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TREATMENT OF GOOD-PROGNOSIS POLYARTERITIS NODOSA AND CHURG–STRAUSS SYNDROME: COMPARISON OF STEROIDS AND ORAL OR PULSE CYCLOPHOSPHAMIDE IN 25 PATIENTS

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SUMMARY

Twenty-five patients with good-prognosis polyarteritis nodosa or Churg–Strauss syndrome entered a prospective, randomized, multicentre study comparing two treatments: either oral corticosteroids and oral cyclophosphamide (CY; 2 mg/kg/day) for 1 yr (group A), or oral corticosteroids and monthly i.v. CY pulses (0.6 g/m^2) (group B) for 1 yr. The objective was to determine the optimal CY regimen. Judgement criteria were the efficacy of the treatment in controlling the disease and the development of side-effects. Among the 25 patients who could be analysed, complete recovery was achieved with the experimental treatment in 9/12 patients in group A and 10/13 patients in group B. Two patients in each group relapsed after the end of therapy and were well controlled by corticosteroids or other drugs. One failure occurred in each group. The mean follow-up was 60.8 ± 14.5 months after the beginning of the treatment. Side-effects associated with the administration of CY and steroids were noted 27 times in group A *vs* 14 times in group B (not significant). The oldest patient in these series (group B) died of pneumonia. No superiority in terms of efficacy could be established between the two regimens; however, the number of patients included was too small to conclude definitively. Toxic side-effects were significantly more frequent in women ($P < 0.02$). The high number of adverse effects leads us to recommend pulse over oral CY and an overall lowering of the doses of immunosuppression.

KEY WORDS: Polyarteritis nodosa, Churg–Strauss syndrome, Cyclophosphamide pulse, Cyclophosphamide oral.

THE prognosis of patients suffering from polyarteritis nodosa (PAN) and Churg–Strauss syndrome (CSS) has been dramatically improved since the introduction of corticosteroid therapy [1, 2]. Fauci *et al.* [3] also demonstrated the beneficial effects of adding an immunosuppressive agent to corticosteroids (CS) when PAN failed to respond to CS. Since August 1980, we have been conducting prospective therapeutic trials to define the most effective treatment for PAN and CSS [4–9], and concluded the following. (i) For PAN without hepatitis B virus (HBV) infection and CSS, the first-line treatment should combine prednisone with cyclophosphamide (CY), which was given orally for 12 months in our first trial [5]. Administration of CY improved disease control despite infectious side-effects [5]. (ii) HBV-related PAN needs a specific treatment and we showed that the association of antiviral agents (vidarabine [7] or interferon-alpha-2b [10]) and plasma exchanges (PE) is effective and attains remission in a majority of patients within 2–3 months. (iii) PE are obviously useful in the treatment of HBV-related PAN [9], but there is presently no argument to support the systematic prescription of PE at the time of diagnosis [6] of PAN without HBV infection or CSS, even when patients present with symptoms of poor prognosis [8, 11]. In patients presenting with factors of good prognosis, we decided to conduct a prospective trial to compare the efficacy of CS and oral CY to that of CS and pulse CY. The results of this prospective randomized study are reported here.

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MATERIALS AND METHODS

Patients

Criteria for study entry. Criteria for inclusion were as follows: (1) age >15 yr and <75 yr; (2) systemic PAN or CSS diagnosed clinically by the presence of multiple system involvement; (3) absence of one or more criteria of poor prognosis as defined below; (4) histological evidence of vascular lesions indicative of a diagnosis of vasculitis (focal or segmental vascular lesions, fibrinoid necrosis and/or pleomorphic inflammatory cell infiltration of the arterial wall; (5) in the absence of histological criteria, arteriographic evidence of vasculitis (microaneurysms, multiple stenoses and/or occlusions of medium-sized arteries; (6) absence of HBs and HBe antigens (Ag). All the patients fulfilled the criteria defined by the American College of Rheumatology for PAN [12] or CSS [13]. Only patients with recent onset of symptoms were included in the study. Except for low-dose CS prescribed to control asthma, previous treatment with CS and/or cytotoxic agents was considered to be a criterion of exclusion. Patients with cutaneous PAN or limited forms of the disease were excluded from

the study, as were patients with other forms of systemic vasculitides.

Prognostic factors. Factors of poor prognosis have been identified in PAN and CSS. We have shown, based on a prospectively followed cohort of 342 patients [11] with PAN or CSS, that mortality was increased in the presence of at least one of the following five items, which define the five-factor score (FFS): renal symptoms [i.e. proteinuria <1 g/day (1 point) and/or creatininaemia >120 μmol/l (1 point)]; gastrointestinal (GI) tract involvement (1 point) characterized by bowel perforation and/or GI tract haemorrhage and/or pancreatitis; central nervous system involvement (1 point); cardiomyopathy related to vasculitis (1 point). Patients were considered to have a good prognosis when the FFS was zero.

Study protocol. Patients fulfilling the inclusion criteria were consecutively enrolled in the trial by the members of the French Cooperative Study Group for Vasculitides. The patients were randomly assigned by investigators at the coordinating centre (Hôpital Avicenne, Bobigny, France) to receive treatment A or B. The study was not blinded. The protocol was approved by the Biomedical Ethics Committee of the University Paris-Nord.

Treatment

Prednisone. The same modalities were used in groups A and B. Every patient took prednisone at a dose of 1 mg/kg/day for 1 month. The daily dose was decreased by 2.5 mg every week until a dose of 10 mg/day was reached at approximately the sixth month. Then, the dose was decreased by 1 mg every week. If a flare of the disease occurred, the dose was increased.

Cyclophosphamide. In group A, oral CY was prescribed at a dose of 2 mg/kg/day for 12 months. In group B, CY pulses were infused once monthly at a dose of 0.6 g/m^2 for 12 months. Patients were hydrated before the pulse with infusion of 1 l of dextrose or by drinking 1 l of mineral water. Prophylaxis against haemorrhagic cystitis was as follows: Mesna, at a dosage of 60% of the CY dose, was administered three times (at the beginning of the CY infusion and 4 and 8 h later). Prophylactic anti-emetic treatment was not systematically prescribed. In addition, treatment with calcium (500 mg/day) and vitamin D (800 IU/day) was recommended. No special screening to search for osteoporosis was carried out before or at the end of treatment.

White blood cell counts were evaluated every 2 weeks for 2 months, then at least every month during the year of treatment; if neutropenia occurred (neutrophil count <1500 cells/mm^3), the CY dose was lowered or temporarily withdrawn until the neutrophil count returned to normal.

Assessment criteria

Treatment efficacy was based on clinical and biological signs: disappearance of fever, improvement of general condition, regression of clinical signs, no new clinical manifestations related to PAN or CSS, normalization of the erythrocyte sedimentation rate (ESR). Patients were considered to be in complete recovery when no manifestations of vasculitis were recorded for at least 18 months after the end of the treatment. If no or insufficient improvement was obtained under treatment or if a relapse occurred, treatment was registered as a failure. Relapses were diagnosed when a new manifestation of PAN or CSS, or worsening of the initial manifestations of the disease, occurred. Development of serious side-effects induced by CS or CY led to transient or definitive drug withdrawal.

Follow-up evaluations

The clinical and laboratory data were collected at the time of study inclusion, 15 and 30 days later, then every month for 6 months, every 3 months for 1 yr and every year for 3 yr. At each visit, compliance with the treatment regimen was assessed, side-effects were recorded and the necessity of adjunctive therapy was evaluated (hypertension, diabetes, osteoporosis). All data were recorded on protocol forms which were then sent to the trial coordinator.

Statistical analysis

A χ^2 test with Yates' correction for small numbers, when appropriate, or Fisher's exact test (e.g. data on remission, relapses, withdrawal from the study, side-effects) were used for comparison of qualitative variables. The non-parametric Mann–Whitney *U*-test was used for comparison of quantitative variables of small samples. Survival time was evaluated relative to the time of diagnosis.

RESULTS

Clinical findings

Between February 1989 and March 1993, 25 patients were eligible for the study. The clinical manifestations of PAN ($n = 17$) or CSS ($n = 8$) in the two groups (12 in group A and 13 patients in group B) are summarized in Tables I–III.

Patients were slightly older in group A, and there were more women; these differences were not statistically significant ($P = 0.15$ in both instances).

Cutaneous signs comprised s.c. nodules, purpura, segmental oedema, urticaria. In every patient with mononeuritis multiplex, at least two peripheral nerves were involved.

Laboratory results

All patients presented histopathological evidence of vasculitis with fibrinoid necrosis of the vessel walls and inflammatory infiltrates.

ESR (>70 mm/l st h) was elevated in eight group A and nine group B patients. Two patients in each group had an ESR between 20 and 69 mm/l st h, and two in each group had an ESR below 20 mm/l st h at the time of the inclusion. The latter two patients were both receiving low-dose CS for asthma.

Antineutrophil cytoplasmic antibodies (ANCA)

TABLE I
Clinical characteristics, manifestations, and laboratory data observed at the time of diagnosis of vasculitis in the 25 patients

Parameter	Group A (n = 12)	Group B (n = 13)	Total (n = 25)
Age (yr), mean ± S.D.	46.5 ± 8.9	38.6 ± 14.2	
Sex ratio M/F	6 M/6 F	11 M/2 F	17 M/8 F
Weight loss, *n* (%)	7 (58.3)	8 (61.5)	15 (60)
Peripheral neuropathy, *n* (%)	8 (66.7)	7 (53.8)	14 (56)
Fever, *n* (%)	7 (58.3)	11 (84.6)	18 (72)
Myalgias, *n* (%)	8 (66.7)	11 (84.6)	19 (76)
Skin involvement, *n* (%)	7 (58.3)	12 (92.3)	13 (52)
Asthma, *n* (%)	6 (50)	2 (15.4)	8 (32)
Arthralgias, *n* (%)	5 (41.7)	7 (53.8)	11 (44)
Polyarthritis, *n* (%)	2 (16.7)	1 (7.7)	3 (12)
Orchitis, *n* (%)	0	1 (9.1)	1 (5.9)
Pericarditis, *n* (%)	2 (16.7)	1 (7.7)	3 (12)
ANCA	2	2	4
ELISA, *n*	2 anti-MPO	1 anti-MPO/1 nd	
IFA, *n*			

Patients were randomly assigned to treatment group A (CS plus oral CY) or group B (CS plus pulse CY) as described under Patients and methods. All between-group comparisons were non-significant.

ANCA, antineutrophil cytoplasmic antibodies; IFA, immunofluorescence assay; ELISA, enzyme-linked immunosorbent assay; MPO, myeloperoxidase; nd, not done

were found in 2/8 patients in group A and in 2/12 patients in group B. Three of these were specific to myeloperoxidase (MPO): two CSS in group A and one PAN in group B. ELISA was not carried out in one patient with PAN in group B, whose fluorescence staining pattern was perinuclear.

Angiography was performed in two group A and four group B patients, and was positive (micro-aneurysms of renal or hepatic arteries) in one case in each group (one CSS in group A and one PAN in group B).

Effects of treatment (Table IV)

The two relapses in group A (oral CY) occurred 2 and 8 months after the end of treatment. A 33-yr-old woman presented isolated mild cutaneous signs with a slight elevation of the ESR, considered to be a cutaneous relapse of PAN. She was successfully treated with colchicine (1 mg/day). A 52-yr-old woman with CSS had a cutaneous relapse requiring prednisone at an initial dosage of 0.5 mg/kg/day.

The two relapses observed in group B developed 1 and 8 months after the end of treatment. A 29-yr-old man had two mild cutaneous relapses controlled with an initial CS dose of 0.4 mg/kg/day for 1 month then decreased progressively over 6 months. The other relapse occurred in a 30-yr-old man who presented with moderate weight loss, low-grade fever and arthralgias 3 months after the last CY infusion. He was successfully treated with 0.5 mg/kg/day of prednisone, but mild relapses reoccurred when the prednisone dose fell below 10 mg/day. The addition of dapsone led to disease remission, but mild clinical symptoms appeared when CS were tapered to 2.5 mg/day.

One failure was recorded in each group. In group A, a 52-yr-old woman had signs of relapse (fever, weight loss, arthralgias, myalgias) at the fifth month of treatment when the CS dose was lowered. In group B, a 72-yr-old man died of a pleural and pulmonary infection with *Aspergillus fumigatus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* that developed after he had received three pulses of CY and CS. He died despite improvement under treatment with resolution of signs of PAN.

Control of vasculitis was similar in the two groups (P = 0.9). After 1 yr, the mean CS dose was higher in group A than B, explained by the higher number of asthmatic patients who required prednisone at $>$10 mg/day to control asthma. All of them continued to be treated after the end of the first year, unlike PAN patients in whom it was possible to stop steroids at 1 yr.

Treatment side-effects

Eighteen patients experienced 41 treatment side-effects (Table V). The seven others tolerated the treatments well. Side-effects were secondary to CS and CY. In group A, 10/12 patients experienced 27 toxic side-effects. Four women developed severe osteopenia leading to femoral neck fissure and bone densitometry at the threshold of vertebral crush fractures; two fractures of the femoral neck were in the same woman in whom it was not possible to decrease CS under 20 mg/day.

In group B, 8/13 patients experienced 14 toxic side-effects. Three infections were observed: urinary tract infection (*Klebsiella pneumoniae*) appearing immediately after the first infusion and repeatedly relapsing over 4 months despite antibiotics; infectious bronchitis, fatal pleuropulmonary infection, with *S. aureus* and *P. aeruginosa* in the pleura, and *A. fumigatus* in pulmonary parenchyma (necropsy) whose symptoms appeared insidiously between the second and third CY infusion; two patients experienced large weight gains, probably secondary to CS (27 and 20 kg), and

TABLE II
Main clinical symptoms, laboratory and radiological investigations in the group of patients receiving steroids and oral cyclophosphamide (group A)

No.	Sex	Age (yr)	Main symptoms	Diagnosis	Histology/angiography	ANCA, IFA, ELISA	Treatment side-effects	Outcome
1	M	47	Weight loss (−13 kg), fever, diarrhoea, mononeuritis multiplex with palpebral ptosis, asthma	CSS	Muscle and nerve; muscle necrosis, no vasculitis, kidney microaneurysms	nd	None	Complete recovery, residual asthma
2	M	35	Fever, myalgias, mononeuritis multiplex, urticaria, pericarditis	PAN	Skin vasculitis	nd	Alopecia, hypertension	Complete recovery
3	F	47	Weight loss (−5 kg), fever, subcutaneous nodules, polyarthritis, asthma, lung infiltrates	CSS	Skin vasculitis	neg	Femoral osteonecrosis, amenorrhoea, osteopenia, haemorrhagic cystitis	Complete recovery, residual asthma
4	F	49	Myalgias, polyarthritis, asthma, mononeuritis multiplex	CSS	Muscle vasculitis	neg	Osteopenia, amenorrhoea, neutropenia, cataract	Complete recovery, neuropathy
5	F	33	Fever, myalgias, segmental oedema	PAN	Muscle vasculitis	neg	Amenorrhoea, alopecia, anxiety	1 relapse then complete recovery
6	M	38	Weight loss (−10 kg), fever, myalgias, arthralgias, subcutaneous nodules, mononeuritis multiplex	PAN	Skin and muscle vasculitis	neg	GI candidiasis, herpes keratitis, skin folliculitis, haemorrhagic cystitis, sinusitis, Cushing's syndrome	Complete recovery
7	F	49	Asthma, pericarditis, mononeuritis multiplex	CSS	Skin and muscle vasculitis	p-ANCA, anti-MPO	Chronic active hepatitis	Relapse at 16 months, then complete recovery
8	M	42	Weight loss (−6 kg), fever, myalgias, arthralgias, segmental oedema, mononeuritis multiplex, retinal vasculitis	PAN	Muscle vasculitis	nd	None	Complete recovery
9	M	53	Fever, myalgias, segmental oedema	PAN	Muscle vasculitis	nd	Hypertension, weight gain, gastric ulcer	Complete recovery
10	F	52	Weight loss (−5 kg), fever, myalgias	PAN	Muscle vasculitis	neg	Bilateral femoral neck fracture due to osteopenia	Relapse at 5 months, received another treatment
11	M	48	Weight loss (−16 kg), myalgias, purpura, asthma, mononeuritis multiplex, lung infiltrates	CSS	Skin, muscle and nerve vasculitis	neg	Skin folliculitis	Complete recovery
12	F	66	Weight loss (−5 kg), arthralgias, asthma, lung infiltrates, mononeuritis multiplex	CSS	Muscle and nerve vasculitis, normal angiogram	p-ANCA, anti-MPO	Neutropenia, osteopenia with vertebral fractures, Cushing's syndrome	Complete recovery

nd, not done; neg, negative; p-ANCA, perinuclear staining pattern

TABLE III
Main clinical symptoms, laboratory and radiological investigations in the group of patients receiving steroids and pulse cyclophosphamide (group B)

No.	Sex	Age (yr)	Main symptoms	Diagnosis	Histology/angiography	ANCA, IFA, ELISA	Treatment side-effects	Outcome
1	M	28	Weight loss (−7 kg), fever, myalgias, arthralgias, subcutaneous nodules	PAN	Skin vasculitis, normal angiogram	neg	None	Complete recovery
2	M	29	Fever, myalgias, arthralgias, subcutaneous nodules	PAN	Skin and muscle vasculitis	neg	None	2 relapses then complete recovery
3	M	25	Fever, myalgias, arthralgias, orchitis, subcutaneous nodules, toe gangrene, mononeuritis multiplex	PAN	Skin vasculitis	neg	Cushing's syndrome	Remission
4	F	33	Weight loss (−4 kg), myalgias, purpura, asthma, mononeuritis multiplex, abdominal pain without demonstration of GI tract involvement	CSS	Skin and muscle vasculitis, normal angiogram	neg	Weight gain, amenorrhoea, urinary tract infections, infectious bronchitis	Complete recovery, residual asthma
5	M	55	Fever, myalgias, arthralgias, purpura	PAN	Skin vasculitis, hepatic artery microaneurysms	nd	Poor tolerance of infusions	Complete recovery
6	F	40	Weight loss (−6 kg), fever, myalgias, asthma, pericarditis, lung infiltrate	CSS	Pleural vasculitis	neg	Amenorrhoea, Cushing's syndrome	Complete recovery, residual asthma
7	M	53	Weight loss (−4 kg), fever, myalgias, subcutaneous nodules, segmental oedema	PAN	Skin vasculitis	neg	Cushing's syndrome, poor tolerance of infusions	Complete recovery
8	M	30	Fever, myalgias, subcutaneous nodules, mononeuritis multiplex	PAN	Skin vasculitis	neg	None	Corticodependent, complete recovery
9	M	29	Fever, subcutaneous nodules, mononeuritis multiplex, abdominal pain without demonstration of GI tract involvement	PAN	Skin vasculitis	neg	Weight gain, acne	Complete recovery
10	M	25	Weight loss (−8 kg), purpura, mononeuritis multiplex	PAN	Skin, muscle and nerve vasculitis, normal angiogram	neg	Poor tolerance of infusions	Complete recovery
11	M	38	Weight loss (−6 kg), fever, myalgias, arthralgias, subcutaneous nodules, segmental oedema	PAN	Skin and muscle vasculitis	neg	None	Complete recovery
12	M	72	Weight loss, fever, myalgias, purpura, segmental oedema, polyarthritis, mononeuritis multiplex	PAN	Muscle vasculitis	c-ANCA, nd	Pneumonia, septicaemia, leading to death	Death
13	M	45	Weight loss (−6 kg), fever, myalgias, arthralgias, mononeuritis multiplex, subcutaneous nodules, segmental oedema	PAN	Muscle vasculitis	-ANCA, anti-MPO	None	Complete recovery

TABLE IV
Outcome of polyarteritis nodosa and Churg–Strauss syndrome in 25 patients

Parameter	Group A CS + oral CY (n = 12)	Group B CS + pulse CY (n = 13)	Total (n = 25)
Mean follow-up	61.4 ± 14.2	60.3 ± 14.6	60.8 ± 14.5
Range (months)	(30–82)	(3–80)	
Complete recovery			
Without relapses	9	10	19
With at least one relapse	2	2	4
Failure	1	1	2

one of them developed acne. One woman who became amenorrhoeic after the third infusion required oestrogen and progesterone therapy for 5 months before her menstrual cycle was re-established.

Side-effects in the group treated orally were more frequent than in the pulse group. In addition, adverse effects were more common in women than in men; 22 side-effects were observed in women (eight patients) and 19 side-effects in men (17 patients). Every woman experienced at least one side-effect, whereas only 10/17 men experienced side-effects ($P < 0.02$).

DISCUSSION

The optimal treatment of PAN and CSS has not yet been definitively established, even if it has been greatly improved: the introduction of CS [1, 2] dramatically increased the survival rate to 48% from 13% for untreated patients; the adjunction of immunosuppressive agents and particularly CY, when the disease remains active despite CS, leads to remission in most cases [3]; specific treatments using antiviral agents in PAN related to viral infection are now available [9].

Nevertheless, it remains necessary to define the best modalities of treatment and especially to evaluate the risk/benefit ratio of the therapeutic regimens available. Despite overall improvement of prognosis, several questions remain and need answers. The French Cooperative Study Group for Vasculitides [4] has shown that oral CY improved the control of the disease, but did not improve the overall prognosis [5], and that PE should not be prescribed as a first-line treatment in primary PAN and CSS, even in the presence of poor prognostic factors [6, 8], but are useful in HBV-related PAN when they are associated with vidarabin [7] or interferon-alpha [10].

In systemic vasculitides, the modalities of administration of CY are empirical. In most series [3, 4], the patients were treated orally. The dose varied between 1 and 3 mg/kg/day. The toxicities of CY have been known for many years, and have been demonstrated in rheumatoid arthritis [14, 15], connective tissue diseases and vasculitis: leucopenia, haemorrhagic cystitis [16, 17], viral, bacterial and parasitic infections [18–22], amenorrhoea and, over the long term, development of malignancies [20]. Pulses have proven to be effective in controlling the nephritis of systemic lupus erythematosus [23] and have also been used to treat vasculitis [24–27]. In some studies [28], they were as effective as oral administration. However, in Wegener's granulomatosis, the initial response to pulse CY was generally favourable, but could not be maintained [25, 29].

The present trial addressed PAN without HBV markers and CSS. These patients were selected based

TABLE V
Treatment side-effects in polyarteritis nodosa and Churg–Strauss syndrome

Side-effect	Group A (n = 12) CS + oral CY		Group B (n = 13) CS + pulse CY		Total (n = 25)
	n	Time of occurrence (months)	n	Time of occurrence (months)	
Osteopenia	4	4 to 30	0		4
Cushing's syndrome	2	3	3		5
Amenorrhoea	3	2, 4, 6	2	3	5
Weight gain	1	2	2		3
Malaise during infusion	0		3	1, 3 8	3
Alopecia	2	not measured	0		2
Haemorrhagic cystitis	2	5, 6	0		2
Neutropenia	2	5, 12	0		2
Hypertension	2	6, 11	0		2
Skin folliculitis	2	2	0		2
Urinary tract infections	0		1	1	1
Hepatitis	1	4	0		1
Herpes keratitis	1	6	0		1
Osteonecrosis	1	11	0		1
Cataract	1	unknown	0		1
Digestive candidiasis	1	1	0		1
Sinusitis	1	3	0		1
Gastric ulcer	1	3	0		1
Pulmonary infection	0		1	4	1
Infectious bronchitis	0		1	unknown	1
Acne	0		1	unknown	1
Total	27		14		41

on their good prognostic factors as assessed by FFS [11]. In this arm with good prognostic factors (FFS = 0 for every patient), two CY regimens were compared: daily oral administration and monthly i.v. pulses. Results were comparable in both groups, with similar numbers of successes and relapses. We did not observe relapses over the long term as in Wegener's granulomatosis [11]. Even if the number of patients is too small to conclude definitively as to the indications of CY in PAN and CSS with good prognostic factors, arguments seem sufficient to use, in this group of patients, CY pulses rather than oral administration. Differences between the treatment responses observed in Wegener's granulomatosis and PAN or CSS clearly show that a homogeneous therapy cannot be prescribed for all vasculitides, and that the regimen must be adapted to the disease and its severity.

Short-term side-effects, induced by both CS and CY, were less frequently observed in the pulse group: 14 *vs* 27. Side-effects attributable to only CY, like neutropenia, haemorrhagic cystitis or alopecia, were recorded only in the oral group. The frequency of ovarian failure was comparable in both groups and observed in all premenopausal women. Infections were observed equally in both groups, with the only severe infection leading to death occurring in the oldest patient in the series; the particular susceptibility to infections of patients over 60 yr of age receiving combined CY + CS therapy has already been shown [18]. The development of infections early during the course of therapy, before the occurrence of neutropenia, is known. The observation of osteopenia only in the oral CY group is explained by the higher number of women in this group exposed to osteoporosis by their sex, amenorrhoea and CS, and possibly by their higher mean age.

The present results advocate the use of pulse rather than oral CY, but also decreasing the CS dose which is responsible for some side-effects and potentiates some CY-related side-effects. It also seems obvious that the risk/benefit ratio is high in PAN and CSS, and it would be highly desirable to adapt treatments individually as a function of age, sex and renal function and, if possible, to reduce doses and/or their duration of administration. The use of CY as first-line therapy in PAN and CSS with good prognostic factors must be evaluated in terms of responses and also in terms of CS sparing. Also to be taken into consideration is the treatment of ovarian failure with a combination of oestrogens and progestins, so as to prevent osteopenia and, in the case of contraindications, the use of bisphosphonates if the patients are osteopenic before the initiation of treatment. Lowering the dose and shortening the treatment duration could also help to limit this side-effect.

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APPENDIX

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