Prevalence and Risk Factors for Major Infections in Patients with Antineutrophil Cytoplasmic Antibody–associated Vasculitis: Influence on the Disease Outcome

Eloi Garcia-Vives, Alfons Segarra-Medrano, Ferran Martinez-Valle, Irene Agraz, and Roser Solans-Laque

ABSTRACT. ***Objective.*** To analyze the role that infections play on the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) outcome.

Methods. A retrospective study of adult patients with AAV diagnosed in a tertiary center. Clinical features, laboratory findings, treatment, relapses, major infections, and outcome were evaluated.

Results. Included were 132 patients [51 microscopic polyangiitis (MPA), 52 granulomatosis with polyangiitis (GPA), 29 eosinophilic GPA (EGPA)] with a mean followup of 140 (96–228) months. ANCA were positive in 85% of cases. A total of 300 major infections, mainly bacterial (85%), occurred in 60% patients during the followup. Lower respiratory tract (64%) and urinary tract infections (11%) were the most frequent, followed by bacteremia (10%). A total of 7.3% opportunistic infections were observed, most due to systemic mycosis. Up to 46% of all opportunistic infections took place in the first year of diagnosis, and 55% of them under cyclophosphamide (CYC) treatment. Bacterial infections were associated with Birmingham Vasculitis Activity Score (version 3) > 15 at the disease onset, a total cumulative CYC dose > 8.65 g, dialysis, and development of leukopenia during the followup. Leukopenia was the only factor independently related to opportunistic infections. Forty-four patients died, half from infection. Patients who had major infections had an increased mortality from any cause.

Conclusion. Our results confirm that major infections are the main cause of death in patients with AAV. (J Rheumatol First Release November 1 2019; doi:10.3899/jrheum.190065)

Key Indexing Terms:
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES
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Antineutrophil cytoplasmic antibodies (ANCA)–associated vasculitides (AAV) are systemic diseases characterized by the presence of necrotizing inflammation predominantly involving small-sized vessels in conjunction with serum ANCA in most cases. Three different entities are distinguished: granulomatosis with polyangiitis (GPA; formerly known as Wegener), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA; classically known as Churg-Strauss syndrome)[1]. GPA typically affects the upper and lower respiratory tract and kidneys; MPA is characterized by severe renal affection usually due to pauciimmune necrotizing glomerulonephritis; and EGPA is characterized by asthma, hypereosinophilia, and nasal polyposis[2].

Historically, patients with untreated AAV died early because of the severity of the disease, with a mortality rate of 80–90% in the first year[3,4], except for EGPA, which showed higher survival rates[5]. The introduction of corticosteroids (CS) and cyclophosphamide (CYC) therapy clearly improved the rate of survival but with a high toxicity[6]. Several randomized trials allowed tailoring the treatment according to the clinical disease severity, but the mortality rate remains high, with fulminant complications[7]. While in the past patients tended to die early owing to uncontrolled disease, today treatment-related toxicity plays a central role in mortality[8]. Several studies have analyzed the prognostic factors associated with AAV mortality, reporting infections

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as one of the most important etiologies, representing up to 66% during the first 12 months[8,9,10].

The aim of the present study was to analyze the prevalence and risk factors of major infections among patients with AAV and its influence on the disease outcome.

MATERIALS AND METHODS

This was a retrospective, single-center study. Adult patients (> 18 yrs) diagnosed as having AAV between January 1990 and January 2016 at the Autoimmune and Systemic Diseases Unit of the Internal Medicine Department and the Nephrology Department of a tertiary center were evaluated. The median followup was 140 [interquartile range (IQR) 96–228] months. Patients were classified according to the 2012 Chapel Hill revised criteria[1]. The following data were collected from clinical files: demographic features, clinical manifestations and main laboratory findings at the time of diagnosis [white blood count (WBC), hemoglobin, creatinine, estimated glomerular filtration rate (eGFR), erythrocyte sedimentation rate, 24-h protein excretion, and ANCA], induction and maintenance therapy, disease complications, number of relapses, and time and cause of death. The total cumulative CYC dose was calculated, taking into account all the CYC courses that patients received initially and during the followup.

The disease activity/severity at time of diagnosis and during the followup was estimated according to the Birmingham Vasculitis Activity Score version 3 (BVASv.3)[11,12], the 1996 Five Factor Score (FFS)[13], and the 2009 FFS[14]. BVASv.3 ≥ 1 defined active disease[12]. Uncontrolled vasculitis was defined as the occurrence of new manifestations or aggravation of manifestations already present despite treatment for the disease. Relapses were defined as recurrence of signs or new symptoms after an initial remission, severe enough to warrant a change in therapy. Acute renal failure was defined according to the Acute Kidney Injury Network[15] as a rapid decline in renal filtration function manifested by an absolute increase in serum creatinine of ≥ 0.3 mg/dl or ≥ 50% from baseline. Chronic kidney disease was defined as an eGFR < 60 ml/min/1.73 m^2 in 2 consecutive analyses separated by at least 3 months. Renal disease was defined according to BVASv.3[11,12,16] by the presence of hematuria ≥ 10 red blood cells per high-power field, proteinuria > 0.2 g/24 h, creatinine ≥ 125 µmol/l (1.41 mg/dl), hypertension, or a rise in serum creatinine > 30% or fall in the eGFR > 25%, not attributable to a medical problem other than vasculitis. Leukopenia was defined by the presence of WBC under 3500 cells/µl in 2 successive blood tests. Pancytopenia was defined as a reduction in each type of peripheral blood cells (hemoglobin < 10 g/dl, leukocytes < 3.500 cells/µl, platelets < 100.000 µl). ANCA were determined by indirect immunofluorescence (IFI) and ELISA or chemiluminescence immunoassay according to the study period. Patients with positive ANCA by IFI but negative specificity were classified as ANCA-negative.

Major infections were defined as those that required hospitalization or intravenous (IV) antibiotics for at least 24 h. Sepsis and its source were individually evaluated in the statistical analysis. Opportunistic infection was defined as the infection caused by an organism (bacterial, viral, fungal, or protozoan) with a low virulence capacity that takes advantage of a weakened immune system, causing disease when it ordinarily would cause mild or no disease in an immunocompetent host.

Patients were treated according to the international recommendations[17] in each period.

Statistical analysis. Categorical variables were expressed as percentages, and continuous variables by mean ± standard error of the mean (SEM), or median and IQR, according to their normal distribution based on the Kolmogorov-Smirnov test. The chi-square test was used to compare categorical data between groups. Continuous data were analyzed with the Student t and ANOVA tests. Welch test was used when variances' differences were found using Levene test. Associations of quantitative data were analyzed with the Student t test and with the nonparametric test. Spearman correlation coefficient was used to analyze the relationship between quantitative variables. Receiver-operating characteristic curves were performed to examine the predictive value of each risk factor. Cutoff values were determined according to the Youden index (Supplementary Methodology, Supplementary Figures 1–2, Supplementary Tables 1–2, available with the online version of this article). For mortality analyses, independent variables that appeared to have statistical significance in the univariate analysis ($p < 0.05$) were included in the multivariate logistic regression model. The OR and their 95% CI obtained in the adjusted regression analysis were calculated. Cox regression model with infection as a time-dependent variable was used to analyze its influence on mortality. The effect was estimated as HR with 95% CI. Survival curves were constructed according to the Kaplan-Meier method and compared with log-rank test. A 2-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS v.21.0 software (IBM Corp.).

Ethical approval. The study was approved by the institutional review board of our hospital [PR(AG)289/2014] and performed in accordance with the ethical standards laid down in the appropriate version of the Declaration of Helsinki. Because of the retrospective features of the study, informed consent was not required.

RESULTS

Epidemiological data. A total of 132 patients (48% men) with a median age of 57.5 (IQR 40.3–68.6) years at the time of diagnosis were included in the study. AAV diagnosis was supported by histology in 115 (89%) cases, and by typical symptoms and clinical findings in conjunction with the presence of ANCA in the remaining cases. Overall, 51 patients (39%) were classified as having MPA, 52 (39%) GPA, and 29 (22%) EGPA. At the time of diagnosis, the ANCA test was positive in 112 patients (85%); 39 (30%) proteinase 3 (PR3)-ANCA, and 73 (55%) myeloperoxidase (MPO)-ANCA. The median BVASv.3 at diagnosis was 16 (IQR 11.3–20.8), with no significant differences among groups. Statistical differences were detected in the 1996 and 2009 FFS between MPA and other AAV subsets ($p < 0.05$), with higher values for MPA. Patients with MPA showed a mean creatinine value of 3.30 ± 0.46 mg/dl and a proteinuria of 1.38 ± 0.2 g/day, both significantly higher than in patients with GPA and EGPA ($p < 0.001$). Nephrotic syndrome was present in only 9% of patients, with no significant differences between MPA and GPA patients. No patients with EGPA showed nephrotic syndrome. The main demographic and clinical features, and laboratory data at diagnosis, are summarized in Table 1.

Treatment. The treatment varied depending on the period of the disease diagnosis. After 2001, treatment was divided into 2 phases: an induction phase of 6 months followed by a maintenance phase of 2 years. All patients received oral CS as induction treatment. Additionally, pulses of methylprednisolone were administered to 82/132 (62%) patients with severe manifestations, prior to oral CS therapy institution. IV CYC was given to 55 (42%) patients and oral CYC to 56 (42%). Methotrexate (MTX) was given to 10 (8%) patients with early forms of GPA. Since 2001, according to the international recommendations[18], patients were progressively treated with CYC pulses instead of oral CYC, with a progressive reduction of oral CYC regimen resulting in a

Table 1. Demographic data, clinical manifestations, and laboratory data at AAV diagnosis.

Variables	Total, n = 132	GPA, n = 51	MPA, n = 52	EGPA, n = 29	p
Epidemiological data					
Sex (male/female)	63/69	27/24	25/27	11/18	0.043
Age at diagnosis, yrs, median (IQR)	57.5 (40.3–68.6)	38.0 (32.0–56.0)	67.5 (58.0–75.7)	55.0 (49.0–67.5)	< 0.001
ANCA-positive	112 (85)	42 (82)	51 (98)	19 (65)	< 0.001
PR3-ANCA	39 (30)	36 (71)	2 (4)	1 (3)	< 0.001
MPO-ANCA	73 (55)	6 (12)	49 (94)	18 (62)	< 0.001
BVAS v.3	16 (9–22), median (IQR)	16.1 ± 1.0, mean ± SEM	17.1 ± 0.9, mean ± SEM	15.2 ± 1.1, mean ± SEM	0.440
FFS 1996, median (IQR)	0 (0–1)	0 (0–1)	1 (0–2)	0 (0–0)	< 0.05
FFS 2009, median (IQR)	1 (0–2)	1 (0–1)	2 (2–3)	1 (0–1)	< 0.001
Clinical manifestations					
Toxic syndrome	101 (77)	35 (69)	44 (85)	22 (76)	0.172
Fever	84 (64)	28 (55)	34 (65)	22 (76)	0.188
ENT involvement	62 (47)	42 (84)	2 (4)	18 (62)	< 0.05
Nasal crusting	28 (21)	25 (49)	0 (0)	3 (10)	< 0.001
Septal perforation	2 (2)	2 (4)	0 (0)	0 (0)	0.316
Otitis media	24 (18)	19 (37)	0 (0)	5 (17)	< 0.05
Paranasal sinus involved	44 (33)	27 (53)	2 (4)	15 (52)	< 0.001
Subglottic stenosis	5 (4)	5 (10)	0 (0)	0 (0)	0.06
Pulmonary infiltrates	60 (45)	16 (31)	24 (46)	20 (69)	0.003
Lung nodules	27 (20)	23 (45)	2 (4)	2 (7)	< 0.001
Alveolar hemorrhage	24 (18)	8 (16)	15 (29)	1 (3)	0.013
Acute renal failure	61 (46)	20 (39)	40 (77)	1 (3)	< 0.001
Pulmonary-renal syndrome	20 (15)	7 (14)	14 (27)	0 (0)	0.004
Nephrotic syndrome	12 (9)	5 (10)	7 (14)	0 (0)	0.126
Neurologic affection	50 (38)	8 (16)	20 (38)	22 (76)	< 0.001
Peripheral neuropathy	11 (8)	0 (0)	8 (15)	3 (10)	0.026
Mononeuritis multiplex	39 (30)	8 (16)	12 (23)	19 (66)	< 0.001
Central nervous system	12 (9)	9 (18)	2 (4)	1 (3)	< 0.05
Stroke	7 (5)	5 (10)	2 (4)	0 (0)	0.184
Aseptic meningitis	5 (4)	5 (10)	0 (0)	0 (0)	0.026
Optical neuritis	1 (1)	0 (0)	0 (0)	1 (3)	NS
Myocarditis	3 (2)	0 (0)	0 (0)	3 (10)	NS
Pericarditis	3 (2)	2 (4)	1 (2)	0 (0)	NS
Intestinal ischemia					
Ulcers	8 (6)	5 (10)	2 (4)	1 (3)	NS
Perforation	2 (2)	2 (4)	0 (0)	0 (0)	NS
Laboratory data, mean ± SEM					
Hemoglobin, g/dl	10.7 ± 0.2	11.2 ± 0.3	9.6 ± 0.2	12.2 ± 0.3	< 0.001
Leukocytes, × 10^9/l	12.96 ± 5.62	11.87 ± 8.59	11.81 ± 5.91	16.94 ± 1.59	0.002
ESR, mmh^{-1}	82 ± 3	82 ± 5	91 ± 3	64 ± 5	0.016
Creatinine, mg/dl	2.11 ± 0.22	1.62 ± 0.22	3.30 ± 0.46	0.85 ± 0.03	< 0.001
Proteinuria, mg/day	925 ± 131	874 ± 218	1379 ± 234	179 ± 29	< 0.001

Values are n (%) unless otherwise indicated. ANCA: antineutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis; BVASv.3: Birmingham Vasculitis Activity Score version 3; ESR: erythrocyte sedimentation rate; FFS: Five Factor Score; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic GPA; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PR3: proteinase 3; IQR: interquartile range; SEM: standard error of the mean.

significant decrease of the total cumulative CYC dose (Figure 1).

As maintenance therapy, azathioprine was given to 37/132 (28%) patients, mycophenolate mofetil to 20 (15%) and MTX to 10 (8%). Trimethoprim/sulfamethoxazole (TMP-SX) was administered to 81 (61%) patients as a prophylaxis of *Pneumocystis jirovecci* pneumonia (PJP; 800/160 mg on alternate days) or adjunctive therapy on those patients who were nasal carriers of *Staphylococcus aureus* (800/160 mg twice daily). Biological therapy was used in 10 (8%) patients, mainly rituximab, in most cases as a rescue therapy; 1 patient received etanercept. Dialysis was needed in 25 (19%) patients.

Relapses. A total of 122 patients were eligible to be analyzed, owing to lack of complete data in 10 patients. Among them, 76/122 (62%) presented 1 or more relapses of the disease during the followup: 34/76 (45%) patients with GPA, 24 (31%) with MPA, and 18 (24%) with EGPA. The mean relapse rate was 1.74 with a maximum of 17 relapses in a patient with GPA. The most relapsing subset of AAV was

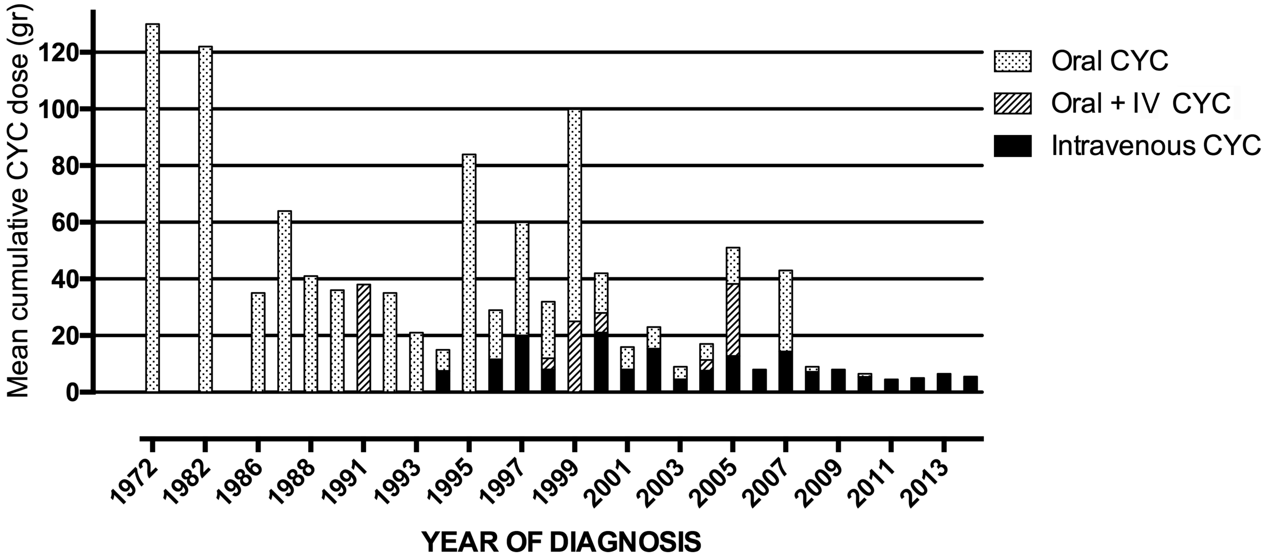

Figure 1. Percentage of patients treated with oral or intravenous CYC and total cumulative dose of CYC according to the year of diagnosis. CYC: cyclophosphamide; IV: intravenous.

GPA, with a mean relapse rate of 2.1 ± 0.4 per patient, followed by EGPA (2.0 ± 0.4) and MPA (1.2 ± 0.2). Patients with ENT involvement at the time of diagnosis presented more relapses than those without (2.23 ± 0.37 vs 1.25 ± 0.19; p = 0.02). Patients with PR3-ANCA had more relapses than those with MPO-ANCA, although no statistical significance was reached (2.3 ± 0.5 vs 1.4 ± 0.2; p = 0.09; data not shown).

BVAS and FFS were not useful for differentiating relapsing from nonrelapsing patients.

Infections. Five patients showed positive serology for hepatitis C virus, with negative RNA. No cases for hepatitis B virus (HBV) anti-core antibody, surface antigen HBV, or human immunodeficiency virus were detected.

A total of 300 major infections occurred in 79/132 (60%) patients during the followup. Thirty-two (24%) patients had 2 or more infections. Infections were more frequently located in the lower respiratory tract (64%), followed by the urinary (11%) and gastrointestinal (8%) tract, soft tissues (6%), and central nervous system (0.3%). Among patients with septicemia (9%), 10 (39%) had a device-related infection (9 catheter sepsis and 1 pacemaker infection), 5 (20%) had urinary tract infections, 3 (12%) abdominal tract infections, and 2 (8%) respiratory tract infections. In 6 (23%) cases, the origin of bacteremia was unknown.

Bacterial etiology was suspected in 255 cases (85%): 113 (44%) acute bronchitis, 62 (24%) pneumonia, 31 (12%) urinary tract infections, 26 (10%) sepsis/bacteremia, and 23 (9%) gastrointestinal tract infections. The pathogen was identified in 142 cases. Viral infection was confirmed in 24 cases, fungal infection in 16, parasite infections in 3, and mycobacterial infections in 3. Seventeen cases of herpes zoster were reported during the followup.

A total of 22 (7.3%) infections were considered opportunistic: 14 systemic mycosis, 3 cytomegalovirus pneumonitis, 3 pulmonary mycobacterial infections, and 2 leishmaniasis. Ten (45.5%) opportunistic infections took place during the first year of diagnosis. Twelve (54.5%) appeared while patients were under CYC treatment and 6 (27.3%) while patients were under CS maintenance therapy. All infection-related data are summarized in the Supplementary Table 3 (available with the online version of this article).

No differences in the infection rate were observed between the different AAV subtypes. Bacterial infections were significantly related to a BVASv.3 > 15 at the disease onset (OR 2.35, 95% CI 1.14–4.76; p = 0.021), a total cumulative CYC dose > 8.65 g (OR 2.67, 95% CI 1.15–4.82; p = 0.008), dialysis requirement (OR 3.07, 95% CI 1.07–8.79; p = 0.04), and development of leukopenia during the followup (OR 2.63, 95% CI 1.23–5.64; p = 0.016).

Opportunistic infections were only significantly related to the presence of leukopenia during the followup (OR 4.31, 95% CI 1.43–12.98; p = 0.006), and leukopenia was significantly related to the mean total cumulative CYC dose (43.3 ± 5.4 g vs 14.1 ± 3.0 g; p < 0.001) and to dialysis requirement (OR 5.5, 95% CI 2.00–15.09; p < 0.001; Supplementary Figure 3, available with the online version of this article).

Outcome. A total of 44 (33%) deaths were registered: 25 (57%) MPA, 11 (25%) GPA, and 8 (18%) EGPA. The mean time to death was 105 ± 14 months. Mortality was higher in patients with MPA than in those with GPA or EGPA (OR 2.97, 95% CI 1.41–6.29; p = 0.005), and in patients with MPO-ANCA compared to those with PR3-ANCA or negative ANCA (OR 2.24, 95% CI 1.05–4.79; p = 0.042; Table 2).

Table 2. Factors associated with increased mortality.

Factors	Nonsurvivors, %	Survivors, %	Univariate Analysis OR	95% CI	p	Multivariate Analysis OR	95% CI	p
Age at diagnosis > 65 yrs	50.0	25.0	3.00	1.40–6.43	0.006	6.78	1.44–31.99	0.016
MPA	56.8	30.6	2.97	1.41–6.29	0.005			
BVASv.3 > 15	72.7	50.0	2.67	1.22–5.84	0.015			
ENT involvement at diagnosis	31.8	54.5	0.39	0.18–0.83	0.016			
Renal failure at diagnosis	59.1	39.7	2.18	1.05–4.57	0.043			
Necrotizing glomerulonephritis	51.2	28.4	2.64	1.24–5.62	0.013			
Bacterial infections	81.8	50.0	4.50	1.88–10.77	0.001			
Pneumonia	45.4	22.7	2.83	1.30–6.15	0.009			
Urinary tract infection	31.8	10.2	4.09	1.60–10.45	0.006			
Sepsis	43.2	4.5	15.95	4.96–51.27	< 0.001	13.06	1.49–114.03	0.020
Opportunistic infections	27.3	9.1	3.75	1.40–10.03	0.009	7.08	1.25–40.18	0.027
Leukopenia	62.8	32.1	3.56	1.65–7.69	0.001			
Pancytopenia	16.3	1.3	15.17	1.78–127.9	< 0.001			
Creatinine > 2 mg/dl	47.7	19.3	3.81	1.72–8.43	0.001	14.86	1.44–153.58	0.024
MPO-ANCA	68.1	48.9	2.24	1.05–4.79	0.042			
Accumulative dosage of CYC > 12.75 g	63.6	36.4	3.06	1.44–6.50	0.005	7.70	1.57–37.77	0.012
TMP-SX	48.8	69.0	0.43	0.20–0.91	0.034			
Dialysis	39.5	9.1	6.54	2.53–16.90	< 0.001			

ANCA: antineutrophil cytoplasmic antibodies; BVASv.3: Birmingham Vasculitis Activity Score version 3; CYC: cyclophosphamide; MPA: microscopic polyangiitis; MPO: myeloperoxidase; TMP-SX: trimethoprim/sulfamethoxazole.

Regarding the causes of death, infection was present in 15 (34%) patients, a combination of active disease and infection in 7 (16%), cardiovascular cause in 7 (16%), uncontrolled vasculitis in 6 (14%), respiratory failure in 4 (9%), and neoplasm in 3 (7%) patients. In 2 cases, the cause of death was unknown. Seven patients (16%) died at an early stage of the disease (≤ 12 mos), while 37 died at a late stage (> 12 mos). Major causes of death in each period are summarized in Supplementary Table 4 (available with the online version of this article). Patients who had a severe infection had an increased mortality from any cause (45% vs 15.4%; HR 3.174, 95% CI 1.205–8.367; p = 0.019; Figure 2). Table 2 shows the risk factors that were associated with death.

Survivors at the end of followup were younger than nonsurvivors (50.2 ± 1.8 vs 64.0 ± 2.2; p < 0.001), had lower BVASv.3 (15.2 ± 0.7 vs 18.4 ± 1; p = 0.011), lower 2009 FFS

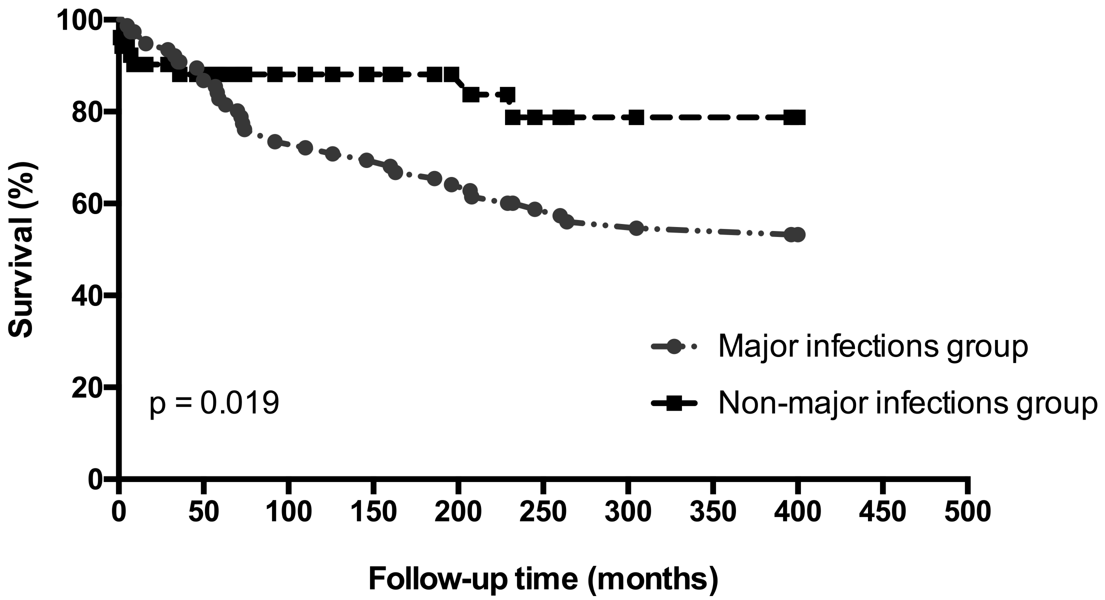

Figure 2. Longterm survival according to major infections. Kaplan–Meier survival analysis (n = 132) comparing patients with and without major infections.

(1.1 ± 0.1 vs 1.8 ± 0.2; p < 0.001) and lower creatinine levels (1.9 ± 0.2 vs 2.6 ± 0.4; p = 0.032) at diagnosis, and a lower rate of infections during the followup (1.3 ± 0.2 vs 2.7 ± 0.4; p < 0.001). Multivariable analysis showed these independent factors related to mortality: age > 65 years and creatinine > 2 mg/dl at diagnosis, sepsis, opportunistic infections, and a total cumulative CYC dose > 12.75 g (Table 2).

DISCUSSION

Although the diagnosis and management of AAV has clearly improved over the last few years, AAV mortality remains significant, not only because of the disease activity but also because of the treatment-related side effects. This study describes the largest cohort of patients from a single center in Spain, to our knowledge, and focuses on the role that major infections play on all-cause mortality.

Epidemiological data and clinical features at diagnosis were similar in our patients to those described in the main European series[8,19,20,21,22]. Major infections were registered in 60% of cases during the followup, a rate clearly superior to that reported in other larger cohorts (26–46%)[21,22,23,24], probably owing to the longterm followup in our cohort and the inclusion criteria (IV treatment for at least 24 h). Similarly described by other authors[10,25], the respiratory tract was the main source of infection (64% of cases), followed by the urinary tract, and sepsis due to vascular catheters used for IV treatment or renal replacement therapy. Bacterial infections were the most frequent cause of infection in our patients, in line with other series[21,22]. The percentage of opportunistic infections, mainly fungal pneumonia, was lower than in other studies[23,25]. PJP was reported in only 2% of cases compared to other series (1–37.5%)[23,26]. This was probably due to our center's routine use of TMP-SX as prophylactic treatment in patients with sustained lymphocyte count $< 1.00 \times 10^9$ cells/l and in all patients with GPA, confirming its efficacy. After 2001, according to the international recommendations for AAV management[18], patients were progressively treated with CYC pulses instead of oral CYC, with a significant decrease in the total cumulative CYC dose and a significant reduction in the infection rate; our data were similar to those previously reported in the literature[3,22].

In our cohort, factors associated with major infections were BVASv.3 > 15 at diagnosis, total cumulative CYC dose > 8.65 g, dialysis requirement, and development of leukopenia during the followup. Our findings suggest that both the need for more intensive immunosuppressive regimens in patients with severe renal or systemic disease, and the need for longer treatments in patients with persistent active disease, are related to a higher rate of infections. A greater percentage of infections has been described in patients treated with high total cumulative CYC dose[22,27], and also during the earliest phase of immunosuppressive treatment[10,21,24,28]. Leukopenia has also been reported in the literature as a surrogate marker of immunosuppression, especially related to an increased risk of sepsis[10,22,29]. Similarly, renal dysfunction has been linked to an increased risk of infections through multiple pathways, including direct impairment of immune function[28]. Moreover, in patients with renal failure, a decreased clearance of the immunosuppressant drugs could lead to an increased drug exposure and a higher toxicity[30]. Finally, the more active disease, the more extensive the organ damage, which could contribute to permanent longterm sequelae such as lung cavities, which may predispose to infections.

Regarding opportunistic infections, the only factor significantly related to its development in our present study was the presence of leukopenia during the followup. Leukopenia was more frequent in patients with high total cumulative CYC dose and in those who required renal replacement therapy, similar to bacterial infections. It is worth noting that almost 50% of all opportunistic infections took place in the first year of diagnosis. Moreover, up to 82% of all cases occurred while patients were under immunosuppressant drugs therapy or CS treatment, although 18% appeared in patients who were not receiving immunosuppressant drugs at the time of infection but who had received a high immunosuppressant load. Leukopenia due to immunosuppressant therapy has already been reported as a risk factor for opportunistic infections in other studies[10,22,29].

In our series, mortality was clearly related to the disease activity and to the presence of major infections, and the strong association between both hampered elucidations of which of the 2 causes was the main factor in some cases. In 34% of all patients who died, infection was considered the main factor and a contributing factor in 16% of the remaining patients. Patients who had a major infection showed a higher mortality rate from any cause than those who never had infections (45% vs 15.4%). Multivariate analysis identified sepsis (OR 13.06, 95% CI 1.49–114.03) and opportunistic infections (OR 7.08, 95% CI 1.57–40.18) as independent factors related to death.

Other factors related to death in our series were age > 65 years at diagnosis, severe renal failure, and total cumulative CYC dose > 12.75 g. Age older than 60 years at the time of AAV diagnosis has been previously identified as a poor prognostic factor[8,9,20,22,29,31–34], probably owing to a greater comorbidity and an increased risk of adverse events and drug intolerance. Decline of eGFR[8,9,25,29,33–38] and renal replacement therapy requirement[33] have been both related to a poor outcome due to a higher risk of infections and treatment toxicity, in line with our results. Finally, morbi-mortality related to high total cumulative CYC dose has been extensively described[22]. No significant relationship between BVASv.3 at diagnosis and disease outcome was found in our study, although it has been described by other authors, suggesting a link between the disease severity at baseline and mortality[8,22,34]. Regarding the AAV subtype, MPA was found to have the worst prognosis compared to the other subsets[8,9,39], probably owing to the more severe renal involvement and the older age of patients at the disease diagnosis[8], as previously suggested. ENT involvement was found to be a protective factor, in agreement with several studies[20,22,32,36], probably because of its predominance in limited or granulomatous forms of GPA, which tend to show less severe renal involvement, mild lung involvement, and better outcome compared to the vasculitic forms[32,40].

The 1- and 5-year survival rates in our cohort were 94.7% and 85.6%, respectively, quite similar to those reported by other authors[4,8,20,36]. The early mortality (< 12 mos) accounted for 16% of all deaths, and was related to a combination of disease activity/infections in up to 57% of all the patients who died. The late mortality was also related to infections and disease activity, with a 59% contribution in all the patients who died. However, a significant increase of cardiovascular causes was observed at this stage, being the main factor in up to 16% of deaths. This could reflect an increased burden on cardiovascular risk associated to inflammation and treatments, as suggested in previous studies[8,9,41]. Malignancies also arose as a late cause of death in 8% of cases. An increased risk of neoplasms, especially for leukemia, urinary bladder, and skin malignancies, has been described in patients with AAV[8,42,43].

The present study has several limitations derived from the retrospective features of the analysis because of the inevitable loss of information, and the possible underestimation of the activity scores. Likewise, the primary cause of death was difficult to elucidate in some cases as a result of the concomitant existence of multiple factors such as disease activity and infection. However, to our knowledge, this is the largest single-center study from a Spanish cohort, compiling detailed information about major infections in patients with AAV and its influence on the patient's outcome.

Although active disease still remains one of the main causes of death in patients with AAV, especially in the first months of followup, infectious events play a key role in the prognosis throughout the disease course. Therefore, it is important to identify predisposing factors such as intensive immunosuppressant treatment, severe renal dysfunction, and leukopenia, and to stratify treatment according to the disease severity, seeking a balance between the risk of relapses and/or persistent activity and the risk of unwanted treatment side effects. New therapies may help reduce the total cumulative CYC dose and the total CS dosage, both clearly related to infectious events. Strategies for preventing infection by the most common pathogens (removal of nonessential intravascular catheters placement, etc.) might also help to reduce the incidence of severe infections. Prophylaxis with TMP-SX must be used to prevent PJP in immunosuppressed patients.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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