Microscopic polyangiitis and non-HBV polyarteritis nodosa with poor-prognosis factors: 10-year results of the prospective CHUSPAN trial

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ABSTRACT

Objective. *To analyse the 10-year outcomes of 64 patients with non-HBV polyarteritis nodosa (PAN) or microscopic polyangiitis (MPA) and Five-Factor Score-defined poor-prognosis factors enrolled (1994-2000) in the prospective, randomised, open-label CHUSPAN trial.*

Methods. *The 64 patients were randomised to receive 12 (33: 23 MPA, 10 PAN) or 6 (31: 17 MPA, 14 PAN) cyclophosphamide (CYC) pulses combined with glucocorticoids. Ten-year follow-up of these patients included times to relapse(s), failure(s) and/or deaths calculated from treatment onset. Data were censored after 120 months of follow-up.*

Results. *Eleven patients were lost to follow-up (mean±SD follow-up: 61.9±35.2 months), with no between-group difference. As previously reported, baseline clinical characteristics and laboratory values were comparable for the 2 groups. After induction, 53/64 (83%) entered remission, with comparable percentages for both groups. The regimen was intensified for 11 initial non-responders: 4 achieved remission and 8 died before doing so. During extended follow-up, 26 patients experienced ≥1 relapse(s): 12 in the 12-pulse group and 14 in the 6-pulse group (p=0.47). At 10 years, overall and disease-free survival rates were 57.4% and 29.9%, with no between-group differences (p=0.185 and p=0.367, respectively). Factors associated with shorter disease-free survival were age ≥65 years and alveolar haemorrhage at diagnosis.*

Conclusion. *Although the 3-year CHUSPAN trial results indicated the superiority of 12 vs. 6 CYC pulses, that early advantage progressively declined and became non-significant by 10 years.*

Introduction

Polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA) are primary systemic vasculitides characterised by necrotising vessel-wall inflammation. Because they share several clinical features, they were formerly considered a single entity (1) and thus treated the same way, with the exception of hepatitis B virus-associated PAN (HBV-PAN) (2, 3) which also requires antiviral therapy. PAN and MPA were subsequently differentiated in the Chapel Hill Consensus Conference (CHCC) Nomenclature (4, 5), with regard to the different sizes of predominantly affected vessels and the detection of anti-neutrophil cytoplasm antibodies (ANCA). PAN is a medium-sized vessel systemic necrotising vasculitis not associated with ANCA (5, 6), whereas MPA is an ANCA-associated small-vessel vasculitis, usually with ANCA specific to anti-myeloperoxidase (MPO) (5, 7-9), and frequent glomerulonephritis and pulmonary capillaritis.

Thirty years ago, it was hypothesised that vasculitis severity should determine the therapeutic strategy rather than the type of vasculitis. The Five-Factor Score (FFS), in its original version (10) and revisited in 2011 (11), is able to predict patient mortality depending on the presence of poor-prognosis factors. The 1996 FFS version was validated in prospective trials to guide the treatment of vasculitides and we showed that severe PAN and MPA manifestations, as defined by 1996 FFS ≥1, require glucocorticoids (GC) combined with an immunosuppressant, usually cyclophosphamide (CYC) or rituximab for severe MPA (12-15). In contrast, 79% of vasculitides without severe manifestations (FFS=0) responded to GC alone (3). An immunosuppressant was only

added when GC failed or the disease relapsed, events affecting 40% (3) or 53%, respectively, after mean follow-up of 5 and 8 years (16).

The French Vasculitis Study Group (FVSG) designed the randomised, prospective, multicentre CHUSPAN trial to determine whether shorter CYC administration would be able to successfully induce and maintain remissions of PAN or MPA with ≥1 FFS-defined poor prognosis factor(s). The 12- and 6-pulse regimens were delivered over 10 and 4 months, respectively. Thereafter, patients received no immunosuppressive maintenance therapy, other than GC that was progressively tapered, as previously done for HBV-PAN (17). After 3 years, 86% of the patients had obtained remissions but 36% relapsed. Moreover, relapse-free and disease-free survival rates were better for patients who had received 12 CYC pulses (18). Given the importance of maintenance therapy in preventing systemic vasculitis relapses (12, 16, 19-21), it became necessary to determine whether or not the 12-pulse advantage over 6 infusions persisted in the long term. Herein, we report the 10-year results of this prospective clinical trial.

Materials and methods

Patient population

Patients in France and Belgium were first enrolled between January 1994 and April 2000 in the prospective, randomised-controlled CHUSPAN trial (3). The institutional review board (Comité Consultatif pour la Protection des Personnes Participant à une Recherche Biomédicale) of the Hospices Civils de Lyon approved the protocol. The study was conducted in accordance with the Declaration of Helsinki and each participant gave signed informed consent. Once the PAN or MPA diagnosis was confirmed, patients were stratified according to the presence or absence of 1996 FFS-defined poor-prognosis factors (10): serum creatinine >140 μmol/L, proteinuria >1 g/day, severe gastrointestinal tract involvement, cardiomyopathy and/or central nervous system (CNS) involvement; each item present was accorded 1 point. Only patients with baseline FFS ≥1 were included in the present analysis.

Treatment regimen at inclusion

All patients initially received 3 methylprednisolone pulses (15 mg/kg/day), followed by oral GC (1 mg/kg/day) that were progressively tapered (see (3) for details). They were randomised at a 1:1 ratio to receive either 12 or 6 CYC pulses that were administered every 2 weeks for 1 month, then every 4 weeks (3). Adjuvant treatments were compulsory: co-trimoxazole, potassium, calcium and vitamin D_3. At relapse, the treating physician was free to modify treatment and choose other immunosuppressants or different administration modalities.

Data collection

Clinical findings were prospectively recorded on standardised case-report forms by the treating physician. Pathologists provided histological reports and slides were reviewed when necessary. All data were entered into a computerised databank.

Every patient's serum was tested for ANCA by indirect immunofluorescence on ethanol-fixed neutrophils, according to EUVAS recommendations (22). When ANCA were detected, their specificity (anti-MPO or proteinase-3) was sought with enzyme-linked immunosorbent assays. Some routine laboratory analyses (complete blood counts, serum creatinine, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], proteinuria, haematuria) and chest x-ray were performed at entry and regularly, as specified by the protocol. When indicated by clinical manifestations, the treating physician could order specific investigations.

After the first CHUSPAN results were reported (3), patients were prospectively monitored routinely in this extended monitoring study (from 2005 through July 2014) until they had reached 10 years of follow-up. All information on relapses, treatments, vasculitis-induced damage and vital status was recorded. Each of their organ systems was assessed for disease activity with the validated 2003 Birmingham Vasculitis Activity Score (BVAS) (23, 24) and the Vasculitis Damage Index (VDI) for sequelae (25). All causes of death were entered. Data were censored at the time of death or after 10 years of follow-up, whichever occurred first. The revised 2012 CHCC Nomenclature was applied retrospectively to define PAN and MPA (5), meaning that ANCA-positivity is an MPA specificity and that these autoantibodies are mainly directed against MPO, while angiographically detected stenosis(es) and/or microaneurysm(s) are specific to PAN.

Definitions

Remission was defined as the absence of disease activity attributable to PAN or MPA manifestations for ≥3 consecutive months, corresponding to BVAS=0, not requiring being off or on a specified GC dose (26). Failure was defined as the absence of clinical remission, appearance of new vasculitis manifestation(s) or death before remission was achieved (26). Relapses were defined as the recurrence, worsening or appearance of new clinical PAN or MPA manifestation(s), following ≥3 months in remission (26). Major and minor relapses were distinguished. Major relapses corresponded to the recurrence or new appearance of major organ involvement, *e.g.* the following, if attributable to active vasculitis: 1) 30% serum creatinine level increase, 25% glomerular filtration rate decrease within 3 months or histological evidence of focal necrotising glomerulonephritis; 2) clinical, radiological or bronchoscopic evidence of alveolar haemorrhage; 3) threatened vision loss attributable to retinal vasculitis; 4) new multifocal neurological lesions or mononeuritis multiplex; 5) acute vasculitis-related limb ischaemia or gangrene; 6) gastrointestinal haemorrhage or perforation; and 7) other manifestations included in the 1996 FFS: proteinuria >1 g/day (if not considered a sequela), cardiomyopathy and/or CNS involvement (10, 26, 27).

Statistical analyses

Data are expressed as means±SD for continuous variables and number (%) for categorical variables. Statistical analyses were computed with SPSS v. 22 software. Student's *t*-tests were used for continuous variables. Fisher's exact

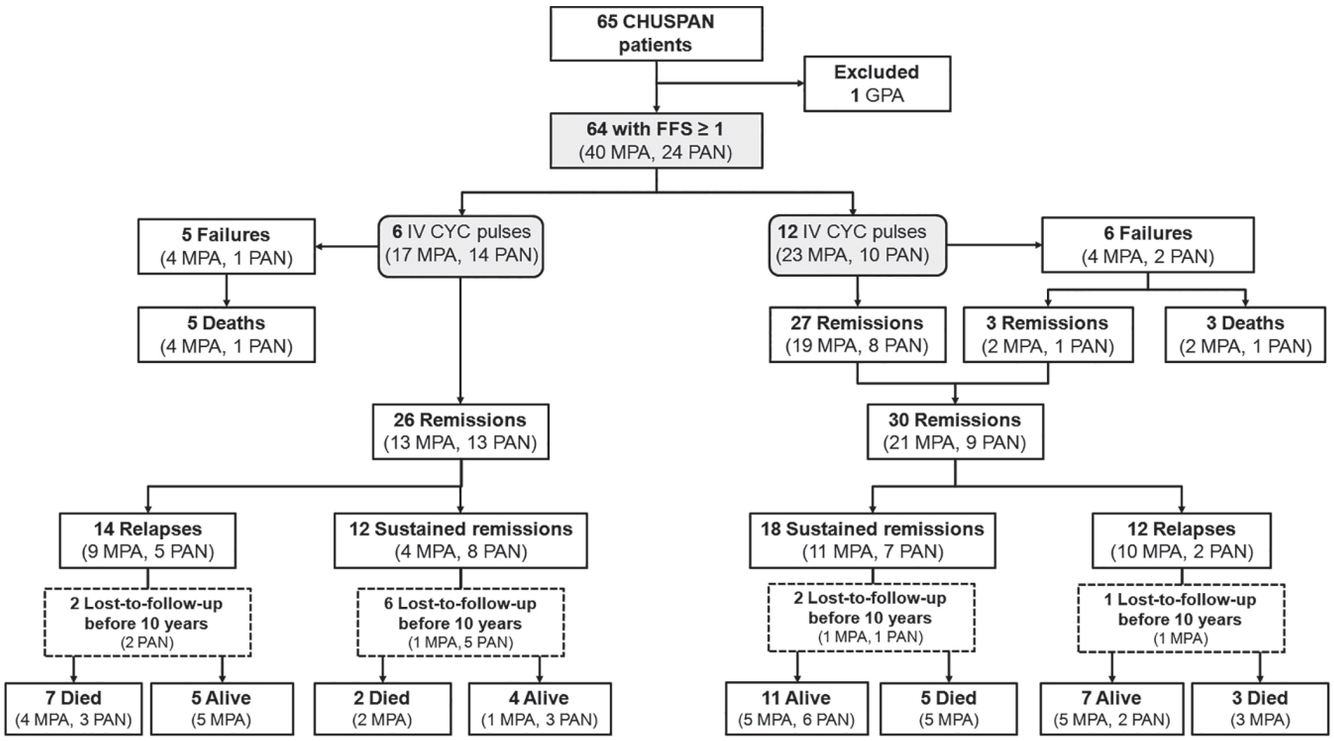

Fig. 1. Flow chart of the study: analysis at 10 years. Data were censored after 120 months of follow-up. CYC: cyclophosphamide; FFS: Five-Factor Score; GPA: granulomatosis with polyangiitis (Wegener's); MPA: microscopic polyangiitis; PAN: polyarteritis nodosa.

or chi-square tests were used, as appropriate, to compare categorical variables. For all statistical analyses, 2-tailed $p<0.05$ defined significance.

Disease-free survival, defined as the time to relapse, failure or death, whichever occurred first, was calculated from the date of randomisation. For survival analyses, data were censored after 120 months of follow-up. Kaplan-Meier curves were plotted using SPSS v. 22 software, and their differences were evaluated with log-rank tests.

A multivariate Cox regression model with backward selection of variables (exit threshold: $p<0.1$) was used to identify baseline variables independently associated with disease-free survival. All variables with $p\leq0.2$ in the univariate analyses were selected for inclusion in the multivariate model.

Results

Baseline characteristics

Sixty-four patients (40 MPA and 24 PAN) were included in this extended study. One patient, who developed typical features of granulomatosis with polyangiitis during follow-up, was excluded. As previously reported, 33 patients (23 MPA, 10 PAN) were randomised to receive 12 CYC pulses and 31 (17 MPA, 14 PAN) to receive 6 CYC pulses (Fig. 1). Patients' baseline clinical and biological characteristics according to vasculitis and treatment arm are summarised in Table I. Notably, MPA patients were older and their BVAS-defined disease severity greater, attributable to higher frequencies of renal, cardiac and pulmonary involvements, than those of PAN patients. More importantly, no significant difference was observed between the 2 treatment groups (12 *vs*. 6 CYC pulses). Creatininaemia was the only item that tended ($p=0.053$) to be higher for patients who received 12 CYC pulses.

As previously reported (18), 53/64 patients (83%, 27 in the 12-pulse group and 26 in the 6-pulse arm; $p=0.83$) achieved remission after induction. For the 11 non-responders, immunosuppressive therapy was intensified: 3 achieved remission and 8 died before remission.

Extended follow-up

Notably, 11/64 patients were lost-to-follow-up before 10 years: 3 in the 12-pulse group and 8 in the 6-pulse group ($p=0.10$), after global mean follow-up of 61.9±35.2 [range: 21.9–111.3] months, with no between-group difference, respectively: 76.8±32.9 months *vs*. 56.3±36.4 ($p=0.42$) (Fig. 1).

Relapses

Among the 56 patients who finally entered in remission, 26 experienced ≥1 relapse(s) (12 in the 12-pulse arm and 14 in the 6-pulse group; Table I) and 20 suffered ≥1 major relapse(s) (10 in the 12-pulse arm and 10 in the 6-pulse group; $p=1.00$). Throughout follow-up, 26 patients developed 40 relapses (mean BVAS: 10.1±7.2), 23 of them major (mean BVAS: 13.6±7.0).

The characteristics of the first relapses that occurred in those 26 patients are summarised in supplementary Table S1. They appeared a mean of 32.2±32.5 months post-inclusion, with no significant differences between PAN and MPA patients or between 12- and 6-pulse groups. Notably, 88% of these 26 relapses were severe, and 46% of the patients were off GC and immunosuppressants when they occurred. No relevant clinical differences were found between PAN and MPA relapses. ANCA were detectable only during MPA relapses. First relapses were more severe

Table I. Main baseline characteristics of the 64 patients included in the study according to vasculitis and treatment arm.

Characteristic	All (n=64)	MPA (n=40)	PAN (n=24)	p^*	12 CYC pulses (n=33)	6 CYC pulses (n=31)	$p^\dagger$
Age at diagnosis	55.2 ± 17.1	60.3 ± 15.4	46.5 ± 16.5	0.001	51.6 ± 16.8	59.0 ± 16.8	0.08
Sex (M/F)	42/22	21/19	21/3	0.004	20/13	22/9	0.38
Vasculitis (MPA/PAN)	40/24	–	–	–	23/10	17/14	0.22
Clinical manifestation at diagnosis							
BVAS	23.6 ± 8.9	26.5 ± 8.3	18.8 ± 7.6	<0.001	25.0 ± 8.9	22.1 ± 8.7	0.19
FFS = 1	27 (42)	12 (30)	15 (63)	0.07	13 (39)	14 (45)	0.40
FFS = 2	29 (45)	22 (55)	7 (29)		16 (48)	13 (42)	
FFS ≥ 3	8 (13)	6 (15)	2 (8)		4 (12)	4 (13)	
General symptoms	62 (97)	38 (95)	24 (100)	0.52	32 (97)	30 (97)	1.00
Myalgias	29 (45)	19 (48)	10 (42)	0.65	16 (48)	13 (42)	0.60
Arthralgias	28 (44)	18 (45)	10 (42)	0.79	16 (48)	12 (39)	0.43
Cutaneous symptoms	29 (45)	20 (50)	9 (38)	0.33	16 (48)	13 (42)	0.60
Ear, nose & throat	8 (13)	7 (18)	1 (4)	0.24	5 (15)	3 (10)	0.71
Pulmonary symptoms	32 (50)	27 (68)	5 (21)	<0.001	19 (58)	13 (42)	0.21
Alveolar haemorrhage	12 (19)	12 (30)	0	0.002	8 (24)	4 (13)	0.25
Cardiac symptoms	20 (31)	17 (43)	3 (13)	0.012	12 (36)	8 (26)	0.36
Specific cardiomyopathy	6 (9)	5 (13)	1 (4)	0.40	4 (12)	2 (6)	0.67
Pericarditis	7 (11)	6 (15)	1 (4)	0.24	6 (18)	1 (3)	0.11
Gastrointestinal symptoms	33 (52)	14 (35)	19 (79)	<0.001	14 (42)	19 (61)	0.13
Abdominal pain	29 (45)	12 (30)	17 (71)	0.001	12 (36)	17 (55)	0.14
Digestive haemorrhage	6 (9)	4 (10)	2 (8)	1.00	3 (9)	3 (10)	1.00
Pancreatitis	3 (5)	0	3 (13)	0.049	0	3 (10)	0.11
Intestinal infarction	6 (9)	2 (5)	4 (17)	0.19	1 (3)	5 (16)	0.10
Surgical abdomen	11 (17)	2 (5)	9 (38)	0.001	5 (15)	6 (19)	0.66
Renal involvement	58 (91)	39 (98)	19 (79)	0.02	32 (97)	26 (84)	0.10
Proteinuria >0.5 g/day	48 (75)	38 (95)	10 (42)	<0.001	27 (82)	21 (68)	0.19
Haematuria >10 red cells/mL	42 (66)	36 (90)	6 (25)	<0.001	23 (70)	19 (61)	0.48
Creatininaemia (µmol/L)	216 ± 212	231 ± 199	191 ± 235	0.47	266 ± 266	164 ± 115	0.053
Orchitis	4 (6)	0	4 (17)	0.02	3 (9)	1 (3)	0.61
Neurological symptoms	43 (67)	29 (73)	14 (58)	0.24	21 (64)	22 (71)	0.53
Mononeuritis multiplex	35 (55)	24 (60)	11 (46)	0.27	17 (52)	18 (58)	0.60
CNS symptoms	3 (5)	1 (3)	2 (8)	0.55	1 (3)	2 (6)	0.61
Laboratory findings at diagnosis							
CRP (mg/L)	94 ± 89	86 ± 91	109 ± 83	0.36	80 ± 74	111 ± 102	0.21
ANCA	35 (55)	33 (83)	2 (8)	<0.001	20 (61)	15 (48)	0.33
cANCA	2/35 (6)	1/33 (3)	1/2 (50)	1.00	0	2/15 (13)	0.22
pANCA	32/35 (91)	31/33 (94)	1/2 (50)	<0.001	19/20 (95)	13/15 (87)	0.21
anti-MPO	28/35 (80)	28/33 (85)	0	<0.001	17/20 (85)	11/15 (73)	0.19
Angiography at diagnosis							
Stenosis(es) and/or microaneurysm(s)	16/30 (53)	0	16/18 (89)	<0.001	8/15 (53)	8/15 (53)	1.00
Outcome (censored after 120 months)							
Remission after induction	53 (83)	32 (80)	21 (88)	0.51	27 (82)	26 (84)	0.83
≥1 relapse(s) during follow-up	26/56 (46)	19/34 (56)	7/22 (32)	0.15	12/30 (40)	14/26 (54)	0.47
VDI‡	2.6 ± 1.7	3.0 ± 1.7	2.0 ± 1.6	0.049	2.6 ± 1.8	2.6 ± 1.7	0.91
Chronic dialysis	7 (11)	7 (18)	0	0.04	5 (15)	2 (6)	0.31
Renal transplantation	2 (3)	2 (5)	0	.	2 (6)	0	–
Deaths	25 (39)	20 (50)	5 (21)	0.02	11 (33)	14 (45)	0.22

Results are expressed as mean ± SD for quantitative variables and n (%) for qualitative variables. ANCA: antineutrophil cytoplasm antibodies; with a cytoplasmic (c) or perinuclear (p) labelling pattern; BVAS: Birmingham Vasculitis Activity Score; CNS: central nervous system; CRP: C-reactive protein; CYC: cyclophosphamide; FFS: Five-Factor Score; MPA: microscopic polyangiitis; MPO: myeloperoxidase; PAN: polyarteritis nodosa; VDI: Vasculitis Damage Index. * MPA *vs*. PAN. † 12 *vs*. 6 CYC pulses. ‡ Calculated only for the 56 patients who achieved ≥1 remission(s).

in the 12-pulse than the 6-pulse group (BVAS: 13.7±6.0 *vs*. 7.6±5.3, respectively) because of more frequent renal involvement (75% *vs*. 36%; p=0.045). The respective global 2-, 5-, 7- and 10-year disease-free survival rates were 59.4%, 41.9%, 36.3% and 29.9%, and were significantly shorter for MPA than PAN patients (p=0.014) and for those ≥65 years old, or with myalgias, alveolar haemorrhage, proteinuria >0.5 g/day or ANCA-positivity at diagnosis (Fig. 2A). The disease-free survival difference between patients that received 12 *vs*. 6 CYC pulses declined during follow-up and was no longer significant at 120 months (p=0.367). Multivariate analyses retained only age ≥65 years and alveolar haemorrhage at disease onset as significantly associated with shorter disease-free survival (Table II).

Complementary treatments

In addition to CYC pulses assigned by

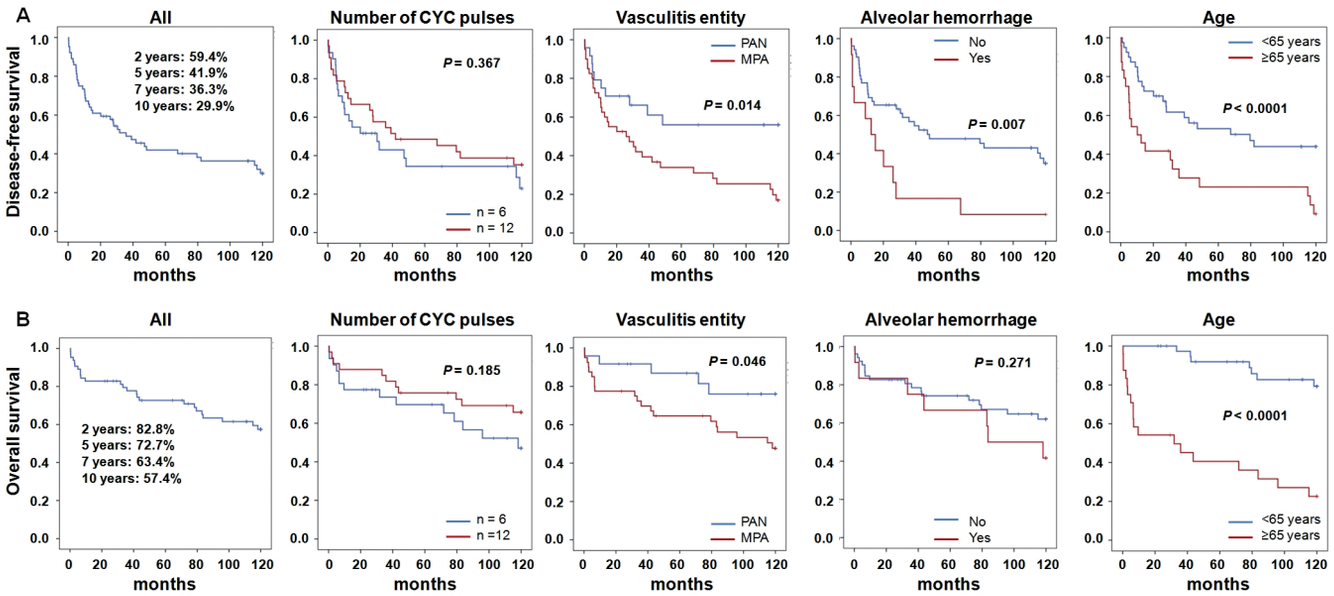

Fig. 2. Disease-free (**A**) and overall survival (**B**) analyses. *p*-values computed with log-rank tests. CYC: cyclophosphamide; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa.

the therapeutic protocol, 25/64 (39%) patients received another immunosuppressant, mainly because the former failed or the vasculitis relapsed. Complementary treatments are detailed in supplementary Table S2. No differences were observed between PAN and MPA patients or 12- and 6- pulse groups. Azathioprine (12, 19%), oral CYC (9, 14%) and mycophenolate mofetil (5, 8%) were the most commonly prescribed immunosuppressants after pulse CYC.

Deaths and overall survival

Twenty-five (39%) patients, significantly more with MPA, died during the extended study, while the treatment groups were comparable: 11 (33%) in the 12-pulse group and 14 (45%) in the 6-pulse arm (p=0.44; Table I). Deaths were caused by active vasculitis (n=8), sepsis (n=5), cancer (n=3: 2 prostate and 1 lymphoma), vascular disease (n=3: 2 myocardial infarctions and 1 rupture of a prosthetic valve), dementia (n=1), postoperative haemorrhage (n=1) or sudden death of unknown origin (n=4). The respective 2-, 5-, 7- and 10-year overall survival rates were 82.8%, 72.7%, 63.4% and 57.4%, and comparable for patients given 12 or 6 pulses (Fig. 2B). Importantly, relapse (p=0.471) and alveolar haemorrhage

Table II. Univariate and multivariate analyses of baseline factors associated with disease-free survival.

Factor	Univariate		Multivariate	
	Hazard ratio	*p*	Hazard ratio	*p*
Vasculitis (MPA *vs*. PAN)	2.17	0.014	–	NS
Age at diagnosis ≥65 years	2.88	0.002	2.28	0.012
Sex		NS		
Clinical characteristics at diagnosis				
Myalgias	1.52	0.187	–	NS
Arthralgias		NS		
Cutaneous symptoms		NS		
Ear, nose & throat symptoms		NS		
Pulmonary symptoms	2.32	0.008	–	NS
Alveolar haemorrhage	3.60	0.007	3.07	0.003
Cardiac symptoms		NS		
Specific cardiomyopathy		NS		
Pericarditis		NS		
Gastrointestinal symptoms	0.65	0.164	–	NS
Severe digestive involvement	0.42	0.021	0.37	0.110
Renal involvement		NS		
Proteinuria >0.5 g/day	2.02	0.040	–	NS
Haematuria >10 red cells/mL		NS		
Orchitis		NS		
Neurological symptoms		NS		
Mononeuritis multiplex		NS		
CNS symptoms		NS		
Laboratory findings at diagnosis				
Creatininaemia >140 μmol/L		NS		
ANCA-positivity	1.85	0.048	–	NS
Treatment				
12 *vs*. 6 CYC pulses		NS	–	NS

All variables with $p \leq 0.2$ in the univariate analyses were selected for inclusion in the multivariate model which was a Cox regression model with backward selection of variables (exit threshold: $p<0.1$).
ANCA: antineutrophil cytoplasm antibodies; CYC: cyclophosphamide; IS: immunosuppressant; MPA: microscopic polyangiitis; NS: non-significant; PAN: polyarteritis nodosa.

Table III. Univariate and multivariate analyses of baseline factors associated with overall survival.

Factor	Univariate		Multivariate	
	Hazard ratio	*p*	Hazard ratio	*p*
Vasculitis (MPA *vs*. PAN)	2.26	0.046	–	NS
Age at diagnosis ≥65 years	10.98	<0.001	7.39	<0.001
Sex		NS		
Clinical characteristic at diagnosis				
Myalgias		NS		
Arthralgias		NS		
Cutaneous symptoms		NS		
Ear, nose & throat symptoms		NS		
Alveolar haemorrhage		NS		
Cardiac symptoms		NS		
Specific cardiomyopathy	3.08	0.189	–	NS
Pericarditis		NS		
Severe digestive involvement		NS		
Renal involvement		NS		
Proteinuria >0.5 g/day	2.14	0.091	–	NS
Haematuria >10 red cells/mL		NS		
Orchitis		NS		
Neurological symptoms		NS		
Mononeuritis multiplex	2.23	0.046	2.28	0.067
CNS symptoms		NS		
Laboratory findings at baseline				
Creatininaemia >140 µmol/L		NS		
ANCA-positivity	2.64	0.016	–	NS
Treatment				
12 *vs*. 6 CYC pulses	1.71	0.185	–	NS

All variables with $p \leq 0.2$ in the univariate analyses were selected for inclusion in the multivariate model which was a Cox regression model with backward selection of variables (exit threshold: $p<0.1$).
ANCA: antineutrophil cytoplasm antibodies; CNS: central nervous system; CYC: cyclophosphamide; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa; NS: non-significant.

at diagnosis (p=0.271) did not impact overall survival, while MPA (compared to PAN), age ≥65 years, mononeuritis multiplex and ANCA-positivity at diagnosis were significantly associated with shorter overall survival in univariate analyses (Table III). Multivariate analyses retained age ≥65 years at diagnosis as the only factor independently associated with shorter survival (p<0.001).

Damage

At the end of the extended study, mean VDI for the 56 patients with ≥1 remission(s) was 2.6±1.7 and comparable for the 2 arms (Table IV). However, VDI was significantly higher for MPA than PAN patients (p=0.049; Table I), which was mainly attributable to MPA patients' higher frequency of renal failure (61% *vs*. 23%; p=0.006). The most frequent VDI items (Table IV) were hypertension (58%), chronic renal failure (46%), peripheral neuropathy (26%) and osteoporosis (13%). Osteoporosis was significantly less frequent in the 12-pulse than the 6-pulse group. Cancer was diagnosed in 4 patients (breast, renal lymphoma, prostate or ENT), all in the 6-pulse group. Eight patients (7 MPA and 1 PAN) progressed to end-stage renal failure and required chronic dialysis; 2 of them, both with MPA, received kidney transplants.

Discussion

The prospective, multicentre, randomised CHUSPAN trial was initially designed to determine whether shorter CYC-induction administration would be able to successfully induce and maintain remission of PAN or MPA with ≥1 FFS-defined poor-prognosis factor(s). Three-year relapse-free and disease-free survival rates were better for patients who had received 12 rather than 6 CYC pulses (18). However, at 10 years of follow-up, disease-free survival had dramatically decreased to 30% and the difference between the 2 treatment groups was no longer significant. This observation highlights that systemic necrotising vasculitides are chronic diseases that require long-lasting maintenance therapy because of their high relapse rates (19). The development of prognosis scores (10, 11), and immunosuppressive regimens using pulse CYC and, more recently, rituximab for MPA (14, 15) have greatly improved the short-term prognoses of systemic necrotising vasculitides but relapses remain common, especially after discontinuation of immunosuppression (12, 14, 15, 28-30). Therefore, we now think that the initial benefit of the 12-pulse regimen at 3 years indeed reflected a "maintenance-like" effect that disappeared as follow-up progressed.

The long-term CHUSPAN-trial results also highlight that accrued damage is a major concern for these patients, especially FFS ≥1 MPA patients who frequently suffer from renal insufficiency (18%). Except for peripheral neuropathy, which is definitely vasculitis-related and a primary cause of disability, the impact of GC-related side effects remains high for all sequelae (osteoporosis [13%], avascular osteonecrosis [9%], cataract [4%], hypertension [58%] and diabetes [7%]), thereby highlighting the need for new GC-sparing therapeutic strategies for vasculitides.

The long-term analysis of this trial also examined factors influencing disease-free survival and overall survival. Pertinently, these analyses prospectively identified alveolar haemorrhage, specific to MPA (6, 7, 31), as the difference between MPA and PAN patients that was independently associated with shorter disease-free survival. Overall survival rates were quite low in this study (83% at 2 years, 63% at 7 years and 57% at 10 years), which probably reflects the absence of immunosuppressive maintenance therapy in this protocol, and highlights the severity of FFS ≥1 MPA and PAN. The FFS is commonly applied in France to guide the choice of the best treatment strategy for systemic necrotising vasculitides (10, 11) and it is admitted its use tends to eliminate a survival difference between patients with FFS=0 and FFS ≥1 (32). These

Table IV. Damage according to the Vasculitis Damage Index (VDI).

VDI damage items[a]	All (n = 56)	MPA (n = 34)	PAN (n = 22)	*p*	12 CYC pulses (n = 30)	6 CYC pulses (n = 26)	*p*
Musculoskeletal							
Marked muscle atrophy or weakness	4 (7)	2 (6)	2 (9)	1.00	1 (3)	3 (12)	0.34
Osteoporosis	7 (13)	3 (9)	4 (18)	0.42	1 (3)	6 (23)	0.044
Avascular osteonecrosis	5 (9)	3 (9)	2 (9)	1.00	2 (7)	3 (12)	0.66
Ocular							
Cataract	2 (4)	1 (3)	1 (5)	1.00	0	2 (8)	0.22
Optic nerve atrophy	1 (2)	1 (3)	0	1.00	1 (3)	0	1.00
Visual impairment	1 (2)	0	1 (5)	0.40	0	1 (4)	0.47
Ear, nose & throat or pulmonary							
Hearing loss	1 (2)	0	1 (5)	0.40	0	1 (4)	0.47
Pulmonary fibrosis	1 (2)	1 (3)	0	1.00	0	1 (4)	0.47
Cardiovascular							
Angina/angioplasty	1 (2)	0	1 (5)	0.40	1 (3)	0	1.00
Myocardial infarction	2 (4)	1 (3)	1 (5)	1.00	2 (7)	0	0.49
Cardiomyopathy	1 (2)	1 (3)	0	1.00	1 (3)	0	1.00
Valve disease	2 (4)	2 (6)	0	0.51	2 (7)	0	0.49
High blood pressure	32 (57)	19 (56)	13 (59)	0.91	17 (57)	15 (58)	0.94
Major vessel stenosis	1 (2)	1 (3)	0	1.00	1 (3)	0	1.00
Claudication	1 (2)	1 (3)	0	1.00	1 (3)	0	1.00
Major tissue loss	1 (2)	1 (3)	0	1.00	0	1 (4)	0.47
Gastrointestinal							
Gut resection	2 (4)	1 (3)	1 (5)	1.00	2 (7)	0	0.49
Mesenteric insufficiency	2 (4)	0	2 (9)	0.16	0	2 (8)	0.22
Renal							
Renal insufficiency (GFR <50%)	25 (45)	20 (59)	5 (23)	0.006	16 (53)	9 (35)	0.13
Proteinuria >0.5 g/day	6 (11)	5 (15)	1 (5)	0.38	2 (7)	4 (15)	0.41
End-stage renal disease (GFR <15 ml/min)	8 (14)	7 (21)	1 (5)	0.13	6 (20)	2 (8)	0.26
Neuropsychiatric							
Peripheral neuropathy	14 (25)	10 (29)	4 (18)	0.31	7 (23)	7 (27)	0.81
Other							
Gonadal failure	5 (9)	4 (12)	1 (5)	0.64	3 (10)	2 (8)	1.00
Diabetes	4 (7)	3 (9)	1 (5)	0.64	3 (10)	1 (4)	0.61
Malignancy	4 (7)	3 (9)	1 (5)	0.64	0	4 (15)	0.044

[a] VDI items not listed here were not considered damage in this study.
Data were censored after 120 months. Values are expressed as n (%).
GFR: glomerular filtration rate; MPA: microscopic polyangiitis; NS: non-significant; PAN: polyarteritis nodosa.

long-term results seem to challenge that paradigm, as we previously reported 97% 3-year and 87% 7-year overall survival rates for FFS=0 MPA and PAN patients treated with first-line GC alone (16). The overall survival difference between FFS=0 and FFS ≥1 increases during follow-up, thereby emphasising that the FFS's prognostic value for systemic necrotising vasculitides remains applicable at diagnosis and during follow-up. We can also advance that this difference between FFS=0 and FFS ≥1 was amplified by the absence of a immunosuppressive maintenance therapy, which is particularly important to prevent relapses of FFS ≥1 PAN and MPA (19,33), whereas GC alone are usually sufficient for FFS=0 PAN and MPA (3, 16).

We also observed in this study that overall survival was shorter for MPA patients (or ANCA-positive patients). Our multivariate analyses clearly explained that the difference reflected the MPA patients' older age. Indeed, age ≥65 years is the predictive factor most strongly associated with death (11), which led the FVSG to assess and validate a specific CYC and GC regimen for these older patients (29).

The main weakness of this trial is the grouping of PAN and MPA patients, which is explained by its having been designed before the CHCC nomenclature clearly distinguished these 2 entities (4, 5). Notably, MPA tends to relapse much more frequently than PAN (16, 34). However, the comparability of the randomised 12 and 6 CYC-pulse groups assured the accuracy of these analyses. The 12-pulse group tended to have higher creatininaemia, which might have decreased its relapse rate and, hence, explained the 12-pulse advantage observed at 3 years (18), because renal insufficiency at diagnosis was associated with a lower risk of relapse (35, 36). That the 2 groups remained comparable concerning other immunosuppressive agents prescribed during follow-up also strengthens the validity of our results. Clearly, the major strength of this study is its long follow-up: 83% of the patients completed this 10-year extended study and monitoring was even long for the 11 patients lost-to-follow-up (range: 22–111 months).

It also must be admitted that patients with severe PAN or MPA are not treated in 2016 as they had been in this trial. It is now strongly recommended that, once remission has been obtained, immunosuppressive maintenance therapy should be started to prevent relapses while assuring the lowest level of toxicity (33, 37, 38). Rather than a weakness, the CHUSPAN-trial therapeutic strategy and its extended 10-year follow-up analyses enabled us to demonstrate that the effect of the number of CYC pulses prescribed at diagnosis progressively declined during the follow-up. That finding supports the concept that initiation of effective maintenance therapy after achieving remission really improves patients' outcomes rather than the induction-therapy intensity. The same conclusion can be drawn for rituximab: the RAVE study results showed that rituximab was as effective as CYC at inducing remission of ANCA-associated vasculitides (15). However, in the absence of maintenance therapy in the rituximab arm of that trial, only 39% of patients remained relapse-free at 18 months (14). By contrast, when rituximab (500 mg) was given every 6 months in the MAINRITSAN trial, only 5% of patients experienced major relapses during the first 28 months of follow-up, regardless of the induction regimen used (pulse CYC or rituximab) (12). Along this line, an inverse relationship between maintenance therapy duration and relapse risk, even after adjustment for prednisone dose, was also demonstrated for granulomatosis with polyangiitis (39), thereby further supporting that, until curative therapies are discovered, patients' outcomes can be markedly improved by long-term maintenance therapy. Taken together, these observations led the FVSG to design the MAINRITSAN 3 study that is assessing the efficacy of prolonged 18 months of maintenance therapy with rituximab.

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