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Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) enrolled in two prospective trials

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ABSTRACT

The purpose of this study was to assess the outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (EGPA) enrolled in 2 prospective, randomized, open-label clinical trials (1994–2005), with or without Five-Factor Score (FFS)-defined poor-prognosis factors, focusing on survival, disease-free survival, relapses, clinical and laboratory findings, therapeutic responses, and factors predictive of relapse. Forty-four patients with FFS ≥ 1 were assigned to receive 6 or 12 cyclophosphamide pulses plus corticosteroids and the seventy-four with FFS $= 0$ received corticosteroids alone, with immunosuppressant adjunction when corticosteroids failed. Patients were followed (2005–2011) under routine clinical care in an extended study and data were recorded prospectively. Mean $\pm$ SD follow-up was 81.3 $\pm$ 39.6 months. Among the 118 patients studied, 29% achieved long-term remission and 10% died. Among the 115 patients achieving a first remission, 41% experienced $\geq$1 relapses, 26.1 $\pm$ 26.8 months after treatment onset, with 57% of relapses occurring when corticosteroid-tapering reached $<$10 mg/day. Treatment achieved new remissions in $>$90%, but relapses recurred in 38%. Overall survival was good, reaching 90% at 7 years, regardless of baseline severity. Age $\geq$65 years was the only factor associated with a higher risk of death during follow-up. The risk of relapse was higher for patients with anti-myeloperoxidase antibodies and lower for those with $>$3000 eosinophils/mm^3. Sequelae remained frequent, usually chronic asthma and peripheral neuropathy. In conclusion, EGPA patients' survival rate is very good when treatment is stratified according to the baseline FFS. Relapses are frequent, especially in patients with anti-myeloperoxidase antibodies and baseline eosinophilia $<$3000/mm^3.

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1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss syndrome), a rare eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small-to-medium–sized vessels, is associated with asthma and eosinophilia [1]. Extrapulmonary manifestations can be serious and life-threatening when heart, central nervous system (CNS), gastrointestinal tract and/or kidneys are affected. EGPA is associated with antineutrophil cytoplasm antibodies (ANCA) in $<$40% of the patients [2,3]. The majority of ANCA-positive patients have a perinuclear (p-ANCA) fluorescence pattern and their IgG recognize myeloperoxidase (MPO), as assessed by enzyme-linked immunosorbent assay (ELISA). ANCA status distinguishes between 2 EGPA phenotypes: positive patients more frequently suffer from renal disease, peripheral nervous system involvement and/or alveolar hemorrhage, while ANCA-negative patients have more common cardiac involvement, lung infiltrate(s) and/or systemic manifestations [2–5]. Despite treatment efficacy, relapses remain frequent and treatment has to be reinitiated or intensified. However, no prospective studies have assessed long-term EGPA outcomes and data are lacking on relapses, and their risk factors and outcomes [4].

Between 1994 and 2005, the French Vasculitis Study Group (FVSG) conducted 2 randomized–controlled, investigator-initiated

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trials on EGPA patients [6,7] that validated therapeutic strategies based on the baseline Five-Factor Score (FFS) [8,9]. For patients without poor-prognosis factors (1996 FFS = 0), corticosteroids (CS) alone, as induction and maintenance therapy, was evaluated in the CHUSPAN study, which found an excellent 5-year survival rate of 92% [7], further validating the FFS. However, only 56% of the patients achieved complete remission, and one-third (35%) eventually required immunosuppressant(s) (IS), 17% because CS alone failed and 25% because of relapse(s) [7]. Among CHUSPAN-study patients with at least 1 poor-prognosis factor (1996 FFS $\geq$ 1), 88% achieved remission with pulse cyclophosphamide (CYC) and CS [6]. However, without maintenance therapy, their relapse rates were high, 86% or 74%, respectively for those who had received 6 or 12 CYC pulses. Furthermore, CS use was prolonged, with 81% of the patients still taking low doses for asthma and relapse prevention at the last follow-up visit. Nevertheless, 5-year overall survival reached 97% [6].

Herein, we analyzed the long-term follow-up of a large cohort of prospectively followed EGPA patients, who had received homogenous therapeutic interventions. The outcomes of the 118 EGPA patients, with or without poor-prognosis factors, enrolled in 2 prospective clinical trials [6,7] were examined, focusing on survival, disease-free survival, relapses, their clinical and laboratory findings, therapeutic responses, relapse outcomes and factors predictive of high risk of relapse.

2. Patients and methods

2.1. Patient population

Patients included in this study were treated in France, Belgium, and the UK. The Institutional Review Board (Comité Consultatif pour la Protection des Personnes Participant à la Recherche Biomédicale) of the Hospices Civiles de Lyon approved the protocols (of both initial trials), which were conducted in accordance with the Declaration of Helsinki. Each participant gave signed informed consent. All the patients had EGPA satisfying the classification criteria established by the American College of Rheumatology [10] and/or the revised Chapel Hill Consensus Conference Nomenclature for vasculitides [1].

Once the diagnosis was confirmed, based on histology and/or clinical findings, patients were stratified according to the presence or absence of 1996 FFS-defined prognosis factors [8]: serum creatinine >140 μmol/L, proteinuria >1 g/day, severe gastrointestinal tract involvement, cardiomyopathy and/or CNS involvement, with each item present accorded 1 point. The FFS determined at diagnosis was validated to predict overall mortality due to EGPA [8]. Patients with FFS $\geq$ 1 were assigned to receive 6 or 12 CYC pulses in combination with CS and patients with FFS = 0 were prescribed CS alone and received IS only when steroids failed to achieve or maintain remission, as previously reported [6,7].

2.2. Data collection

Clinical reports, recorded on standardized report forms and filled in by the treating physician, were obtained prospectively. Pathologists provided histologic reports and slides were reviewed when necessary. All data were entered into a computerized databank. From 2005 through 2011, patients were routinely monitored in an extended follow-up study with data on relapses, treatments, sequelae and vital status. Patients were assessed at baseline and during follow-up for EGPA manifestations in each organ system using the validated 2003 Birmingham Vasculitis Activity Score (BVAS) [11,12].

Every patient's serum was tested for ANCA-positivity by indirect immunofluorescence, on ethanol-fixed neutrophils with sera diluted 1/16, according to EUVAS recommendations [13]. When ANCA were detected, enzyme-linked immunosorbent assay (ELISA) determination of their specificity (anti-MPO or proteinase-3 [PR3]) was recommended but not mandatory. ANCA were sought at diagnosis before starting treatment. When ANCA were initially positive, trial protocols specified that they be checked at each subsequent visit. Thereafter, ANCA were tested when the treating physician thought it necessary. ANCA were routinely tested in the Immunology Department of each participating hospital using commercially available tests. In France, the reproducibility and specificity of biologic and immunologic tests are guaranteed by a Ministry of Health commission. Some routine biologic analyses (complete blood counts, creatininemia, electrolytes, proteinuria, hematuria, transaminases) and chest X-ray were performed at entry and at each visit as specified by the protocol. Electrocardiogram was compulsory at entry but was optional thereafter. When indicated by clinical manifestations, the treating physician could order more specific investigations (echocardiography, catheterization).

2.3. Definitions

Remission was defined as the absence of disease activity attributable to EGPA vasculitis manifestations (parenchymal lung disease, peripheral nerve involvement, skin, cardiac, renal and/or gastrointestinal signs) for $\geq$3 consecutive months, corresponding to BVAS = 0, not requiring being off or on a specified CS dose when it was pursued for isolated asthma, sinusitis or rhinitis [14]. Failure was defined as the absence of clinical remission, occurrence of new vasculitis manifestation(s) or death while receiving treatment [14]. Relapses were predefined as the recurrence, worsening or appearance of new clinical EGPA manifestation(s), following a $\geq$3-month period of remission, and requiring IS addition or change and/or CS reinstitution or dose intensification more than twice the previous dose and >30 mg/day [14]. Major and minor relapses were distinguished. The former corresponded to the recurrence or new appearance of major organ involvement, e.g. the following, if attributable to active vasculitis: 1) 30% increase of serum creatinine level or 25% decrease of glomerular filtration rate within 3 months or histologic evidence of focal necrotizing glomerulonephritis; 2) clinical, radiologic or bronchoscopic evidence of pulmonary hemorrhage (pulmonary infiltrates were not considered severe manifestations); 3) vision threat related to retinal vasculitis; 4) new multifocal neurologic lesions or mononeuritis multiplex; 5) gastrointestinal hemorrhage or perforation; and 6) other manifestations included in the 1996 FFS: proteinuria (>1 g/day), cardiomyopathy and/or CNS involvement [8,14,15].

Eosinophil-count increases, without any other clinical EGPA manifestations; isolated asthma, sinusitis or rhinitis exacerbations, with or without concomitant eosinophil-count rise; or mild clinical EGPA manifestations that only required CS-dose increase of less than twice the previous one, or <30 mg/day without IS prescription, were recorded but not considered failures, or recurrent EGPA manifestations or relapse *per se*, and were registered as therapeutic adjustment(s) and analyzed separately.

All causes of deaths were recorded. Data were censored at the time of death or last follow-up visit, whichever occurred first.

For each event (failure, relapse, therapeutic adjustment), clinical signs (BVAS items), biologic parameters (eosinophil count and ANCA when available), treatment being taken when relapse occurred, treatment started thereafter and its outcomes were collected. BVAS was calculated at the time of each event. Sequelae were evaluated with the Vasculitis Damage Index (VDI) [16], calculated at each follow-up visit and then retrospectively based on mail updates.

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2.4. Statistical analyses

Data are expressed as means ± SD for continuous variables and no. (%) for categorical variables. Statistical analyses were computed using SAS v9.3 software (SAS Institute). Student's *t*-test and chi-square test were used, when appropriate. For all statistical analyses, a 2-tailed $P \leq 0.05$ was considered significant.

Times to relapse, death or any event were calculated from treatment onset. Kaplan–Meier curves were plotted using SPSS v19 software, and their differences were evaluated using the log-rank test. Disease-free survival was calculated as the time from treatment onset to relapse, failure or death, whichever occurred first.

A multivariate Cox regression model with backward selection of variables (exit threshold: $P < 0.1$) was used to identify baseline variables independently associated with relapse. Candidate variables were selected from among clinically relevant patient and disease characteristics (phenotype and severity), FFS and all nonredundant variables with $P \leq 0.2$ in the univariate survival analysis.

3. Results

3.1. Baseline characteristics

Among the 122 EGPA patients included in these 2 prospective trials [6,7], 4 were excluded from the analysis because of missing follow-up data (Fig. 1). After receiving the protocol-assigned treatment regimen, 108/118 patients achieved remission; 10 (9%, 5 without and 5 with poor-prognosis factors) patients required second- or third-line therapy before 7 of them (5 without and 2 with poor-prognosis factors) achieved remission. Hence, 115/118 (97%) patients achieved remission; the remaining 3 (3%) died before remission could be obtained.

The demographic, clinical, laboratory and therapeutic characteristics of the 118 EGPA patients, stratified according to their 1996 FFS are summarized in Table 1. Among them, 74 (63%) had FFS = 0 and 44 (37%) FFS ≥ 1. The mean follow-up (81.3 ± 39.6 months) was comparable for the 2 patient groups. As expected, BVAS was significantly higher for the FFS ≥ 1 group. FFS = 0 patients more frequently had preexisting asthma and/or sinusitis. Although eosinophil counts rose to 8231 ± 7068/mm^3, they did not differ between patient groups. ANCA were detected in 41% of the patients, with comparable percentages in the 2 groups. ANCA were predominantly directed against MPO (71%), with 4% directed against PR3 and 25% having no specificity. All patients with FFS ≥ 1 received CS and intravenous CYC as specified in the protocol. After first-line therapy, 108 patients (92%) entered remission with no significant difference between FFS groups. During follow-up, 34/118 (29%) achieved long-term remission without relapse or therapeutic adjustment(s) and 12 (10%) died.

3.2. Relapses

Among the 115 patients achieving first remissions, 47 (41%) experienced ≥1 relapse(s) that occurred a mean of 26.1 ± 26.8 months after treatment onset (Table 2). Relapsers came equally from the 2 groups: 62% had been treated for good-prognosis EGPA. These first relapses were severe for 26/47 (55%) patients manifesting as neurologic flares in 20/26 (77%). Fourteen (30%, half in each group) patients had ≥1 therapeutic adjustment(s) before

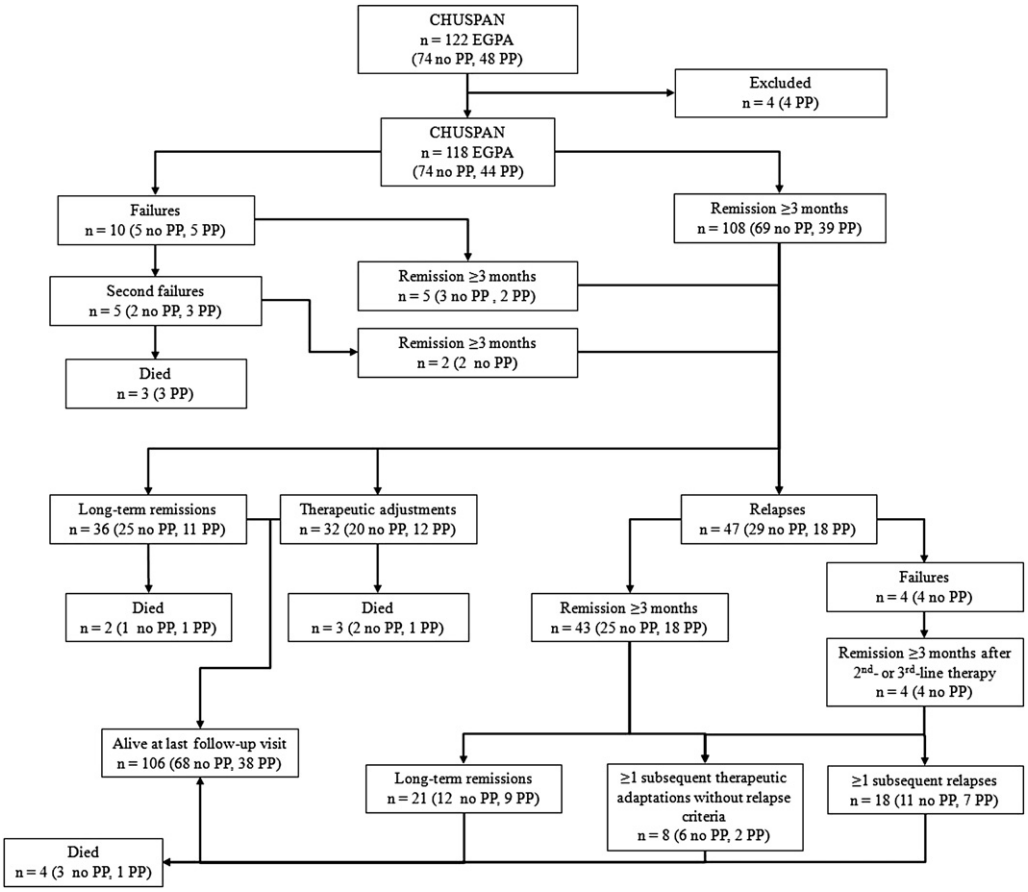

Fig. 1. Flow chart of the study. PP = poor-prognosis factors at baseline (FFS ≥ 1). No PP = no poor-prognosis factors at baseline (FFS = 0).

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Table 1
Characteristics of EGPA patients at diagnosis.

Characteristic	All ($n = 118$)	FFS = 0 ($n = 74$)	FFS ≥ 1 ($n = 44$)	P[a]
Demography				
Age, mean ± SD (years)	51.9 ± 14.7	52.1 ± 14.4	51.7 ± 15.4	0.89
Sex (M/F)	64/54	39/35	25/19	0.66
Medical history, no. (%)				
Asthma	106 (90)	70 (95)	36 (82)	0.026
Oral corticosteroids for asthma	31 (26)	21 (28)	10 (23)	0.47
Sinusitis	37 (31)	29 (39)	8 (18)	0.013
Clinical presentation				
FFS, no. (%)				<0.001
0	74 (63)	74 (100)	–	
1	23 (19)	–	23 (52)	
2	17 (14)	–	17 (39)	
3	4 (3)	–	4 (9)	
BVAS, mean ± SD	21.8 ± 8.0	18.6 ± 6.2	27.3 ± 7.9	<0.001
General symptoms, no. (%)	101 (86)	62 (84)	39 (89)	0.47
Fever >38 °C	58 (49)	33 (45)	25 (57)	0.20
Weight loss	76 (64)	44 (59)	32 (73)	0.15
Myalgias	60 (51)	35 (47)	25 (57)	0.32
Arthralgias	38 (32)	27 (36)	11 (25)	0.20
Cutaneous symptoms, no. (%)	57 (48)	36 (49)	21 (48)	0.92
Subcutaneous nodules	14 (12)	10 (14)	4 (9)	0.47
Purpura	33 (28)	20 (27)	13 (30)	0.77
Urticaria	22 (19)	15 (20)	7 (16)	0.56
Livedo reticularis	6 (5)	3 (4)	3 (7)	0.51
ENT symptoms, no. (%)	88 (75)	56 (76)	32 (73)	0.72
Crusting	11 (9)	6 (8)	5 (11)	0.56
Sinusitis (CT scan)	80 (68)	51 (69)	29 (66)	0.74
Otitis	6 (5)	3 (4)	3 (7)	0.51
Pulmonary symptoms, no. (%)	116 (98)	73 (99)	43 (98)	0.71
Asthma	111 (94)	69 (93)	42 (95)	0.62
Pulmonary infiltrates	71 (60)	49 (66)	22 (50)	0.08
Pleuritis	22 (19)	11 (15)	11 (25)	0.17
Alveolar hemorrhage	6 (5)	3 (4)	3 (7)	0.51
Respiratory distress syndrome	5 (4)	3 (4)	2 (5)	0.90
Cardiac symptoms, no. (%)	45 (38)	15 (20)	30 (68)	<0.001
Pericarditis	29 (25)	11 (15)	18 (41)	0.001
Specific cardiomyopathy	26 (22)	0	26 (59)	<0.001
Gastrointestinal symptoms, no. (%)	34 (29)	12 (16)	22 (50)	<0.001
Abdominal pain	33 (28)	12 (16)	21 (48)	<0.001
Gastrointestinal hemorrhage	3 (3)	0	3 (7)	0.023
Cholecystitis	2 (2)	0	2 (5)	0.06
Intestinal infarction	1 (1)	0	1 (2)	0.19
Ischemic colitis	3 (3)	0	3 (7)	0.023
Renal involvement, no. (%)	32 (27)	10 (14)	22 (50)	<0.001
Proteinuria >0.2 g/day (1+)	24 (20)	6 (8)	18 (41)	<0.001
Hematuria >10 red cells/ml (1+)	18 (15)	5 (7)	13 (30)	<0.001
Neurologic symptoms, no. (%)	87 (74)	54 (73)	33 (75)	0.81
Mononeuritis multiplex	71 (60)	44 (59)	27 (61)	0.84
Distal polyneuropathy	14 (12)	8 (11)	6 (14)	0.65
CNS symptoms, no. (%)	6 (5)	0	6 (14)	0.001
Confusion	3 (3)	0	3 (7)	0.023
Ischemic lesions on MRI	3 (3)	0	3 (7)	0.023
Laboratory findings				
Eosinophil count, mean ± SD (/mm^3)	8231 ± 7068	8811 ± 7877	7255 ± 5388	0.25
Creatinine, mean ± SD (μmol/liter)	89.9 ± 35.8	81.7 ± 17.6	103.6 ± 51.4	0.001
125–249, no. (%)	8 (7)	0	8 (18)	<0.001
250–500, no. (%)	1 (1)	0	1 (2)	0.19
ANCA, no. (%)	48 (41)	29 (39)	19 (43)	0.67
Anti-MPO	34 (29)	19 (26)	15 (34)	0.33
Anti-PR3	2 (2)	2 (3)	0	0.27
Treatment at baseline, no. (%)				
Corticosteroid pulses (15 mg/kg)	77 (65)	46 (62)	31 (72)	0.19
Corticosteroids (1 mg/kg/day)	118 (100)	74 (100)	44 (100)	1
Cyclophosphamide pulses	44 (37)	–	44 (100)	<0.001
Outcome after first-line therapy				
Remission ≥3 months, no. (%)	108 (92)	69 (93)	39 (89)	0.38
Last follow-up visit				
Follow-up (months), mean ± SD	81.3 ± 39.6	81.3 ± 35.1	81.3 ± 46.6	1.00
Survival, no. (%)				0.34
Dead	12 (10)	6 (8)	6 (14)	
Alive	106 (90)	68 (92)	38 (86)	

[a] FFS = 0 versus FFS ≥ 1 EGPA (student's t-test or chi-square test). ANCA = antineutrophil cytoplasm antibodies; BVAS = Birmingham Vasculitis Activity Score; CNS = central nervous system; CT = computed tomography; EGPA = eosinophilic granulomatosis with polyangiitis; ENT = ear nose and throat; FFS = Five-Factor Score; MPO = myeloperoxidase; MRI = magnetic resonance imaging; PR3 = proteinase-3. Specific cardiomyopathy was defined as clinical cardiac symptoms (chest pain, cardiac insufficiency, dyspnea, heart rhythm disorders) that were EGPA-related after exclusion of other causes and anomalies detected on cardiac MRI or echocardiography.

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Table 2
Characteristics of the first 47 relapses in a cohort of 118 EGPA patients followed prospectively.

Characteristic	Value
Months after 1st treatment day (mean ± SD) [range]	26.1 ± 26.8 [5.8–124.9]
Treatment being taken at relapse	
CS + immunosuppressant, no. (%)	2 (4%)
CS, no. (%)	37 (79%)
CS dose <10 mg/day, no. (%)	27 (57%)
CS dose (mg/day), mean ± SD	10.9 ± 11.5
No treatment	10 (21%)
BVAS	
Mean ± SD [range]	9.5 ± 4.3 [3–19]
<6, no. (%)	8 (17%)
≥6 but <10, no. (%)	19 (40%)
≥10, no. (%)	20 (43%)
Clinical presentation, no. (%)	
General signs	22 (47%)
Fever ≥38°5C	6 (13%)
Weight loss	7 (15%)
Myalgias	13 (28%)
Arthralgias	8 (17%)
Skin lesions	9 (19%)
Purpura	4 (9%)
Livedo	1 (2%)
Urticaria	3 (6%)
ENT signs	18 (38%)
Rhinitis	11 (23%)
Bloody nasal discharge	2 (4%)
Sinusitis (CT scan)	14 (30%)
Otitis	3 (6%)
Pulmonary signs	38 (81%)
Asthma	35 (74%)
Lung infiltrates	9 (19%)
Pleuritis	2 (4%)
Alveolar hemorrhage	3 (6%)
Respiratory distress syndrome	1 (2%)
Cardiovascular signs	5 (11%)
Cardiomyopathy	1 (2%)
Pericarditis	5 (11%)
Gastrointestinal signs	6 (13%)
Abdominal pain	6 (13%)
Digestive hemorrhage, surgical abdomen	0
Renal symptoms	1 (2%)
Proteinuria >0.2 g/day (1+)	1 (2%)
Hematuria >10 red cells/ml (1+)	1 (2%)
Creatininemia >125 μmol/L	0
Neurologic signs	20 (43%)
Mononeuritis multiplex	17 (36%)
Distal polyneuropathy	2 (4%)
CNS involvement	1 (2%)
Confusion	1 (2%)
Ischemic lesions on MRI	1 (2%)
Laboratory findings	
Eosinophil count >500/mm^3, no. (%)	37/43 (86%)
Eosinophil count (/mm^3), mean ± SD	2170 ± 1622

BVAS = Birmingham Vasculitis Activity Score; CNS = Central nervous system; CS = corticosteroids; CT = computed tomography; ENT = ear nose and throat; MRI = magnetic resonance imaging.

relapsing. Only 2 (4%) patients with FFS ≥ 1 at baseline were still receiving IS and CS when they relapsed, whereas 27 (57%) were taking <10 mg/day of CS and 10 (21%) had stopped oral CS and IS, after respective means of 20.5 ± 15.3 and 12.2 ± 15.9 months before relapse. Clinical features of relapses are summarized in Table 2. Pulmonary symptoms predominated (81%), with 74% asthma flares and 19% pulmonary infiltrates. Ear, nose and throat (ENT) signs were present in 38%, essentially related to sinusitis. Mononeuritis multiplex, which occurred in 17 (36%) patients, was the main cause of severe relapse. Cardiomyopathy and CNS involvement were rarely observed (2% each), and neither renal failure nor severe gastrointestinal involvement occurred at the time of first relapse. Consequently, the mean BVAS was significantly lower than at baseline, respectively: 9.5 ± 4.3 versus 22.7 ± 4.4 ($P < 0.001$); 57% of the first relapses yielded BVAS < 10. Eosinophil counts were elevated during 37/43 (86%) relapses, with a mean count of 2170 ± 1622/mm^3.

Relapses required CS-dose increases for 43/47 (92%, 25 major and 18 minor relapses) patients and IS for 30/47 (64%, 19 major and 11 minor relapses): azathioprine (AZA) for 13, intravenous CYC for 11 or oral CYC for 6. New remissions were obtained in 43/47 (92%) patients but not in 4 (2 major and 2 minor relapses) patients who had received CS and IV CYC. Two of the latter achieved remission after receiving second-line therapy: oral CYC with plasma exchanges (PE) for 1 and oral CYC and intravenous immunoglobulins (IVIg) for the second. The 2 other patients failed to benefit from oral CYC for 1 and PE for the other; their successful third-line therapy consisted of mycophenolate mofetil (MMF) or oral CYC and IVIg, respectively. After relapse, 21/47 (45%) patients entered long-term remission, whereas 18/47 (38%) suffered ≥1 subsequent relapses, and 8/47 (17%, 6 without and 2 with poor-prognoses) experienced ≥1 subsequent therapeutic adjustments without any new relapse.

3.3. Therapeutic adjustments

Throughout follow-up, ≥1 therapeutic adjustment(s) without criteria of relapse were made for 32/115 (28%, 20 baseline FFS = 0, 12 FFS ≥ 1) patients. The first adjustment was required to treat isolated asthma and/or sinusitis in 25 (78%) patients or minor symptoms that resolved under oral CS (<30 mg/day) in 7 (22%). At the time of adjustment, 27 (89%) patients were still on CS and 19 (59%) with daily doses <10 mg/day. Eosinophil counts were >500/mm^3 for 29/32 (91%) patients, with a mean value of 9923 ± 7683/mm^3. Clinically, pulmonary symptoms were common: asthma (81%) and pulmonary infiltrate(s) (6%), as were ENT symptoms: rhinitis (47%), sinusitis (44%) and otitis (6%); myalgias and arthralgias were observed in 3% and 6%, respectively. Notably, no cutaneous, cardiac, digestive or neurologic manifestations were observed.

Table 3
Sequelae ($n = 115$).

Sequelae	No. (%)
Musculoskeletal	
Severe muscular atrophy	5 (4)
Osteoporosis/vertebral collapse	35 (30)
Avascular necrosis	4 (3)
Skin	
Cutaneous ulcers	2 (2)
Ocular	
Cataract	7 (6)
Optic nerve atrophy	4 (3)
ENT	
Hearing loss	4 (3)
Nasal blockage/chronic discharge	40 (35)
Chronic sinusitis	22 (19)
Pulmonary	
Chronic asthma	95 (83)
Chronic breathlessness	13 (11)
Impaired lung function	1 (1)
Cardiovascular	
Cardiomyopathy	16 (14)
Pericarditis >3 months	1 (1)
Diastolic BP > 95 mm Hg or antihypertensives needed	15 (13)
Renal	0
Neurologic	
Cerebrovascular accident	3 (3)
Peripheral neuropathy	52 (45)
Others	
Gonadal failure	6 (5)
Diabetes	7 (6)
Malignancy	6 (5)

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3.4. Causes of death

A total of 12/118 (10%, half from each group) patients died during follow-up, at a mean of 42.9 ± 37.2 [range: 2.6–108] months after starting treatment. Three poor-prognosis patients died before remission could be obtained: 2 from infectious complications (1 septic shock and 1 cytomegalovirus pneumonia) and 1 was severely debilitated with EGPA-related neurologic damage. Five patients (2 FFS = 0 and 3 FFS ≥ 1) died of EGPA-related causes: 2 infectious complications, 2 severe cardiomyopathies and 1 respiratory distress syndrome following methotrexate (MTX)-related toxicity. Four other patients, all FFS = 0 at baseline, died of causes unrelated to EGPA: 1 mesothelioma, 1 cerebral glioblastoma, 1 massive stroke and 1 severe cardiac insufficiency unrelated to EGPA.

3.5. Sequelae and last follow-up visit

The mean VDI score, calculated for the 115 patients who obtained ≥1 remission(s) was 3.1 ± 1.8 [range: 0–12]. Only 1 patient had VDI = 0. VDI was 1–4 for 99/115 (86%) patients. Details of sequelae are presented in Table 3. The most frequent residual damage was chronic asthma (83%), peripheral neuropathy (45%),

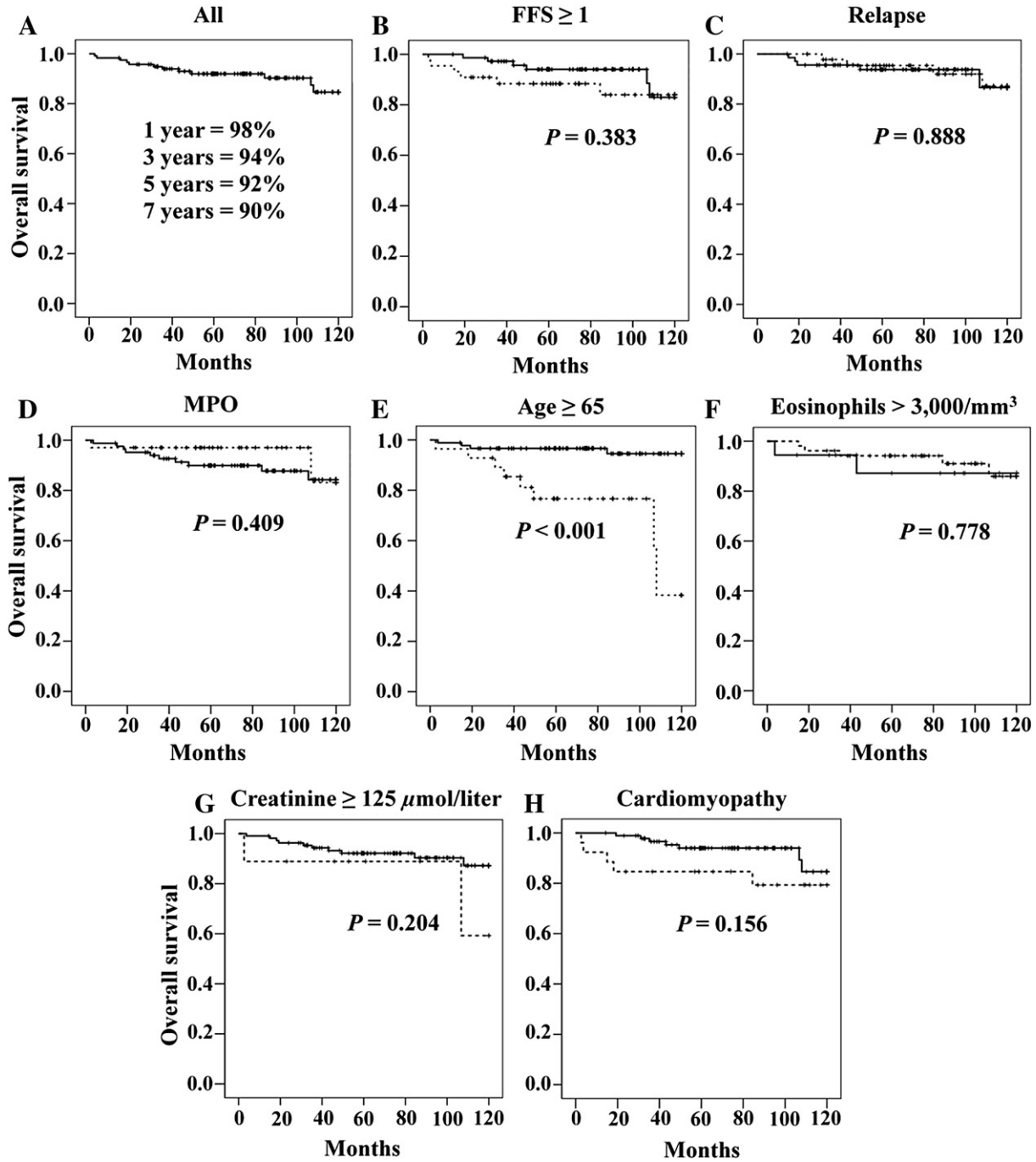

Fig. 2. Overall survival of 118 EGPA patients (A) and according to the presence (dashed lines) or absence (continuous lines) of poor-prognosis factors at baseline (FFS ≥ 1) (B), relapse during follow-up (C), anti-MPO ANCA-positivity (D); age ≥65 years (E); eosinophil count >3000/mm^3 (F), creatininemia ≥125 μmol/L (G) or cardiomyopathy (H) at baseline. *P* determined with log-rank tests. Data were censored after 120 months of follow-up.

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osteoporosis (30%), chronic rhinitis (35%) and chronic sinusitis (19%). Other CS-related sequelae were: hypertension (13%), diabetes (6%), cataract (6%) and optic nerve atrophy (3%). Six patients developed malignancies: 1 cerebral glioblastoma, 1 mesothelioma, 1 myelodysplasia, 1 patient had 2 cancers (colon adenocarcinoma and spinocellular skin carcinoma) and 2 high-grade colon dysplasias.

Among the 115 survivors that achieved remission, 94/115 (82%) were still receiving oral CS (mean dose: 10 ± 9 mg/daily) at the last follow-up visit; 27/115 (24%) were taking a combined IS: AZA for 17 (68%), MTX for 2 (8%), MMF for 3 (12%), oral CYC for 2 (8%), IVIg for 1 (4%) and omalizumab for 2 (8%).

3.6. Survival

Overall survival 1-, 3-, 5- and 7-year rates were: 98%, 94%, 92% and 90%, respectively (Fig. 2). Age ≥65 years was the only factor significantly associated with higher mortality ($P < 0.001$). Patients with baseline cardiomyopathy tended to have a lower survival rate. Survival rates did not differ significantly between patients without or with poor-prognosis EGPA, those who relapsed or not, MPO-positivity, eosinophil counts >3000/mm^3 or creatininemia ≥125 μmol/L at baseline (Fig. 2).

The majority of events (death, failure or relapse) considered for disease-free survival are shown in Fig. 3. Disease-free survival was significantly better for patients MPO-negative at baseline and, although those with baseline eosinophil counts >3000/mm^3 tended to fare better, the difference was not significant. Other factors, e.g. FFS and age ≥65 years had no impact on disease-free survival. For the EGPA poor-prognosis group, disease-free survival tended to be shorter for patients that had received 6 CYC pulses versus those given 12 pulses ($P = 0.092$) (not shown).

Relapse-free 6-month, and 1-, 3-, 5- and 7-year survival rates were 99%, 83%, 68%, 62% and 57%, respectively (Fig. 4A). The impact of all baseline variables given in Table 1 on the time to relapse was analyzed; the only clinical and biologic factors identified in our univariate analyses are shown in Fig. 4. Patients with baseline positive anti-MPO ANCA or rhinitis had higher risks of relapsing, unlike those with baseline eosinophil counts >3000 or pulmonary infiltrates.

Variables included in the multivariate analysis were: baseline FFS ≥ 1 (yes/no), eosinophil count >3000/mm^3 (yes/no), MPO-ANCA status (positive/negative), arthralgias (yes/no), ENT symptoms (yes/no), pulmonary infiltrates (yes/no), pleuritis (yes/no), proteinuria >0.2 g/day (yes/no) and neurologic symptoms (yes/no). Only 2 baseline factors were retained as being significantly associated with the risk of relapse: anti-MPO ANCA-positivity carried a higher risk (hazard ratio [HR] = 2.18; 95% confidence interval, 1.21–3.91; $P = 0.009$) and eosinophil count >3000/mm^3 a lower one (HR = 0.50; 95% confidence interval, 0.27–0.91; $P = 0.023$).

4. Discussion

The results of this study demonstrated good survival of a large cohort of EGPA patients enrolled in 2 clinical trials, regardless of their initial vasculitis severity, who were treated according to their FFS and prospectively followed for a mean of >80 months [6,7,17]. Moreover, the therapeutic strategy based on distinguishing between patients with baseline FFS = 0 or higher validated the prognostic value of this score and supported the accuracy of this approach adapted to EGPA severity, even after this long follow-up [5–7,18]. Overall survival was not affected by baseline anti-MPO–ANCA status, or eosinophil count, or the occurrence of relapses. Age ≥65 years, which was included in the revisited 2011 FFS [9], was the only factor that remained significantly associated with a higher risk of death during follow-up. This finding highlights the essential question of how to treat vasculitis in the elderly, especially the

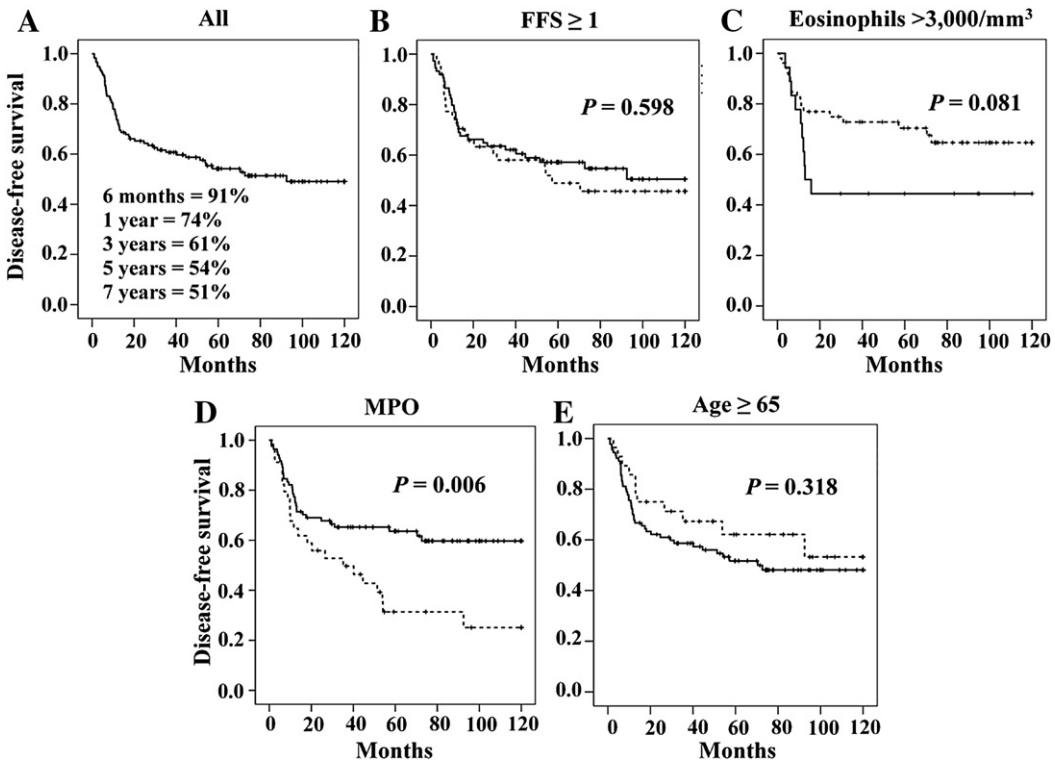

Fig. 3. Disease-free survival of all 118 EGPA (A) and according to the presence (dashed lines) or absence (continuous lines) of prognosis factors at baseline: FFS ≥ 1 (B), eosinophil count >3000/mm^3 (C), anti-MPO ANCA-positivity (D); age ≥65 years (E). *P* determined with log-rank tests. Data were.

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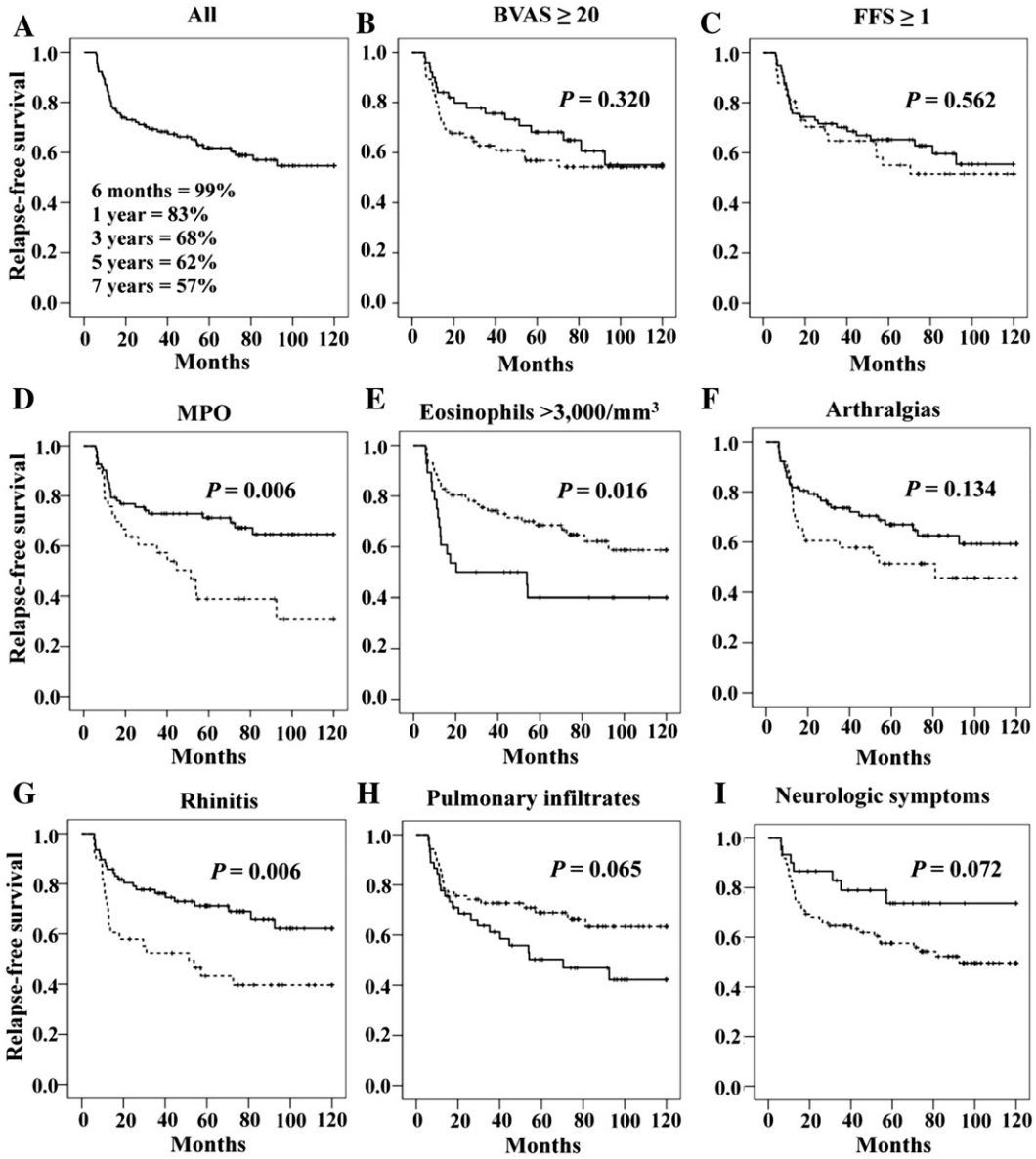

Fig. 4. Relapse-free survival of all 115 patients that entered remission (A), and according to the presence (dashed lines) or absence (continuous lines) of prognosis factors at baseline: BVAS ≥ 20 (B), FFS ≥ 1 (C), anti-MPO ANCA-positivity (D), eosinophil count >3000/mm^3 (E), arthralgias (F), rhinitis (G), pulmonary infiltrates (H) and neurologic symptoms (I). *P* determined with log-rank tests. Data were censored after 120 months of follow-up.

management of treatment-related toxicity, which was evaluated in the FVSG's CORTAGE trial [19].

During follow-up, 41% of the patients relapsed and their frequency did not reflect their initial vasculitis severity. Relapses occurred at a mean of 2 years after treatment onset, when IS had been stopped for almost all patients, most of whom were receiving <10 mg of CS/day. Pertinently, clinicians must monitor EGPA patients carefully once this CS level is reached and know that the vast majority of our patients were still taking low-dose CS at their last follow-up visit. Intriguingly, relapse severity, as assessed by BVAS, was always milder than the initial disease. The great majority of major relapses exhibited peripheral nervous system symptoms. Treatment reintroduction or intensification was able to achieve new remissions in >90% of the patients but 38% subsequently relapsed during follow-up. However, relapse did not impact survival, as overall survival was comparable for patients with or without ≥1 relapse(s).

The results of this prospective cohort study demonstrated that the risk of late relapse was significantly higher for anti-MPO ANCA-positive patients at diagnosis, whereas baseline eosinophil count >3000/mm^3 was associated with a lower risk of relapse. Those observations were confirmed by our disease-free survival analysis. Furthermore, they strongly support the current concept of distinguishing EGPA patients according to their ANCA status [2–5]. Such an impact of ANCA on relapses was previously reported for ANCA-associated vasculitides (AAV). In a recent study assessing 535 AAV (granulomatosis with polyangiitis [Wegener's] [GPA] and microscopic polyangiitis [MPA] but not EGPA), anti-PR3 ANCA and cardiovascular involvement were independently associated with higher risks of relapse, whereas creatininemia >200 μmol/L at diagnosis was strongly associated with a lower risk of relapse [20]. The association between anti-MPO ANCA-positivity and risk of EGPA relapse was also reported previously [4] but that study included only 38 patients, data had been collected retrospectively

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and no multivariate analysis was performed. The findings of another study focusing on anti-MPO AAV (MPA, GPA and EGPA) [21] showed that relapses were associated with MPO-antibody–titer increases for the majority of patients, with positivity having 90% predictive value for relapse. However, only 5 patients among the 38 with vasculitides studied had EGPA. In our study, ANCA levels were not systematically determined at each visit and before relapse, so that we were not able to confirm that observation.

Sinico et al. [3] assessed the clinical significance of ANCA in 93 EGPA patients, and found that 5-year survival and relapse rates were similar for both groups (91.8% and 46.3% for ANCA-positive patients versus 97.1% and 35.4% for ANCA-negative patients, respectively). However, their ANCA-positive patients were more likely to have received CYC. This difference between our analysis and that of Sinico et al. is likely due to the definition of relapses. Like us, Sinico et al. did not consider persistent asthma or an isolated eosinophilia rise relapses. However, they defined relapses as the occurrence or recurrence of a clinical manifestation attributable to EGPA, regardless of the treatment prescribed to treat this event, whereas we distinguished between relapses and therapeutic adjustments. This difference in relapse definitions and their shorter follow-up might explain why their ANCA-positive EGPA patients only tended to have a higher risk of relapse, without reaching significance [3].

To our knowledge, although the authors of several studies have described 2 distinct EGPA-patients phenotypes, based on ANCA status [2–5], the impact of this phenotype on outcome and especially the risk of relapse has never been demonstrated prospectively for a large cohort of EGPA patients.

Despite our patients' very good survival rate, residual damage remained frequent. Indeed, at the last follow-up visit, 83% suffered from chronic asthma and 35% from chronic rhinitis, so CS were still prescribed to >80% of our patients, resulting in high percentages of CS-related side effects, like osteoporosis, diabetes, hypertension and cataracts, all of which were probably underestimated herein because reporting them was not specified in the protocol. Furthermore, 45% had peripheral, severely handicapping neuropathy sequelae. Additional studies on EGPA patients are needed to define alternative therapeutic strategies to minimize the burden of damage induced by the vasculitis and its treatment.

Deaths were essentially caused by infectious complications under IS and/or CS. EGPA-related mortality was essentially cardiomyopathy-related, as previously reported [18]. However, detection of cardiomyopathy at baseline was not associated with a lower survival rate in our study, probably because of a lack of power, explained by the relatively few deaths (10%). Malignancies remained rare and, notably, no urinary tract carcinoma was observed.

The 2 main limitations of our study are the lack of continuous, routine ANCA determinations that prevented us from confirming their value to predict relapses, and the absence of maintenance IS therapy after CYC for poor-prognosis EGPA, which probably contributed to overestimation of the relapse rate for this group. The latter has become irrelevant, since all patients now receive maintenance therapy.

However, our study has several notable strengths: its prospective follow-up, the large number of patients included and its follow-up, which is one of the longest ever reported. Moreover, patients were treated uniformly, according to the therapeutic regimens of the clinical trials in which the patients had been enrolled. Patients without and with poor-prognosis EGPA were included in the analysis, thereby providing a representative spectrum of this vasculitis [2–5,7]. Finally, a predefined definition of relapses [14,15] was applied, allowing us to distinguish between real relapses and minor symptoms requiring only therapeutic adaptation, which probably correspond to different events reflecting different severities.

5. Conclusion

In summary, we prospectively confirmed that, after >80 months of follow-up, the therapeutic strategy distinguishing baseline EGPA severity as FFS = 0 or FFS ≥ 1 is accurate. Despite an excellent survival rate, relapses remain frequent, especially in patients with initial anti-MPO ANCA-positivity and eosinophilia <3000/mm^3.

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