0.582, *P*=0.017), and between percentage of vasculitis affected glomeruli and serum creatinine (measured initially and at introduction of immunosuppressant therapy *vs*. end of follow up). Interestingly, the highest correlation was recorded between the percentage of vasculitis affected glomeruli and serum creatinine measured at the end of follow up (R=0.767, *P*=0.001). Negative correlation was found between disease activity and chronicity (R=0.869, *P*=0.00003), and positive correlation between disease chronicity and serum creatinine (Fig. 1).

Analysis of patient subgroups according to outcome (Table 4) showed that there were no significant differences according to age and ANCA titer measured initially or during treatment. Patients with remission had a higher initial ANCA titer; however, the difference did not reach statistical significance. These patients had lowest final ANCA titer; yet, statistically significant difference was only recorded between the subgroups with lethal outcome and dialysis patients.

Table 3. Significance between selected pairs of study variables

Pairs of variables	n	R*	*P*-level
Age : Cr.cl.$_1$ ** (mL/s)	17	–0.494	0.04
Age : Cr.cl.$_2$ ** (mL/s)	16	–0.606	0.01
Age : cyclophosphamide dose	16	–0.541	0.03
Cr.cl.$_1$ (mL/s) : Cr.cl.$_2$	16	0.812	0.0001
Cr.cl.$_1$ (mL/s) : Cr.cl$_3$**	15	0.654	0.01
Cr.cl.$_2$ (mL/s) : Cr.cl.$_3$	15	0.605	0.012
Cr.cl.$_1$ (mL/s) : proteinuria *2*	15	–0.581	0.018
Percentage of affected glom. : ser. creatinine$_1$ (μmol/L)	15	0.532	0.041
Percentage of affected glom. : ser. creatinine$_2$ (μmol/L)	15	0.645	0.009
Percentage of affected glom. : ser. creatinine$_3$ (μmol/L)	15	0.767	0.001
Percentage of affected glom. : MPO-anca titer$_3$	15	0.684	0.029
Activity : chronicity	15	–0.869	0.00003

R* = Spearman rank order correlation test; **Cr.cl. = creatinine clearance (mL/s)

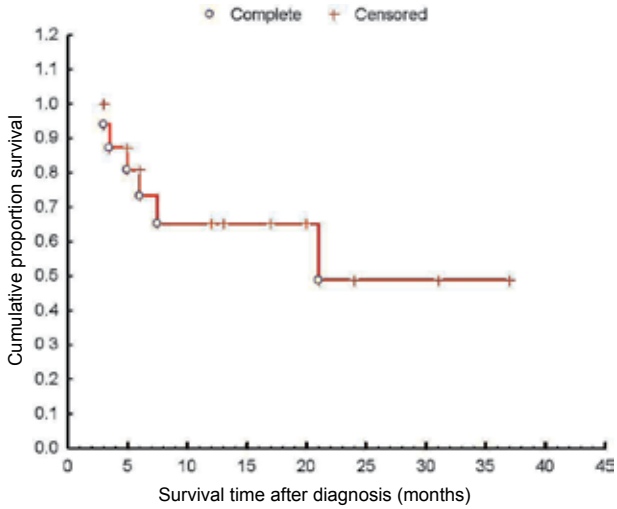

Fig. 2. Kaplan-Meier analysis of patient survival after diagnosis.

Patients with disease remission showed highest initial creatinine clearance in comparison to the deceased and dialysis patients. Final creatinine clearance was significantly higher in patients with remission than in dialysis patients and those with partial remission but not those with lethal outcome. The latter subgroup of patients received the highest dose of cyclophosphamide. Patients with disease remission had highest initial and lowest final daily proteinuria. At the end of follow up, highest proteinuria was measured in dialysis patients.

Three relapses recorded in two patients occurred upon discontinuation of immunosuppressant therapy and were accompanied by an increase in the titer of MPO-ANCA autoantibodies. None of the patients with disease remission had >75% of glomeruli involved with vasculitis and pronounced signs of chronic disease. All dialysis patients showed >50% of glomeruli

Table 4. Outcome analysis according to patient subgroups

Outcome	Death		Responders		Dialysis dependent (non-responders)		Partial responders (CRF)		*P*-level
	(1)		(2)		(3)		(4)		
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	
Age (yrs)	71.60	5.60	65.67	2.52	63.40	12.90	67.25	12.79	
MPO-anca titer$_1$ (U/L)	53.98	38.24	118.10	56.43	78.17	55.07	47.83	27.72	
MPO-anca titer$_2$ (U/L)	20.93	12.24	4.50	0.00	28.35	32.03	28.35	24.25	
MPO-anca titer$_3$ (U/L)	7.43	9.95	2.05	1.20	22.57	2.52	13.20	12.30	$P_{1:3}$=0.100
Cr.cl.$_0$ (mL/s)	0.52	0.26	0.73	0.24	0.34	0.34	0.53	0.54	
Cr.cl.$_1$ (mL/s)	0.27	0.10	0.74	0.21	0.22	0.19	0.50	0.44	$P_{1:2}$=0.057 $P_{2:3}$=0.071
Cr.cl.$_2$ (ml/s)	0.57	0.33	0.96	0.05	0.18	0.18	0.39	0.21	$P_{2:3}$=0.035 $P_{2:4}$=0.057
Proteinuria$_1$ (mg/24 h)	1950.2	1641.9	4897.7	2553.6	2537.8	1613.1	1482.8	295.5	$P_{1:2}$=0.071 $P_{2:4}$=0.057
Proteinuria$_2$ (mg/24 h)	758.0	579.2	484.3	214.5	2910.0	2927.9	866.9	1026.2	$P_{1:3}$=0.063 $P_{2:3}$=0.035
Cyclophosphamide dose (mg/day)	90.33	82.74	32.80	2.83	16.88	10.05	28.75	25.66	$P_{1:3}$=0.063 $P_{2:3}$=0.095
Cyclophosphamide dose (mg/kg/day)	0.48	0.35	0.68	0.54	0.34	0.10	0.38	0.07	

CRF = chronic renal failure; cr.cl. = creatinine clearance

*Table 5. Outcome related to renal biopsy results**

	Death		Responders		Hemodialysis dependent (non-responders)		Partial responders (CRF)	
	n	%	n	%	n	%	n	%
Percentage of affected glomeruli								
25%-50%	1	6.7	2	13.3	0	0.0	0	0.0
50%-75%	1	6.7	1	6.7	1	6.7	2	13.3
>75%	1	6.7	0	0.0	4	26.7	2	13.3
Chronicity								
Mild	1	6.7	2	13.3	0	0.0	0	0.0
Moderate	1	6.7	1	6.7	2	13.3	0	0.0
Severe	1	6.7	0	0.0	3	20.0	4	26.7
Activity								
Mild	1	6.7	0	0.0	3	20.0	2	13.3
Moderate	0	0.0	1	6.7	2	13.3	2	13.3
Severe	2	13.3	2	13.3	0	0.0	0	0.0

*sample size too small for statistical testing; CRF = chronic renal failure

affected with vasculitis, moderate to severe chronic lesions on renal biopsy, and mild to moderate vasculitis activity (Table 5).

One-year and two-year cumulative patient survival rate was 64% and only 50%, respectively (Fig. 2). The respective figures for kidney survival were 64% and only 38% (Fig. 3).

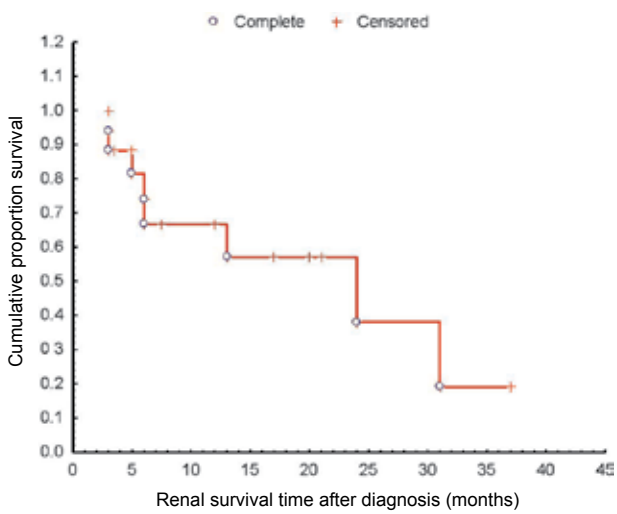

Fig. 3. Kaplan-Meier analysis of renal survival after diagnosis

Discussion

In the present study, an attempt was made to find possible correlations between some parameters of pauci-immune ANCA-positive renal limited vasculitis and origin of the disease in patients treated with the same immunosuppressive protocol. The patient group was small, thus the conclusions should not be considered definitive.

In our study, patients with disease remission initially had highest titer of ANCA autoantibodies, creatinine clearance and 24-h proteinuria. Their renal biopsy specimens showed least pronounced signs of chronicity and most pronounced signs of disease activity, with no case of >75% glomerular vasculitis involvement. Non-responders showed highest percentage of glomerular vasculitis involvement with moderate to severe chronicity, without signs of severe disease activity.

A number of studies investigated clinical[16,17], serologic[8,9] and histopathologic parameters[10,16-19] as prognostic indicators of patient and kidney survival in ANCA-associated vasculitis (but as part of clinical syndrome like polyangiitis and Wegener's granulomatosis). In ANCA-positive systemic vasculitis, pulmonary hemorrhage[4,17], advanced age[3,6,8,17,20], rate of renal

disease relapses[3,9,11,20], elevated initial serum creatinine level[4,6,11,17,21] and infections as a consequence of immunosuppressive therapy[6,8,9] were found to be most important indicators of patient survival. The higher the initial serum creatinine, the higher was the risk of ESRD development[3,4,6-9,21]. The chronic nature of lesions was another unfavorable predictor of poor renal function outcome[6,18,19]. The percentage of glomeruli not affected with vasculitis was the major histopathologic predictor of favorable outcome[18,19,21,22].

In our study, chronicity and elevated initial serum creatinine were also found to predict unfavorable renal outcome, whereas no such role was observed for disease activity. None of the patients with active lesions detected in kidney biopsy specimens achieved remission, and none of those with pronounced chronicity achieved complete remission.

In some studies, disease activity was a predictor of favorable outcome, supporting the hypothesis that vasculitis can be at least in part reversible if timely diagnosed and treated[11,21,23]. Other studies, however, did not confirm this concept[17,22]. Maybe there is a critical point in lesion progression when recovery is not possible anymore, and which can only lead to chronic irreversible changes[17,22,23]. It should be noted that in our study patients with remission had higher initial and significantly lower final proteinuria as compared to patients with partial remission and those with lethal outcome. At the end of follow up, patients with remission also had significantly lower proteinuria than dialysis patients. Franssen *et al.*[24] demonstrated that proteinuria in MPO-ANCA positive patients was an unfavorable marker of renal function. Neumann *et al.*[25] found positive correlation between proteinuria at diagnosis and chronicity on repeated kidney biopsy, both being significant unfavorable indicators of late renal function. Our dialysis patients showed higher proteinuria at the end of follow up than those with remission, which may have been due to discontinuation of immunosuppressive therapy.

ANCA-positive, mostly MPO-ANCA positive, pauci-immune glomerulonephritis of microscopic polyangiitis and renal vasculitis may frequently progress to ESRD, even without relapse[7,18,24]. These variations may be of paramount importance for the choice of cyclophosphamide therapy. Pulsed dosage is preferred in the management of renal limited vasculitis, and continuous therapy for Wegener's granulomatosis[25]. Cohen *et al.*[20] report on 22 patients with renal vasculitis included in their study group to have had higher initial serum creatinine levels than other patients.

The proportion of seronegative patients was comparable to the results described by other authors, ranging from 7% to 23%. Mortality rate was quite high in our patients, which was attributable to the complications of immunosuppressive therapy, infections in particular, as also emphasized elsewhere[2,4,6,7]. In addition, there were a high proportion of dialysis patients, probably due to chronic renal lesions that had failed to be recognized on time because of their scanty clinical picture, thus only relying on pathologic urine finding[10].

In conclusion, based on our own results and literature data, we are inclined to describe pauci-immune ANCA-positive renal vasculitis as a rare disease presenting with a clinical picture of rapidly progressing glomerulonephritis; however, it may frequently progress slowly, with gradual aggravation of renal function. The symptomatology is scanty, thus the diagnosis is late, and histopathologic signs of chronicity on kidney biopsy are more common than the signs of disease activity. The course of the disease is by no means benign. It is a disease of advanced age and mortality rate is high due to immunosuppressive therapy.

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Sažetak

KLINIČKI TIJEK I POKAZATELJI ISHODA ANCA-POZITIVNOG PAUCI-IMUNOG NA BUBREGE OGRANIČENOG VASKULITISA

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Cilj rada bio je procijeniti klinički tijek i ishod ANCA-pozitivnog pauci-imunog na bubrege ograničenog vaskulitisa, njihovu korelaciju s laboratorijskim i histopatološkim parametrima zabilježenim na početku praćenja te tijekom liječenja, kako bi se utvrdili mogući pokazatelji ishoda tijeka bolesti. U ispitivanje je bilo uključeno 17 bolesnika s biopsijskim, kliničkim i histopatološkim parametrima, koji su ispunjavali kriterije za dijagnozu pauci-imunog ANCA-pozitivnog glomerulonefritisa bez izvanbubrežnih manifestacija bolesti. Na početku praćenja, tijekom liječenja te na kraju razdoblja praćenja određivali su se klirens kreatinina (mL/s), 24-satna proteinurija, a u 15 bolesnika učinjena je biopsija bubrega. Podaci su obrađeni Spearmanovim koeficijentom korelacije, Mann-Whitneyjevim testom, a preživljavanje Kaplan-Meireovim testom. Manji postotak zahvaćenosti glomerula, bolja početna bubrežna funkcija mjerena serumskim kreatininom ili klirensom kreatinina te slabije izražen kronicitet na biopsiji bili su pokazatelji povoljnog ishoda bubrežne funkcije. Bolesnici koji su dobro odgovorili na terapiju imali su najvišu početnu i najnižu završnu 24-satnu proteinuriju. Najviša završna 24-satna proteinurija zabilježena je u bolesnika ovisnih o dijalizi. Kumulativno jednogogodišnje i dvogodišnje preživljavanje bolesnika je bilo 64% i 50%, a bubrega 64% i 38%.

Ključne riječi: *Antitijela, antineutrofilna citoplazmatska; ANCA-pozitivni vaskulitis; Bubrežne bolesti; Glomerulonefritis*