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Original Investigation

Relapse in patients with ANCA-associated vasculitis: A cohort study from a centre for rheumatic diseases in Colombia

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ABSTRACT

Introduction: Relapses are common in patients with ANCA-associated vasculitis (AAV), which results in a significant burden of morbidity, mortality, impact on quality of life, disability, and cost. However, evidence in the Colombian population is scarce.
Objective: The objective of this study was to estimate the relapse-free survival during the first year and describe clinical and serological variables of patients with AAV in a specialized centre for rheumatic diseases in Colombia.
Materials and methods: A retrospective follow-up study was conducted on a cohort based on medical records of patients over 18 years old with confirmed diagnosis of AAV by the treating rheumatologist and who had achieved remission. Information on AAV relapse and clinical, immunoserological, and treatment-related characteristics was extracted. The relapse-free survival function during the first year was estimated.
Results: A total of 56 patients were included, 69.9% of whom were women, with a median age of 60 (IQR = 48–63). According to the clinical phenotype, 64.3% were classified as granulomatosis with polyangiitis (GPA), 23.2% as microscopic polyangiitis (MPA), and 12.5% as eosinophilic granulomatosis with polyangiitis (EGPA). According to the European Vasculitis Study Group (EUVAS) classification, 39.3% had generalized AAV at debut, 23.2% had localized AAV, 21.4% had severe renal AAV, and 16.1% had systemic AAV. The median Five Factor Score (FFS) was 1 (IQR = 0–2). The cumulative relapse-free survival at one year was 82.2%.
Conclusions: The relapse-free survival observed in this cohort was similar to other reports in clinical studies and AAV registries.

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Recaída en pacientes con vasculitis asociadas a ANCA: un estudio de cohorte en un centro de enfermedades reumatológicas en Colombia

Palabras clave:
Vasculitis asociadas a ANCA
Recaída
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RESUMEN

Introducción: Las recaídas son comunes en pacientes con vasculitis asociadas a ANCA (VAA), lo cual conlleva una carga significativa en morbimortalidad, impacto en calidad de vida, discapacidad y costo. No obstante, se cuenta con poca evidencia en población colombiana.
Objetivo: El objetivo de este estudio fue estimar la supervivencia libre de recaída durante el primer año en pacientes con VAA en un centro especializado en enfermedades reumatológicas en Colombia y describir las características clínicas y serológicas en esta población.
Materiales y métodos: Estudio de seguimiento retrospectivo a una cohorte basado en los registros médicos de pacientes mayores de 18 años con diagnóstico confirmado de VAA por el reumatólogo tratante y que habían alcanzado la remisión. Se extrajo información sobre recaída de VAA y sobre las características clínicas, inmunoserológicas y relacionadas con el tratamiento farmacológico. Se estimó la función de supervivencia libre de recaída durante el primer año.
Resultados: Se incluyeron 56 pacientes, el 69,9% mujeres, con edad mediana de 60 (RIC = 48–63). Según el fenotipo clínico, se clasificó el 64,3% como granulomatosis con poliangitis (GPA), el 23,2% como poliangitis microscópica (PAM) y el 12,5% como granulomatosis eosinofílica con poliangitis (GEPA). Según la clasificación del Grupo de Estudio de Vasculitis Europeo (Euvas), el 39,3% debutó con VAA generalizada, el 23,2% con localizada, el 21,4% con renal grave y el 16,1% con sistémica. La mediana de Five Factor Score (FFS) fue de 1 (RIC = 0–2). La supervivencia acumulada libre de recaída al año fue del 82,2%.
Conclusiones: La supervivencia libre de recaída observada en esta cohorte fue similar a la reportada en estudios clínicos y registros de VAA.

Introduction

Anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitides are systemic autoimmune diseases characterized by inflammation of blood vessels, endothelial injury, and tissue damage. They include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1] These diseases mainly affect the small-caliber vessels of the upper respiratory tract, the lungs and the kidneys, and are associated with the presence of specific antibodies against myeloperoxidase (MPO) and proteinase 3 (PR3) present in the neutrophils.[2]

The epidemiology of ANCA-associated vasculitis (AAV) is heterogeneous.[3] In the United States, an annual incidence of 3.3 cases per 100,000 inhabitants was estimated between 1995 and 2015, with a higher incidence in men and older people. In this population, the prevalence was 42.1 per 100,000 people in 2015[4]; lower figures have been reported in other countries. In a study conducted in Argentina, incidences of 0.9 and 1.4 per 100,000 person-years were observed for GPA and PMA, respectively. Likewise, it was found a prevalence of 7.4 per 100,000 people for GPA and of 5.2 per 100,000 people for PMA.[5] In patients with AAV, mortality is higher during the first year and is usually associated with infections or active vasculitis.[6]

Relapses are common during the course of the AAVs, which entails a significant burden of disease, negative impact on quality of life, and increased risk of disability and death.[7] In addition, patient relapses generate additional costs for the health systems.[8] The treatment used to prevent these relapses is not exempt from toxicity, which in turn can cause morbidity in the patients. Therefore, it is essential to identify which patients are at high risk of relapses and focus efforts on their prevention.[9]

In Colombia, AAV constitutes a group of rare diseases about which there is not enough information. A literature review published in 2009 managed to collect data on 857 primary vasculitides, of which 20% were AAV.[10] On the other hand, a report of patients treated over a 12-year period in a university hospital described clinical characteristics, outcomes, and in-hospital mortality in a series of 106 AAVs.[11] However, studies that characterize relapses in our population have not been reported. The objective of this study was to estimate the relapse-free survival during the first year and to describe the clinical and serological variables during the follow-up of a cohort of patients with AAV in a center specialized in rheumatological diseases in Colombia.

Methods

This report follows the guidelines for reporting observational studies recommended by the Strobe statement.[12]

Study design and context

A retrospective follow-up study was carried out on a cohort, based on the medical records of patients treated in the period 2014–2021 at Artmedica IPS, an outpatient institution specialized in rheumatology with presence in seven cities in Colombia. In the case of patients who at the time of admission to our cohort had diagnoses and behaviors that had been established at another institution, this was documented in the institutional medical record during the first clinical encounter. Follow-up was carried out until the occurrence of the relapse or administrative censorship at one year of follow-up.

Participants

All patients over 18 years of age with a diagnosis of AAV confirmed by the treating rheumatologist and who had achieved remission were consecutively included. Patients whose records in the medical history were not compatible with AAV according to the criterion of a rheumatologist of the research group; those with incomplete records related to the AAV; those with AAV refractory to induction therapy, and those who had already experienced a relapse prior to their admission to the institution were excluded. The first relapse after the first line of induction therapy was considered the event of interest to be analyzed, for which patients with previous relapses and refractory were excluded, considering that these subgroups could have a higher risk of new events and other factors associated with relapse, compared to a first event.

Variables

The outcome variable was defined as the time to relapse of AAV during the first year of follow-up. Variables such as the clinical phenotype, the initial classification of AAV severity according to the criteria of the European Vasculitis Study Group (EUVAS)[13] and the Five Factor Score (FFS)[14] were included, and are presented in Table 1. Clinical, immunoserological and pharmacological treatment-related characteristics were also taken.

The cut-off points for quantitative laboratory variables were determined by each laboratory in which the studies were performed.

Bias control

To control for information bias, data were extracted from medical record registries by researchers previously trained by an expert researcher from the clinical information group and supervised by a rheumatologist. The data were extracted to a Google Forms, in which their internal validation and standardization were carried out. A dictionary of variables linked to the collection instrument was created. Unavailable data were recorded as missing data.

In order to reduce selection bias, the identification of the patients was carried out in two stages: search in administrative records and confirmation of eligibility by reviewing the medical records. The rheumatologist confirmed the fulfillment of the eligibility criteria.

Table 1 – Clinical and demographic characteristics of the patients with ANCA-associated vasculitis.

	n	%
Age, years, median (IQR)	60	(48–63)
Women	39	69.64
BMI, median (IQR)	24	(22–27)
Smoking habit	12	21.43
Months between onset of symptoms and diagnosis, median (IQR)	5.8	(2–12.2)
Months between diagnosis and entry into the cohort, median (IQR)	20.7	(3.8–59.4)
Phenotype		
Granulomatosis with polyangiitis	36	64.29
Microscopic polyangiitis	13	23.21
Eosinophilic granulomatosis with polyangiitis	7	12.50
FFS, median (IQR)	1	(0–2)
Initial classification of severity according to EUVAS		
Generalized	22	39.29
Located	13	23.21
Severe renal	12	21.43
Systemic onset	9	16.07

EUVAS: European Vasculitis Study Group; FFS: Five Factor Score; BMI: body mass index.

Sample size

It was taken the population census of the patients treated with a diagnosis of AAV.

Statistical analysis

Descriptive analyses of the total sample of patients with AAV and of the subgroup of patients with relapse were performed. The categorical variables were described using frequencies and percentages and the quantitative variables using median and interquartile range (IQR).

Relapse-free survival at one year was estimated using the Cox survival model for interval-censored data. The lower limit of the interval was taken as the last date on which the patient was observed without relapse, and the upper limit was taken as the first date on which the patient was assessed with relapse. The survival function at one year is presented. Analyses were obtained with Stata version 18 (College Station, TX, USA).

Ethical considerations

The protocol of this study was approved by the Institutional Committee on Ethics of Research in Human Beings of the CES University (Ae-709) as risk-free research, in accordance with Resolution 8430 of 1993. Upon entry into the program, informed consent was obtained from the patients for the use of their clinical history data under conditions of confidentiality and anonymity for research purposes.

Table 2 – Involvement by systems of patients with ANCA-associated vasculitis.

	Total (n = 56)	GPA (n = 36)	MPA (n = 13)	EGPA (n = 7)
Renal Involvement	32 (57.1)	18 (50)	12 (92.3)	2 (28.6)
Rapidly progressive glomerulonephritis	22 (39.3)	12 (33.3)	9 (69.2)	1 (14.3)
Nephritic syndrome	5 (8.9)	3 (8.3)	2 (15.4)	0 (0.0)
Chronic kidney disease	4 (7.1)	2 (5.6)	1 (7.7)	1 (14.3)
Isolated hematuria	1 (1.8)	0 (0.0)	1 (7.7)	0 (0.0)
IgA nephropathy	1 (1.8)	1 (2.8)	0 (0.0)	0 (0.0)
ENT involvement	29 (51.8)	24 (66.7)	1 (7.7)	4 (57.1)
Rhinosinusitis	27 (48.2)	22 (61.1)	1 (7.7)	4 (57.1)
Nasal or mouth ulcers	10 (17.9)	9 (25.0)	1 (7.7)	0 (0.0)
Destruction of nasal cartilage	10 (17.9)	10 (27.8)	0 (0.0)	0 (0.0)
Nasal deformity	7 (12.5)	7 (19.4)	0 (0.0)	0 (0.0)
Subglottic or tracheal stenosis	5 (8.9)	5 (13.9)	0 (0.0)	0 (0.0)
Hearing loss	5 (8.9)	4 (11.1)	0 (0.0)	1 (14.3)
Airway obstruction	3 (5.4)	3 (8.3)	0 (0.0)	0 (0.0)
Nasal polyps	3 (5.4)	0 (0.0)	0 (0.0)	3 (42.9)
Recurrent otitis media	1 (1.8)	0 (0.0)	1 (7.7)	0 (0.0)
Lung involvement	26 (46.4)	13 (36.1)	6 (46.2)	7 (100.0)
Alveolar hemorrhage	12 (21.4)	5 (13.9)	6 (46.2)	1 (14.3)
Pulmonary nodules	7 (12.5)	7 (19.4)	0 (0.0)	0 (0.0)
Asthma	6 (10.7)	0 (0.0)	0 (0.0)	6 (85.7)
Interstitial lung disease	4 (7.1)	2 (5.6)	1 (7.7)	1 (14.3)
Bronchiectasis	3 (5.4)	1 (2.8)	0 (0.0)	2 (28.6)
Cavitation	3 (5.4)	3 (8.3)	0 (0.0)	0 (0.0)
Neurological involvement	17 (30.4)	7 (19.4)	8 (61.5)	2 (28.6)
Motor or sensory neuropathy	16 (28.6)	6 (16.7)	8 (61.5)	2 (28.6)
Pachymeningitis	1 (1.8)	1 (2.8)	0 (0.0)	0 (0.0)
Longitudinally extensive transverse myelitis	1 (1.8)	1 (2.8)	0 (0.0)	0 (0.0)
Ocular involvement	13 (23.2)	12 (33.3)	1 (7.7)	0 (0.0)
Scleritis	7 (12.5)	7 (19.4)	0 (0.0)	0 (0.0)
Uveitis	4 (7.1)	4 (11.1)	0 (0.0)	0 (0.0)
Episcleritis	3 (5.4)	2 (5.6)	1 (7.7)	0 (0.0)
Orbital inflammatory disease	2 (3.6)	2 (5.6)	0 (0.0)	0 (0.0)
Cutaneous involvement	11 (19.6)	5 (13.9)	4 (30.8)	2 (28.6)
Purpura	9 (16.1)	3 (8.3)	4 (30.8)	2 (28.6)
Skin ulcer	2 (3.6)	2 (5.6)	0 (0.0)	0 (0.0)
Livedo reticularis	1 (1.8)	0 (0.0)	1 (7.7)	0 (0.0)
Vascular involvement	7 (12.5)	4 (11.1)	0 (0.0)	3 (42.9)
Venous thromboembolism	5 (8.9)	3 (8.3)	0 (0.0)	2 (28.6)
Cerebrovascular event	2 (3.6)	1 (2.8)	0 (0.0)	1 (14.3)
Musculoskeletal involvement	4 (7.1)	3 (8.3)	0 (0.0)	1 (14.3)
Arthralgias	3 (5.4)	2 (5.6)	0 (0.0)	1 (14.3)
Myalgias	1 (1.8)	1 (2.8)	0 (0.0)	0 (0.0)
Cardiac involvement	1 (1.8)	0 (0.0)	0 (0.0)	1 (14.3)
Pericarditis	1 (1.8)	0 (0.0)	0 (0.0)	1 (14.3)

EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; ENT: otorhinolaryngological; MPA: microscopic polyangiitis.

Results

Participants

A total of 56 patients from seven cities in Colombia (in order of frequency: Medellín, Rionegro, Manizales, Pereira, Armenia, Cali and Tunja) were included, which provided 554.3 months of follow-up; on average, 9.9 months per patient.

Baseline clinical characteristics

The clinical and sociodemographic characteristics of the patients are detailed in Table 1. Of the 56 patients included in the study, 39 (69.6%) were women, with a median age at admission of 60 years (IQRI = 48–63). In terms of clinical phenotype, 36 patients (64.3%) were classified as GPA, 13 (23.2%) as MPA and 7 (12.5%) as EGPA. The involvement by systems and the specific manifestations are presented in Table 2, being renal involvement the most frequent, followed by otorhinolaryngological, pulmonary, neurological, ocular, cutaneous, vascular, musculoskeletal and finally, cardiac commitment. According to the EUVAS classification, 22 patients (39.3%) debuted with generalized AAV, 13 (23.2%) with located AAV, 12 (21.4%) with severe renal AAV and 9 (16,1%) with AAV of systemic onset. The FFS score had a median of 1 (IQR = 0–2).

Table 3 – ANCA results according to the clinical phenotype.

	[0,2-3]Total (n = 56)		[0,4-5]GPA (n = 36)		[0,6-7]MPA (n = 13)		[0,8-9]EGPA (n = 7)	
	n[a]	Cases[b]	n[a]	Cases[b]	n[a]	Cases[b]	n[a]	Cases[b]
PR3	43	21 (48.8)	28	18 (64.3)	10	1 (10.0)	5	2 (40.0)
MPO	38	14 (36.8)	21	3 (14.3)	12	10 (83.3)	5	1 (20.0)
Negative by ELISA	46	11 (23.9)	28	6 (21.4)	12	2 (16.7)	6	3 (50.0)
c-ANCA	33	14 (42.4)	22	12 (54.5)	8	1 (12.5)	3	1 (33.3)
p-ANCA	33	8 (24.2)	22	1 (4.5)	8	7 (87.5)	3	0 (0.0)
Negative by IIF	33	11 (33.3)	22	9 (40.9)	8	0 (0.0)	3	2 (66.7)
PR3 o c-ANCA	53	28 (52.8)	35	24 (68.6)	12	2 (16.7)	6	2 (33.3)
MPO o p-ANCA	50	18 (36.0)	31	4 (12.9)	13	13 (100.0)	6	1 (16.7)
Negative by IIF and ELISA	55	5 (9.1)	35	4 (11.4)	13	0 (0.0)	7	1 (14.3)

c-ANCA: anti-neutrophil cytoplasmic antibodies cytoplasmic pattern; ELISA: enzyme-linked immunoassay; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; IIF: indirect immunofluorescence; MPO: myeloperoxidase; MPA: microscopic polyangiitis; p-ANCA: anti-neutrophil cytoplasmic antibodies perinuclear pattern; PR3: proteinase 3.

[a] n: patients with available data.

[b] cases: frequency and percentage of the finding among patients with available data.

Laboratory findings

The available results of antibody status are summarized in Table 3. 21 patients (48.8%) with positivity for PR3 and 14 (36.8%) for MPO were identified, with only one patient being positive for both antibodies by enzyme-linked immunoassay (ELISA). Regarding the results of indirect immunofluorescence (IIF), 14 patients (42.4%) showed a c-ANCA (cytoplasmic) pattern, while 8 (36.8%) presented a p-ANCA (perinuclear) pattern. Five patients (9.0%) were negative for ANCA in both laboratory methods. The diagnosis of AAV in ANCA-negative patients was based on a combination of clinical findings with the result of biopsies that were consistent with this entity.

Histological findings

Records of one or more histological results were obtained in 37 patients (66.1%). Of the 22 patients with renal biopsy data, 18 (81.8%) presented findings of glomerulonephritis, 15 (68.2%) showed extracapillary proliferation with crescents, 12 (54.5%) evidenced necrosis, 4 (18.2%) had chronic changes due to glomerular sclerosis and interstitial fibrosis, and one (4.5%) showed IgA nephropathy. Results of nasal or paranasal sinuses biopsies were recorded in 6 patients, of which 4 (66.7%) showed necrotizing inflammation, 3 (50.0%) presented granulomas, and one (16.7%) showed changes of vasculitis. As for the lung biopsies performed in 4 patients, 2 (50.0%) showed granulomas, 2 (50%) presented eosinophilic infiltrate, one (25.0%) evidenced vasculitis and the other (25.0%) showed nonspecific interstitial pneumonia. Five skin biopsies were carried out, all showed findings of necrosis, 4 (80.0%) showed vasculitis, 2 (40.0%) reported granulomas and one (20.0%) evidenced eosinophilic infiltrate.

Treatment

The pharmacological treatment is presented in Table 4. The majority of patients (94.6%) received glucocorticoids with variable schemes. Regarding the use of induction immunosuppressants, 37 patients (66%) received cyclophosphamide and 4 (7.1%) received rituximab. As for maintenance, the most commonly used was azathioprine in 39 patients (69.6%), followed by rituximab in 12 patients (21.4%). In addition, 5 patients (8.9%) underwent plasma exchange and 11 (19.6%) received antibiotic prophylaxis with trimethoprim sulfamethoxazole.

Table 4 – Treatment of patients with ANCA-associated vasculitis.

	n	%
Glucocorticoids	53	94.6
Induction immunosuppressants		
Cyclophosphamide	37	66
Rituximab	4	7.1
Azathioprine	5	8.9
Methotrexate	3	5.3
Plasma exchanges	5	8.9
Without information	8	14.2
Maintenance immunosuppressants		
Azathioprine	39	69.6
Rituximab	12	21.4
Methotrexate	9	16.1
Mycophenolate	4	7.1
Without information	2	3.6

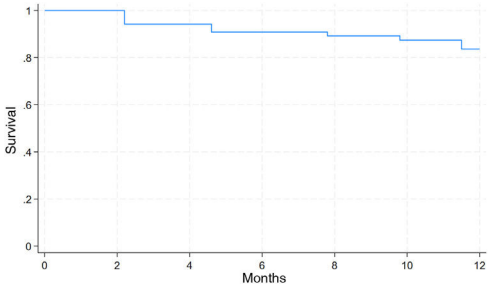

Fig. 1 – Relapse-free survival function in the first year in patients with ANCA-associated vasculitis.

Relapse-free survival of AAV

Fig. 1 presents the relapse-free survival function, which was estimated at 82.2% at one year of follow-up.

Characteristics of the patients who presented relapse of AAV

Table 5 presents the characteristics of the 8 patients who experienced relapse. It was documented a median of 3 months (IQR = 2.0–4.3) between the diagnosis of remission and the relapse. 75% were women, with a median age of 61 years (IQR = 47.7–62.5). Seven of these patients (87.5%) had a diagnosis of GPA. At the time of diagnosis, 5 patients (62.5%) had a generalized disease according to the EUVAS classification, with otorhinolaryngological involvement in 7 of them (87.5%), renal involvement in 4 (50.0%) and pulmonary involvement in 3 (37.5%). c-ANCA/PR3 antibodies were identified in 5 patients (62.5%) and p-ANCA/MPO in 2 (25.0%). One patient was negative for ANCA; however, the measurement of ANCA by ELISA was performed after the initiation of the induction therapy, and the diagnosis was established according to the clinical manifestations and compatible histological results.

During the relapses, the mainly affected systems were the otorhinolaryngological system in 4 patients (50.0%) and the nervous system in 3 of them (37.5%). It was observed that 5 patients (62.5%) experienced relapses that involved a single organ, while the rest had relapses that affected multiple organs. Of the patients with relapses, 5 (62.5%) experienced major life-or organ-threatening relapses, while 3 (37.5%) had minor relapses. Regarding the maintenance treatment at the time of the relapse, the most commonly used therapy was azathioprine, in 3 patients (37.5%), while only one patient (12.5%) was receiving rituximab, methotrexate or mycophenolate. Two patients (25.0%) experienced relapses during the induction therapy with cyclophosphamide. As for reinduction treatment, a combination of glucocorticoids was used in 7 patients (87.5%), rituximab in 4 (50.0%), methotrexate in two (25.0%), azathioprine in two (25.0%) and cyclophosphamide or leflunomide in one (12.5%).

Discussion

This study aimed to estimate the relapse-free survival during the first year in patients with AAV, which was found to be 82.2%. In addition, we provided a clinical, histological, laboratory and treatment characterization, both for the total number of patients with AAV and for the patients who presented relapse.

It is important to highlight that studies on AAV in the Latin American population are scarce, despite its clinical, socioeconomic and health system relevance. In Colombia in particular, there are few studies available, such as that of Fernández-Ávila et al.,[11] which describes 106 patients with AAV, and the one of Ochoa et al.,[10] with 455 patients with AAV. Therefore, our work adds to these publications on the subject, providing additional information on the follow-up and relapses in these patients.

With reference to the clinical manifestations, the main system involved was the renal, in 57.1% (Table 2), similar to what was reported in the Argentinian,[15] Spanish[16] and Swedish[17] series, but lower than the report of 84% in the study of Fernández-Ávila et al.[11] However, a lower percentage of patients with MPA, who present more frequently with renal involvement were included in our study, in addition to including patients with limited GPA and EGPA in an outpatient setting; this added to the use of a different definition of renal involvement, since in ours, high blood pressure was not considered as a renal manifestation.

The percentages of pulmonary, otorhinolaryngological, neurological, cutaneous and ocular involvement are similar to those reported by other authors, although it is worth mentioning that having a greater proportion of patients with GPA, it was identified a percentage of sinusitis higher than in other studies of the Hispanic population.[11,15,16]

On the other hand, our study adds to what has been reported in the literature on the associations between certain clinical manifestations and the phenotype. Renal involvement is almost constant in MPA and infrequent in EGPA, while otorhinolaryngological involvement is more frequent in GPA and EGPA, and ocular involvement in GPA.[11,16,18–20]

As for the measurement of ANCAs, our study had a percentage of positivity for PR3 and MPO of 48.8% and 36.8%, respectively. These results are similar to the Swedish registry, which reports 51% for PR3 and 43% for MPO.[21] However, given the retrospective nature of our study, not all patients had an ANCA report available and in some of them there were only reports of ANCA measured by IIF, which before 2017 was considered the initial study in case of suspicion of AAV.[22] If the results of ANCA by IIF are included, the percentage of positivity increases, reaching 52.8% for PR3 or c-ANCA, which is higher than in the Spanish (36%) and the Argentinian (42.5%) cohorts, probably due to the fact that our study had a greater proportion of patients with GPA in relation to MPA, compared to the other two cohorts, in which the proportion of these diseases was similar. In turn, the positivity of MPO or p-ANCA was lower in our study than in the Spanish and Argentinian cohorts, for the same reason.[15,16]

In our study, the majority of patients with GPA had PR3 or c-ANCA and the majority of patients with MPA had MPO or p-ANCA, similar to what was reported in the Spanish and French registries.[16,18,19] In the Swedish, Spanish, and Argentinian cohorts, the prevalence of ANCA-negative in the total group of patients with AAV was low and similar to ours, being of 6.0%, 13.6% and 8.6%, respectively.[15,16,21]

With respect to treatment, the majority of patients received glucocorticoids and cyclophosphamide as induction therapy, as in other cohorts due to their well-established indication in AAV.[11,15,16] The scarce use of rituximab as induction therapy is explained by the exclusion of patients with refractory disease or relapses prior to admission. In our study, the most commonly used medication for maintenance was azathioprine, despite the fact that currently the preferred therapy in this scenario is rituximab, possibly because in many cases it had been started prior to the dissemination of the MAINRITSAN study[23] and because of the greater availability of azathioprine in our environment due to its lower cost. On the other hand, in the study conducted by Fernández-Ávila et al.[11] plasma exchanges were used more frequently than in our study (17.9% *vs*. 8.2%, respectively), which could be due to the change in the trend in its use since the PEXIVAS study and to the higher percentage of diffuse alveolar hemorrhage.[24]

The relapse-free survival at one year found in our study (82,2%) has a tendency to behave similarly to that of the CYCAZAREM[25] and WEGENT[26] studies and to the azathio-

Table 5 – Characteristics of patients with ANCA-associated vasculitis who presented relapse in the first year of follow-up.

	Sex, age	Clinical phenotype	Form (EUVAS)	ANCA	Initial manifestation	Induction	Maintenance	Months to relapse[a]	Type of relapse	Manifestation of relapse	Treatment of relapse
1	F, 38	GPA	G	MPO	Rhinosinusitis, alveolar hemorrhage, RPGN	GC + CYC	RTX	3	Minor	Rhinosinusitis, arthritis	GC + MTX + RTX
2	M, 38	GPA	L	c-ANCA	Rhinosinusitis	GC + AZA	MTX	4	Minor	Rhinosinusitis	MTX + LFN
3	F, 51	GPA	L	PR3	Rhinosinusitis, otomastoiditis, sensorineural hearing loss	GC + AZA	AZA	5	Major	Pachymeningitis, pulmonary nodule	GC + CYC
4	M, 62	GPA	G	PR3	Nephritic syndrome, rhinosinusitis	GC + CYC	MMF	10	Major	Nephritic syndrome	GC + RTX
5	F, 60	GPA	G	Neg[b]	Rhinosinusitis, subglottic stenosis, pulmonary nodules, orbital pseudotumor, skin ulcer	GC + CYC	–[c]	1,5	Major	Pachymeningitis	GC + RTX
6	F, 64	GPA	SR	PR3, c-ANCA	CKD, rhinosinusitis, arthritis, alopecia, mouth sores	ND	AZA	2	Major	Sinusitis	GC + AZA
7	F, 67	GPA	G	c-ANCA	Rhinosinusitis, saddle nose, lung cavitation, bronchiectasis, orbital inflammatory disease	GC + AZA	AZA	2	Major	Rhinosinusitis, mastoiditis, orbital inflammatory disease	GC + AZA
8	F, 62	MPA	G	MPO, p-ANCA	nephritic syndrome, purpura, sensory-motor neuropathy, fatigue	GC + CYC	–[c]	3	Major	Sensory-motor neuropathy	GC + RTX

ANCA: anti-neutrophil cytoplasmic antibodies; AZA: azathioprine; c-ANCA: anti-neutrophil cytoplasmic antibodies cytoplasmic pattern; CYC: cyclophosphamide; CKD: chronic kidney disease; EUVAS: European Vasculitis Study Group; F: female; G: generalized; GC: glucocorticoids; RPGN: rapidly progressive glomerulonephritis; GPA: granulomatosis with polyangiitis; L: located; LFN: leflunomide; M: male; MMF: mycophenolate mofetil; MPO: myeloperoxidase; MTX: methotrexate; Neg: negative; MPA: microscopic polyangiitis; PR3: proteinase 3; SR: severe renal; RTX: rituximab; ND: no data.

[a] Months between diagnosis of remission and relapse.

[b] ANCA negative by immunofluorescence and by enzyme immunoassay at the time of entry into the cohort.

[c] Relapse during induction treatment.

prine arm of the MAINRITSAN[23] and RITAZAREM[27] studies; however, it is lower than that of the rituximab arm in these two studies, which can be explained because in our study the majority of patients received azathioprine for maintenance and only 21.4% received rituximab. Likewise, the relapse-free survival reported by the studies of the French Vasculitis Study Group Registry of GPA, MPA and EGPA has a behavior similar to ours.[18–20]

Even though a low statistical power for association analysis was established in our study, the majority of patients who relapsed had a diagnosis of GPA, positivity for c-ANCA/PR3 and upper airway involvement, findings that are consistent with what has been reported in the literature.[9,28,29]

This study has several strengths. It is the first to estimate relapse-free survival in patients with AAV and one of the few that characterize this disease in Colombia. In addition, a detailed description of the cases that experienced relapses was carried out, which provides a better understanding of how these relapses manifest in our population. It should be noted that all patients in the cohort were assessed by rheumatologists, which represents the standard method for the diagnosis of these diseases. This reduces the possibility of incorporation into the cohort of other diseases that may have similar clinical manifestations.

The main limitation of this study is its retrospective nature based on secondary sources. Some patients had even been diagnosed in a hospital or in other outpatient centers years prior to their admission to the institution. The median time between the diagnosis and the entry into the cohort was 20.7 months, so the clinical presentation at diagnosis, the initial paraclinical tests, and the induction scheme could be incomplete. On the other hand, by excluding refractory patients and those with previous relapses, the number of events is reduced and, therefore, it may be lower than that observed in non-selected populations.

Conclusion

This article provides relevant information on the characteristics of the patients with AAV in Colombia, and of those who relapsed. The relapse-free survival observed in this cohort was similar to that reported in clinical studies and registries of AAV.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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