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CLINICAL CHARACTERISTICS AND PROGNOSTIC FACTORS IN AN ARGENTINIAN COHORT WITH ANCA-ASSOCIATED VASCULITIS

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Abstract ANCA-associated vasculitis is a heterogeneous group of rare autoimmune conditions of unknown cause. Clinical characteristics and prognostic factors were analyzed in 47 patients: 20 (42.5%) with granulomatosis with polyangiitis, 17 (36.2%) with microscopic polyangiitis, 6 (12.8%) with renal-limited vasculitis, and 4 (8.5%) with eosinophilic granulomatosis with polyangiitis. Mean age at diagnosis was 53.5 ± 16.5 years and the median of BVAS (Birmingham Vasculitis Activity Score) was 14 (4-42). The most frequent clinical manifestations were: general in 44 (93.6%), renal in 30 (63.8%) and respiratory in 28 (59.6%). All received corticosteroids at the beginning of treatment. Intravenous cyclophosphamide was associated in 20 (42.5%) and oral route in 14 (29.8%); azathioprine in 3 (6.4%) and rituximab in 2 (4.2%). At a median follow-up of 35.5 months (range 0.14-234), 21 relapses were recorded in 14 patients. Overall mortality was 3.5 deaths per 100 patient-year in the whole group. Those over 55 years old, the presence of alveolar hemorrhage, those with FFS (Five Factor Score) of 2, and patients with MPA had poor prognosis. Renal involvement, ANCA pattern and BVAS were not associated to a poorer prognosis.

Key words: ANCA associated vasculitis, systemic vasculitis, microscopic polyangiitis

Resumen ***Características clínicas y factores pronósticos en una cohorte argentina de vasculitis asociada a ANCA.*** Las vasculitis asociadas a ANCA son un grupo heterogéneo de entidades autoinmunes, poco frecuentes, de etiología desconocida. Analizamos las características clínicas y factores pronóstico en 47 pacientes: 20 (42.5%) granulomatosis con poliangeítis, 17 (36.2%) poliangeítis microscópica, 6 (12.8%) vasculitis limitada al riñón y 4 (8.5%) granulomatosis eosinofílica con poliangeítis. La edad promedio al diagnóstico fue 53.5 ± 16.5 años y la mediana de BVAS (*Birmingham Vasculitis Activity Score*) 14 (4-42). Las manifestaciones clínicas más frecuentes fueron: generales en 44 (93.6%), renales 30 (63.8%) y respiratorias en 28 (59.6%). Todos recibieron corticoides al inicio del tratamiento. Se asoció ciclofosfamida endovenosa en 20 (42.5%) y oral en 14 (29.8%); azatioprina en 3 (6.4%) y rituximab en 2 (4.2%). En una mediana de seguimiento de 35.5 meses (rango 0.14-234), se registraron 21 recaídas en 14 pacientes. La mortalidad fue 3.5 por cien pacientes-año en todo el grupo. Los mayores de 55 años, con presencia de hemorragia alveolar, FFS (*Five Factor Score*) de 2, y los casos con poliangeítis microscópica tuvieron peor pronóstico. El compromiso renal, el patrón de ANCA y el BVAS no se asociaron a peor pronóstico.

Palabras clave: vasculitis asociadas a ANCA, vasculitis sistémicas, poliangeítis microscópica

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KEY POINTS

- ANCA-associated vasculitis affects small to medium-sized vessels
- They can be associated with irreversible damage to the organ function or even the death of the patient
- The generalized and severe clinical forms were the most frequent
- Survival rate was lower in patients with microscopic polyangiitis, Five Factor Score of 2, age ≥ 55 years old and alveolar hemorrhage

Anti-neutrophil cytoplasmic antibodies (ANCA) were first described in 1982 in a patient with pauci-immune glomerulonephritis[1]. ANCA-associated vasculitides encompass four entities: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome), microscopic polyangiitis (MPA) and renal-limited vasculitis (RLV)[2]. In Argentina, Pierini estimated the incidence rate of GPA and MPA at 9 and 14 cases per million person-year, respectively, and the prevalence rate at 7.4 and 5.2 cases/100,000 people, respectively[3].

GPA often involves upper and lower respiratory tract and biopsy samples typically show the presence of granulomas. Often MPA occurs as pulmonary capillaritis associated with renal involvement, with no granulomas on biopsy. Asthma is the principal clinical feature of EGPA. Eosinophilia and vasculitis manifestations appear later; the histology reveals granulomas with plenty of eosinophils. Although all forms of vasculitides may appear as rapidly progressive glomerulonephritis, the characteristic of RLV is that clinical manifestations are limited to the kidneys with no other organ involvement. The pathological findings are indistinguishable from those in the other entities[4].

Treatment options depend on the severity of clinical manifestations. In general, treatment includes two phases: remission induction and maintenance. Despite the fact that significant progress has been made in both phases during the last decades, the relapse rates and the toxicity associated with treatment remain high[5, 6].

The factors associated with prognosis include, among others, older age, a higher initial BVAS (Birmingham Vasculitis Activity Score) or FFS (Five Factor Score), MPO-ANCA positivity, renal involvement and a high VDI (Vasculitis Damage Index)[7-10].

The aim of the present study was to describe the clinical features, as well as the prognostic factors, of the patients with ANCA-associated vasculitides treated in a university hospital in Buenos Aires during the last 35 years.

Materials and methods

A descriptive study by reviewing the medical records of patients with ANCA-associated vasculitis who had their first symptoms between July 1984 and March 2019 was carried out. The study included patients over 18 years old who met the American College of Rheumatology (ACR) classification criteria for GPA or EGPA, or the GPA, EGPA or MPA definitions according to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature[4, 11, 12]. It was considered that a diagnosis of pauci-immune glomerulonephritis confirmed by renal biopsy in an ANCA-positive patient with no clinical manifestations other than renal involvement was consistent with RLV. The protocol was approved by the Ethics Committee of the Institution and was conducted in accordance with the guidelines set by Act 3301/09 of the Ministry of Health of the Government of the City of Buenos Aires and those of the Helsinki Declaration.

Our Institute has had indirect immunofluorescence (IIF) for ANCA detection since 1992 and enzyme immunoanalysis technique (ELISA) since 1996. At least one determination of these antibodies using anyone of these methods was recorded for each of the patients included in the study. Two patterns were identified by IIF: cytoplasmic (c-ANCA) and perinuclear (p-ANCA), which were considered to correspond to autoantibodies against Myeloperoxidase (MPO) and Proteinase 3 (PR3) antigen respectively, according to ELISA.

Demographic data were collected, as well as clinical manifestations at diagnosis, the complementary studies performed and the treatments received during the course of the disease. Diagnosis delay was defined as the time to diagnosis after the onset of vasculitis-related symptoms. Pulmonary-Renal Syndrome (PRS) was defined by the occurrence of renal and respiratory failure as a manifestation of rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage. Anemia was defined as hemoglobin in blood < 12 g/dl and < 13 g/dl in men and women, respectively[13]. BVAS was calculated at diagnosis, after treatment and at every relapse, and 2009 FFS was calculated at diagnosis[5, 14].

EULAR (*European League Against Rheumatism)* recommendations for conducting clinical studies in systemic vasculitides were used to assess the stages of the disease, the response to treatment and relapses. Localized forms were defined as the upper and/or lower respiratory tract involvement, with no systemic involvement. Early systemic forms were defined as systemic involvement with no threat either to the function of the organ or to the patient's life. Generalized forms of vasculitis were described as involving kidneys or other organs as well as their functions, with creatinine in blood lower than 5.6 mg/dl. Severe forms were defined as those including renal or another organ involvement, with creatinine higher than 5.6 mg/dl. Progressive refractory forms were defined as those that do not respond to corticosteroid or cyclophosphamide treatments[15]. To assess the effects of treatment, remission was defined as the absence of active disease (BVAS = 0) for at least 3 months with doses of prednisone or equivalent ≤ 7.5 mg/day, whether or not associated with a steroid sparing agent (methotrexate, azathioprine or mycophenolate). Response to treatment is defined as a reduction in BVAS ≥ 50%. Refractory forms were considered to include at least one of the following: 1) greater activity measured by BVAS with or without change in treatment after 4 weeks with cyclophosphamide and corticosteroids; 2) lack of response with <50% reduction in disease activity score (BVAS) and/or lack of improvement of at least one major item after 4-6 weeks' treatment; (3) chronic persistent disease, defined as the presence of at least one major item or three minor items on BVAS in spite of 8 weeks' treatment. Persisting minor symptoms that responded to a modest increase in the medication and did not require a further escalation of treatment were recorded as low activity disease[14]. The re-occurrence of disease activity attributable to active inflammation was considered a relapse. A major relapse

was defined as the re-occurrence of organ- or life-threatening disease activity that could not be treated with an increase of corticosteroids alone and required further escalation of treatment. All other relapses were classified as minor relapses.

The results are expressed as percentages for categorical variables and as mean ± standard deviation or median (range) for numerical variables. To compare groups defined by prognosis scores and disease activity, Chi-square test or Fisher test were used for proportions and one-way ANOVA or Kruskal-Wallis test for numerical variables.

Survival analysis was performed using Kaplan-Meier method. Follow-up time was computed in years between diagnoses and death or until the last clinical evaluation available in the medical records. Cox proportional analysis was used to evaluate factors associated with mortality. A p value below 0.05 was considered statistically significant.

Results

Forty-seven patients with ANCA-associated vasculitides were included in the analysis, 28 women (59.6%) and 19 men. Mean age at diagnosis: 53.5 ± 16.5 years. Twenty patients were diagnosed with GPA (42.5%), 17 with MPA (36.2%), 6 with RLV (12.8%) and 4 with EGPA (8.5%). Median diagnosis delay was 2.46 (range = 0-411) months and 70.2% of the patients were diagnosed less than 6 months after the onset of the symptoms. Table 1 and Table 2 show demographic, epidemiological characteristics and clinical manifestations at diagnosis. In 11 patients, the initial presentation was as Pulmonary-Renal Syndrome (PRS).

All patients started treatment with corticosteroids (1 mg/kg/day of prednisone or equivalent). Severe cases (28 patients, 59.6%) were initially treated with a pulse therapy of methilprednisolone (0.5-1g/pulse/day) for 1-3 days. Another immunosuppressant, including cyclophosphamide (CYC), was added in 39 (83%) patients (Table 3). The median of the duration of the treatment with oral CYC was 13 months (range 3.8-66.5). The median of number of intravenous (IV) CYC pulses was 6 (range 1-16). Seven patients were later switched to azathioprine (AZA) and 2 to mycophenolic acid. Rituximab (RTX) was used in 2 cases and one of them was treated later with AZA for maintenance. Six patients were treated with plasmapheresis and 12 needed dialysis (4 on a temporary basis).

The outcome results after not less than 3 months from the onset of the initial treatment could be recovered in 42 patients (Fig. 1).

In a median follow-up period of 35.5 months (range 0.14-234) there were 21 relapses in 14 patients (6 with

TABLE 1.– *Demographic and epidemiological characteristics at diagnosis*

Characteristics	Total (n = 47)	GPA (n = 20)	MPA (n = 17)	EGPA (n = 4)	RLV (n = 6)
Gender (female/male)	28/19	9/11	12/5	2/2	5/1
Age, years (mean ± SD)	53.5 ± 16.5	52.1 ± 16	58.1 ± 18.8	51 ± 10.2	46.6 ± 14.8
Diagnosis delay, months	2.46 (0-411)	5.5 (0-150)	1.7 (0-28.3)	19.5 (1.25-411)	1.07 (0.4-2.46)
Median (range)					
BVAS	14 (4-42)	14.5 (4-42)	14 (6-24)	6 (6-11)	12 (12-12)
Median (range)					
FIVE FACTOR SCORE					
FFS = 0	11 (23.4)	6	2	2	1
FFS = 1	19 (40.4)	5	9	2	3
FFS = 2	17 (36.2)	9	6	0	2
ANCA n (%)					
ANCA negative	4 (8.6)	2	1	1	0
ANCA c-PR3	20 (42.5)	15	0	3	2
ANCA p-MPO	23 (48.9)	3	16	0	4
Clinical subgroup					
Localized	5	4	0	1	0
Early systemic	4	2	2	0	0
Generalized	18	8	7	2	1
Severe	17	5	6	1	5
Progressive refractory	3	1	2	0	0

BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; FFS: five factor score; GPA: granulomatosis with polyangiitis; MPA microscopic polyangiitis; n: number of cases; RLV: renal-limited vasculitis; SD: standard deviation

TABLE 2.– *Clinical manifestations at diagnosis*

Clinical manifestations n (%)	Total (n = 47)	GPA (n = 20)	MPA (n = 17)	EGPA (n = 4)	RLV (n = 6)
General	44 (93.6)	18	17	4	5
Anemia	33 (70.2)	11	16	2	4
Fever	18 (38.3)	12	3	2	1
Weight loss	15 (31.9)	7	6	0	2
Arthralgia/arthritis	10 (21.3)	7	1	2	0
Renal	30 (63.8)	11	13	0	6
Deterioration of renal function (measured by creatinine)	26 (55.3)	9	13	0	4
Renal involvement confirmed by biopsy	18 (38.3)	6	6	0	6
Edemas	10 (21.3)	4	3	0	3
Respiratory system	28 (59.6)	15	9	4	0
Alveolar hemorrhage	14 (29.8)	5	9	0	0
Pulmonary infiltrates	10 (21.3)	5	4	1	0
Pulmonary nodules/cavities	9 (19.1)	7	2	0	0
Asthma onset at adult age	4 (8.5)	0	0	4	0
Endobronchial involvement	2 (4.3)	2	0	0	0
Cutaneous-mucus	15 (31.9)	9	5	1	0
Palpable purpura	12 (25.5)	7	4	1	0
Oral/nasal ulcers	4 (8.5)	4	0	0	0
Erythema nodosum	2 (4.3)	1	1	0	0
Skin ulcers/gangrene	2 (4.3)	2	0	0	0
Ocular and upper airways	11 (23.4)	8	1	2	0
Bloody/ mucous purulent nasal discharge	6 (12.8)	5	1	0	0
Rhinosinusitis	6 (12.8)	4	0	2	0
Conjunctivitis/keratitis	2 (4.3)	2	0	0	0
Nasal crusts	2 (4.3)	2	0	0	0
Conductive hearing loss	1 (2.1)	1	0	0	0
Subglottic stenosis	1 (2.1)	1	0	0	0
Nervous system	12 (25.5)	7	4	1	0
Mononeuritis multiplex	6 (12.8)	4	1	1	0
Sensory neuropathy	6 (12.8)	3	3	0	0
Meningitis	2 (4.3)	2	0	0	0
Stroke	1 (2.1)	1	0	0	0

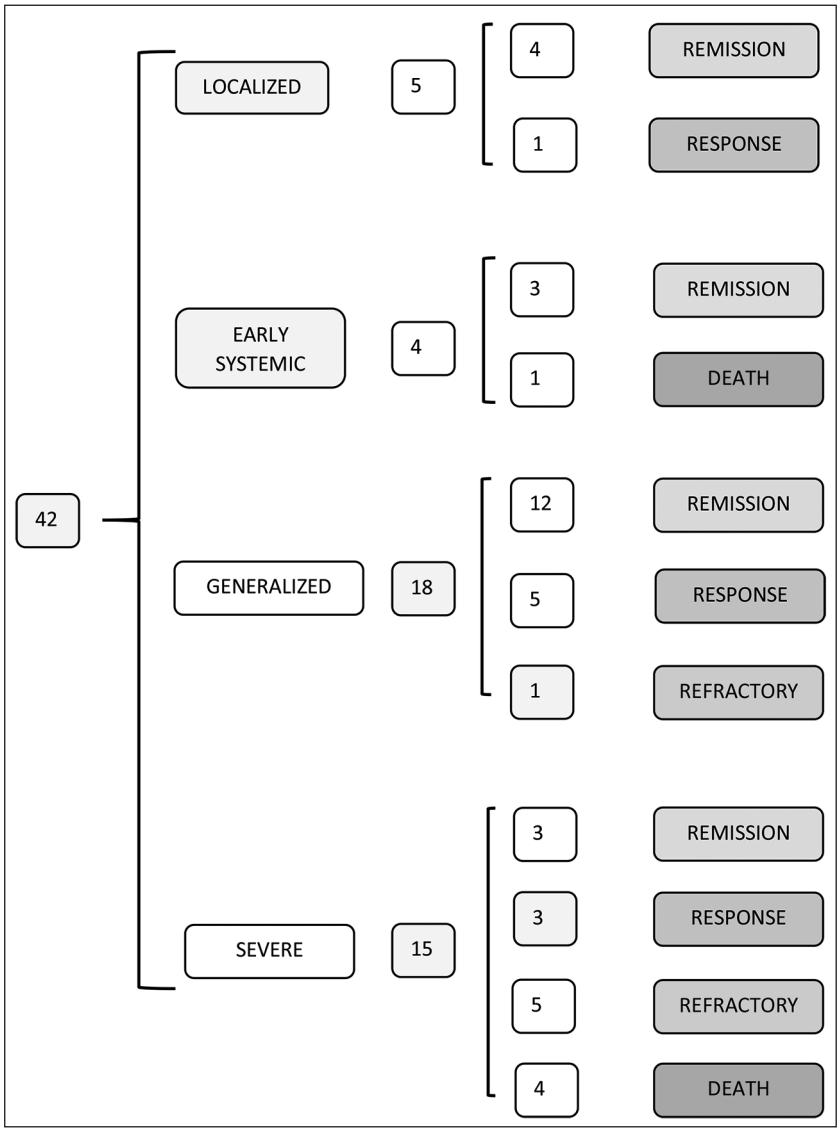
EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; n: number of cases; RLV: renal-limited vasculitis

TABLE 3.– *Initial treatment*

Initial treatment n (%)	Total (n = 47)	GPA (n = 20)	MPA (n = 17)	EGPA (n = 4)	RLV (n = 6)
Oral CYC (1-2 mg/kg/day)	14 (29.8)	10	4	0	0
IV CYC (0.5-0.7 g/m^2 body-surface area/pulse)	20 (42.5)	4	9	1	6
GCS without any other IS (1 mg/kg/day)	8 (17)	2	3	3	0
AZA (2 mg/kg/day)	3 (6.4)	2	1	0	0
RTX (1 g/doses x 2 doses)	2 (4.2)	2	0	0	0

AZA: azathioprine; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; GCS glucocorticoids; GPA: granulomatosis with polyangiitis; IS: immunosuppressant; IV: intravenous; MPA: microscopic polyangiitis; n: number of cases; RLV: renal-limited vasculitis; RTX: rituximab

Fig. 1.– Outcome after the initial treatment in 42 patients



MPA, 6 with GPA, 2 with EGPA). Table 4 shows data for the patients who had a relapse and Table 5 for those with multiple relapses and refractory vasculitis.

After diagnosis, 32 infection episodes which required hospitalization were recorded for 16 patients: pneumonia (11), sepsis (11), infections by opportunistic pathogens (6, which included 3 by fungi, 2 by herpes zoster and 1 by *Clostridium difficile*), pyelonephritis (3) and dacryocystitis (1). Three patients had neoplasia (2, skin and 1, colon). There were 15 cardiovascular events in 10 patients: heart failure (6), venous thromboses (4), acute myocardial infarction (2), hypertension urgency (1), dilated cardiomyopathy (1) and atrial fibrillation (1).

Nine patients died (4: GPA and 5: MPA), the causes of death were disease activity (5), infection (2) and cardiovascular (2). Of 11 patients who had PRS, 4 died within 16 weeks from diagnosis. Overall mortality was 3.5 deaths per 100 patient-year and was almost the same in subgroups defined by gender and BVAS at diagnosis. Out of 11 patients who had PRS, 4 died within 16 weeks. There were statistically significant differences comparing patients under 55 years old and ≥ 55 years old ($p = 0.029$) and between those who had had alveolar hemorrhage and those who had not ($p = 0.011$). Figure 2 shows survival curves. Survival was lower for patients with MPA ($p = 0.074$) and in patients with an FFS of 2 compared to 1 ($p = 0.07$), but the differences did not have statistical significance.

Discussion

ANCA-associated vasculitides are a heterogeneous group of rare autoimmune conditions, of unknown cause, that

TABLE 4.– *Patients experiencing one relapse*

Type	P	Gender/ Age	Form (EUVAS)	Clinical presentation at diagnosis*	Initial Tx**	Duration of Tx (months)	Result of Tx	Time to relapse (months)	Type of relapse	Clinical manifestation at relapse*	BVAS	Tx**	Result of Tx
MPA	1	F/62	G	Cutaneous	Oral CYC	10.1	REM	169	Major	Renal	15	IV CYC	NA
	2	F/80	G	Renal, Neurological	IV CYC	18	REM	28	Major	Cutaneous Renal	2	IV CYC	NA
	3	F/68	G	Neurological	IV CYC+MMF	19	REM	21	Major	Renal	12	IV CYC + PE + AZA	RES
GPA	4	F/45	L	UAW	Oral CYC	20.2	REM	10	Major	UAW	3	Oral CYC + AZA	REM
	5	M/73	G	Cutaneous, Renal, Respiratory Neurological	GCS (alone)	6	RES	1	Major	Respiratory, Renal	12	IV CYC	RES
	6	F/43	G	UAW, Cutaneous, Renal	Oral CYC	3.8	RES	6	Minor	Ocular, UAW, Renal	22	Oral CYC	REM
EGPA	7	M/51	S	UAW, Cutaneous, Respiratory, Renal	GCS (alone)	36	RES	76	Major	UAW, Respiratory, Renal	7	Oral CYC	NA
	8	F/63	L	Respiratory (alone)	GCS	3	RES	2	Minor	General (alone)	2	AZA	REM

AZA: azathioprine; CT: short time follow-up for evaluation of results; CYC: cyclophosphamide; EGPA: eosinophilic granulomatosis with polyangiitis; EUVAS: European League Against Rheumatism; F: female; G: generalized; GCS: glucocorticoids; GPA: granulomatosis with polyangiitis; IV: intravenous; L: localized; M: male; MMF: mycophenolate mofetil; MPA: microscopic polyangiitis; NA: not available; P: patient; PE: plasmapheresis; REM: remission; RES: response; S: severe; Tx: treatment; UAW: upper airway

**They all had general associated manifestations*

***They all received corticosteroids*

affect small to medium-sized blood vessels. They may involve many organs, including the upper airway, lung and kidney. Their incidence increases with age and they are more common in people of 60 years or older[16, 17]. Our study evidenced a predominance of women, greater in MPA, according with findings by Cisternas, Paolini and Di Benedetto[18-20] for the same continent and Schirmer JH et al[24] in Germany. Although some studies described a similar sex distribution or a slight predominance in men[17]. Table 6 shows a comparison of the data of this study with those reported for other South American and European cohorts. All described a median age at diagnosis higher in MPA than in GPA[18-21].

Delayed diagnosis of vasculitis may lead to irreversible damage to the organ function or even to death. There is great disparity among the different series[17, 19, 21, 22]. In this study, 70.2% of the patients were diagnosed less 6 months after the onset of the symptoms. This could be accounted for by the fact that this is a third-level complexity center with experience in rare pathologies and the availability to perform biopsies and determine specific antibodies.

In GPA, upper airway involvement is often more frequent than pulmonary involvement; it may appear as frequent nasal discharge, crusts, rhinosinusitis or even potential structural damage such as “saddle” nose deformity and subglottic stenosis. In one of the largest GPA series, with 158 patients, Hoffman et al reported upper (73%) and lower (45%) airway involvement at diagnosis[25]. In Argentina, Paolini showed greater pulmonary involvement at diagnosis (see table)[19]. Orden showed in 37 patients with GPA, after 6.2 years’ follow-up, that 48.6% had upper airway involvement and 81.1% had lower airway involvement[26]. In this study, we had similar results to those reported by these authors, with a predominance of lower airway involvement.

TABLE 5.– *Patients with multiple relapses and patients with progressive refractory disease*

Type	P	Gender/ Age	Forms (EUVAS)	N° of relapses	Clinical presentation at diagnosis*	Initial Tx**	Clinical manifestation at follow-up*	Subsequent treatments**	Last visit
MPA	1	F/28	S	3	Respiratory, Renal	GCS (alone)	UAW, Respiratory, Renal	IV CYC/ AZA	CKD, permanent dialysis
	2	F/54	PR	PR	Cutaneous, Respiratory, Renal	IV CYC	Cutaneous Respiratory, Renal	Oral CYC / IV CYC	CKD, permanent dialysis
	3	F/44	PR	PR	Cutaneous, Renal	Oral CYC	Renal, Neurological	Oral CYC	Response under treatment
GPA	4	M/41	G	2	Cutaneous, respiratory	Oral CYC	UAW, Renal, cutaneous	Oral CYC	Death
	5	M/42	PR	PR	Cutaneous, Respiratory	Oral CYC	Cutaneous, Respiratory, Renal	PE + oral CYC	Death
	6	M/54	G	2	UAW, Cutaneous, Respiratory, Neurological	Oral CYC + AZA	Ocular, UAW, Renal	MTX/oral CYC / AZA	Remission, without treatment

AZA: azathioprine; CKD: chronic kidney disease; CYC: cyclophosphamide; F: female; G: generalized; GCS: glucocorticoids; GPA: granulomatosis with polyangiitis; IV: intravenous; M: male; MPA: microscopic polyangiitis; MTX: methotrexate; P: patient; PE: plasmapheresis; PR: progressive refractory; S: severe; UAW: upper airway

*They all had general associated manifestations

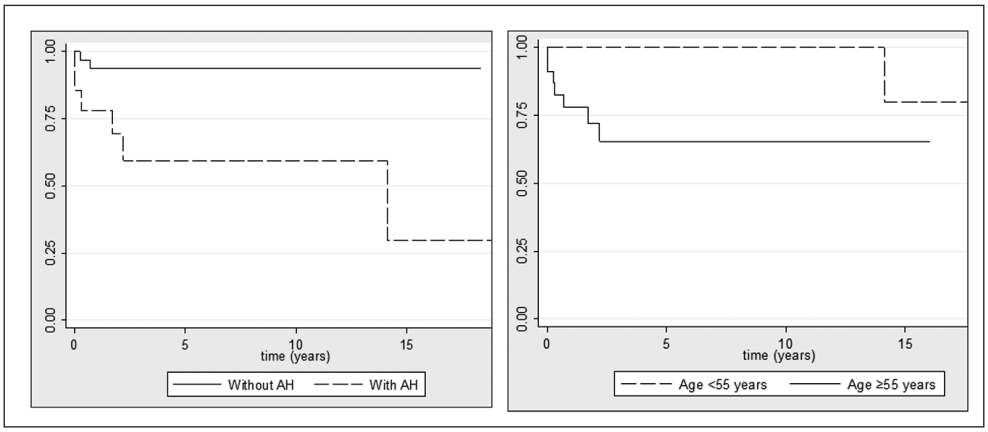
**They all received corticosteroids.

TABLE 6.– *Comparison with other cohorts*

	Cisternas MM. et al (Chile) 2005[18]		Solans-Laqué R et al. (Spain) 2017[21]		Paolini MV et al. (Argentina) 2013[19]		Keller R et al. (Germany) 2000[23]	Schirmer JH et al. (Germany) 2015[24]	This study	
Type of vasculitis	GPA	MPA	GPA	MPA	GPA	MPA	GPA	MPA	GPA	MPA
Female/male, n	33/25	44/21	90/9	83/84	11/12	12/3	79/76	79/65	9/11	12/5
Age at diagnosis	50.8	58.7	49.9	63.8	51.4	54.6	48	59.3	52.1	58.1
Follow-up time *Months*	20	15	82	82	30.4	41.2	84	72	35.5	35.5
Organ system involvement at diagnosis (%)										
• Renal	78	68	56	86.2	65	93	53.5	79.2	55	76.5
• Pulmonary	62	28	62.5	42.5	48	40	54.8	50	70	58.8
• Ear/Nose/Throat	85	NR	72.3	10.2	39	13	93.5	2.1	35	5.8
• PNS	17	59	22.3	28	4	13	20.6	38.9	35	23.5
• Cutaneous	NR	32	25	16.8	9	7	23.2	16.7	40	29.4
Mortality (%)	23	21	22.3	44.3	27	13.3	14	17.4	20	29.4

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; n: number of patients; NR: not reported; PNS: peripheral nervous system

Fig. 2.– Long-term survival. Kaplan-Meier curves. In: a) based on the presence or absence of alveolar hemorrhage; b) based on age (< 55 years and ≥ 55 years)



FFS: five factor score; AH: alveolar hemorrhage

In MPA, clinical presentation generally includes less frequent involvement of upper airway and more severe renal involvement sometimes due to late diagnosis, also accompanied by greater renal damage and poor therapeutic response[29]. In this study, diagnosis delay was similar in patients with MPA and patients with other entities, but MPA was associated with poorer prognosis, possibly related to older age at diagnosis and higher frequency of alveolar hemorrhage and renal involvement.

Pulmonary-Renal Syndrome (PRS), described by Goodpasture in 1919, may result in a life-threatening condition for patients and requires immediate immunosuppressive therapy[27]. It is characterized by crescentic glomerulonephritis and pulmonary capillaritis at pathological anatomy. The most frequent causes of this syndrome are associated with ANCA vasculitides[28]. In this series, out of 11 patients who had PRS, 4 died within 16 weeks from diagnosis and the presence of AH was associated with poor prognosis.

With respect to ANCA antibodies, patients with GPA are usually c-ANCA positive, especially in the generalized and active forms of the disease, while p-ANCA positivity is more frequent in MPA and LRV. Up to 40% of the patients with EGPA are ANCA positive, predominantly p-ANCA[30, 31]. In the present study, the proportions of ANCA positivity in GPA, MPA and LRV were similar to those studies, but patients with EGPA were mostly c-ANCA positive.

The treatment of ANCA-associated vasculitides has changed over time, always with the purpose of achieving remission with the least possible toxicity. So, the high doses of cyclophosphamide reported by Fauci and Wolff in 1973 and 1974, respectively, were switched to an induction phase with IV CYC pulses followed by a maintenance phase with less-toxic drugs[32-34]. Nowadays, rituximab appears as a new alternative in selected cases. This study covers a 35-year period and is representative of this treatment trend. During the first years covered by this study, most patients were treated with CYC during long periods of time, without maintenance treatment with another safer medication. Later, in an attempt to reduce toxicity, there was a switch to intermittent pulse intravenous CYC and maintenance therapy with methotrexate, azathioprine or mycophenolate

In 2011, Flossmann et al. reported on the long-term follow-up of the most important clinical trials in ANCA-associated vasculitides. According to their findings, advanced age, glomerular filtration rate below 15 ml/min, high BVAS and low levels of hemoglobin at diagnosis were higher mortality predictors[35].On the other hand, in a long-term follow-up of patients diagnosed with GPA and MPA enrolled in the WEGENT study, advancing age was the only factor significantly associated with the risk of death; each additional year of age increased the probability of death by 9%[36]. In this series, age, alveolar hemorrhage, FFS and MPA were related with prognosis. Unlike other series, renal involvement, ANCA pattern and BVAS were not associated to poor prognosis[7-9, 19].

BVAS was developed and validated in 1994 for use in the assessment of vasculitis activity and was subsequently modified to the current version: BVAS v.3. It is recommended by EULAR for use in clinical trials. It has proved to be a useful tool in the assessment of disease activity and response to treatment and as a prognostic factor[14, 15]. In this series, the median BVAS at diagnosis was lower than that reported in other studies[21, 29, 37], but similar to other cohorts[34, 38]. The initial BVAS was not associated with mortality.

FFS was initially designed to predict survival at diagnosis in patients with polyarteritis nodosa, EGPA and MPA. It was developed by the French Vasculitis Study Group (FVSG) for use in a cohort the results of which were published in 1996. A revised version in 2009 included patients

with GPA and established that the following variables have a score of one point each: age above 65 years, heart failure, renal insufficiency (stabilized peak Cr ≥ 1.7 mg/dl), gastrointestinal involvement and absence of ear, nose and throat involvement[5]. The 5-year mortality rates for FFS 0, 1 and ≥ 2 were 9%, 21% and 40%, respectively. A number of studies reported results on the use of this tool in the treatment of their patients, which included making therapeutic decisions or predicting relapses[38-42]. In this study, patients with an FFS of 2 had poor prognosis.

This study is limited by the size of the sample which did not allow for the adjustment of the analysis, and by its retrospective design that includes patients diagnosed during a 35-year period, under heterogeneous treatments which depended on the discretion of the treating physician at a given historical context. The strength of the study lies in the rare occurrence of this group of entities and the scarcity of literature on the subject in this region.

In summary, in this study we found a predominance of the female gender, mainly in MPA and greater involvement of lower airway in GPA, as other authors. Those over 55 years old, the presence of alveolar hemorrhage, those with FFS of 2 and patients with MPA had poor prognosis. Renal involvement, ANCA pattern and BVAS were not associated to a poorer prognosis.

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