

CORTAGE

TREATMENT OF NECROTIZING VASCULITIDES FOR PATIENTS OLDER THAN 65 YEARS.

COMPARISON OF TWO STRATEGIES COMBINING STEROIDS WITH OR WITHOUT IMMUNOSUPPRESSANTS

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1. Trial Overview

Entry and randomization

Active, Systemic Necrotizing vasculitides: WG, MPA, PAN without HBV markers, CSS

≥ 65 years

previous treatment with corticosteroids (CS) (according to protocol) no longer than 1 month



Induction regimen =

The reference strategies, already validated in the literature

versus

“low dose strategy” oral corticosteroids + pulse cyclophosphamide



Evaluations

every 2 weeks for 1 month,

then every 3 or 4 weeks until remission,

then every 3 or 6 months depending on arm and disease severity



Study end

36 months

2. Aims of CORTAGE

Because SNV occurring in elderly patients are known to carry high risks of treatment side effects and increased mortality [1], the aims of CORTAGE are to optimize therapy by evaluating the efficacy of a new strategy based on lower doses of oral corticosteroids (OCS) and immunosuppressants (cyclophosphamide - CYC). Preliminary data indicate that Systemic Necrotizing vasculitides (SNV) occurring in patients over 65 years have a poorer outcome than younger patients (76% vs 69% at 5 years, respectively) and that 68.4% of the elderly experience treatment side effects [2]. Therefore, patients will be randomized to receive either low-dose OCS and immunosuppressants (CYC then azathioprine - AZA) or OCS with or without immunosuppressants prescribed according to regimens already published and validated in the international literature [3]. The aims of this trial are: to lower the morbidity rate in elderly SNV patients and, consequently, to reduce mortality and improve outcome.

3. Study design

3.1 Hypothesis

A combination of low-dose OCS and low-dose pulse CYC followed, at the time of remission by AZA, is able to reduce morbidity and improve outcome of elderly patients with SNV.

3.2 Inclusion criteria

- 1) Newly diagnosed WG, MPA, PAN without HBV infection, or CSS
- 2) Patients may be entered within 1 month after starting therapy if they are being treated according to protocols already validated in the literature
- 3) Age \geq 65 years

3.3. Exclusion criteria

- 1) Any cytotoxic drug within previous year, unless started within 1 month of entry
- 2) Co-existence of another multisystem autoimmune disease, *e.g.*, SLE, RA
- 3) Virus-associated vasculitides
- 4) Known HIV positivity (HIV testing will not be a requirement for this trial)
- 7) Previous malignancy (usually excluded unless approved by the trial co-ordinator)
- 8) Age < 65 years
- 9) Inability to give informed consent

3.4. Interventions

3.4.1. Drug regimens

1) After randomization, comparison of 2 steroid doses with or without immunosuppressants with 2 different regimens.

2) Arm A (conventional strategy):

Induction:

- a. Oral CS at the dose recommended in *Appendix A.2.1*
- b. Immunosuppressants prescribed according to the FFS score, *i.e.*:
 - i. Steroids alone for CSS or PAN without poor prognostic factors FFS = 0 (*see Appendix A.2.1*)
 - ii. Pulse CYC for CSS or PAN with a FFS score ≥ 1 point
 - iii. Pulse CYC for every patient with ANCA⁺ SNV (WG and MPA)
- c. When prescribed, CYC will be administered at the dose of 0.5 g/m² on D1, D15, D29, then every 3 weeks until remission of ANCA⁺ SNV or every 4 weeks until remission of CSS or PAN with poor prognostic factors
- d. **Maintenance:** AZA 2 mg/kg/d for 18 months.

3) Arm B (low-dose strategy):

Induction:

- a. Pulse CYC, 500 mg (fixed dose) on D1, D15, D29 then every 3 weeks until remission (maximum 6 infusions).
- b. Maintenance: AZA 2 mg/kg/d for 18 months.
- c. Prednisone: 30% less than the EUVAS regimen (*see Appendix A.2.1*)

4) Adjuvant treatments in both arms:

- bisphosphonates (risedronate monosodium 35 mg/week or alendronate monosodium 70 mg/week), unless contraindicated or not tolerated
- oral calcium and vitamin D₃, unless contraindicated or not tolerated
- aspirin (100 mg/day)
- folic acid (5 mg/day)
- statin (pravastatin or fluvastatin is preferred because of fewer drug interactions, at minimal dose in the absence of hypercholesterolaemia), unless contraindicated or not tolerated

3.4.2. Evaluations (*see also Appendix A.3*)

- 1) Study parameters will be determined on D1, D15, D29, then every 3 or 4 weeks until remission depending on trial arm and disease severity, then every 3 or 6 months until 3 years after the patient's inclusion in the study.
- 2) Birmingham vasculitis activity score (BVAS) and vasculitis damage index, (VDI) will be calculated on D1, D15, D29, then every 3 or 4 weeks until remission depending on arm and disease severity, then every 3 or 6 months until 3 years after the patient's inclusion in the study.
- 3) Short form-36 questionnaire (SF-36) and the Health Assessment Questionnaire Disability Index (HAQ-DI) will be determined on D1, D15, D29, then every 3 or 4 weeks until remission depending on arm and disease severity, then every 3 or 6 months until 3 years after the patient's inclusion in the study.
- 4) Optional. Blood will be drawn on D1, D15, D29, then every 3 or 4 weeks until remission depending on arm and disease severity, then every 3 or 6 months until 3 years after the patient's inclusion in the study.

3.5. End points

- 1) The primary end point is the number of side effects at 3 years.
- 2) Secondary end points are:
 - i. survival at 3 years
 - ii. relapse rate until the 3rd year
 - iii. cumulative exposure to OCS and AZA
 - iv. cumulative BVAS, VDI, HAQ-DI and SF-36 values

3.6. Adverse effects reporting

- 1) The presence of any adverse effects will be actively sought and will be recorded on standardised forms in the patient's record book.
- 2) Adverse effects of therapy will be reported to the Independent Review Board.
- 3) Adverse effects necessitating withdrawal of the protocol treatment will be determined after discussion with the trial coordinator.

3.7. Withdrawal

- 1) Patient's or patient's physician's request with no further explanation. When possible, reason for withdrawal should be noted in the patient's record book.

- 2) Patients not achieving remission within a prolonged induction phase of 6 months in arm A or 6 CYC pulses in arm B are considered failures and will be withdrawn from the trial. Their subsequent treatment will follow local practices.
- 3) Changes of the treatment regimen dictated by the physician's and patient's choice (drug intolerance, relapse *etc.*) will result in withdrawal from the trial but should be recorded in the patient's record book.

4. Statistical analysis

4.1. Power

The number of patients required for the study is based on the comparison of event-free survival rates at 3 years using the log-rank test. Our goal is to lower the rates of events from 70% to 40%, with 3-year event-free survival rising from 30% to 60%. Based on the comparison of 3-year event-free survival rates for the two arms with 5% significance and a power of 80, 44 patients per arm will be required [4]. Considering that 10% patients will be lost-to-follow-up, a total of 98 patients will have to be enrolled.

4.2. Analysis

Analysis will be based on intention-to-treat. Data will be expressed as means \pm standard deviation or median with its interquartile range, and percentages with 95% confidence intervals for qualitative data. Means will be compared using Student's t-test or, if required, a Wilcoxon test. Percentages will be compared using a Pearson chi-2 test or Fisher's exact test.

The main analyses of side effects and mortality will compare survival curves using the log-rank test (univariate analysis) and Cox models for multivariate analysis.

Analyses will also use the Q-TWiST method (Quality-adjusted Time Without Symptoms and Toxicity) [5, 6]. This method enables weighting of the clinical efficacy by the quality of life associated with the successive health states of the patients. Each health state is associated with a 'utility' coefficient comprised between 0 and 1 (0 = as bad as death, 1 = as good as the best health state possible) and reflects the patient's choices.

Three health states will be identified in this trial: during disease progression (Prog), during treatment-related toxicity (Tox) and when neither disease progression nor toxicity is present (TwIST). The mean duration (and variance) of each health state will be determined using the Kaplan–Meier method for each arm.

Toxicity will be defined as any event occurring secondary to treatment, and death attributed to or favoured by the prescribed regimen. The criteria retained to define disease progression are: treatment

failure (absence of vasculitis response to therapy), relapse (reappearance of clinical and/or biological manifestations of vasculitis). Disease progression will also be evaluated using BVAS.

The judgment criterion will be survival duration adjusted by its quality, calculated for each group with the following equation: $Q\text{-TWiST} = U_{\text{tox}} \times \text{Tox} + \text{TWiST} + U_{\text{Prog}} \times \text{Prog}$, where U_{tox} and U_{Prog} are utility coefficients attributed by the patient to toxicity and progression, respectively, according to the quality of life during those times. The 2 arms will be compared by sensitivity analyses conducted by varying the values accorded utility coefficients associated with the 3 health states. Threshold values will eventually be identified that will lead us to prefer one treatment to the other (at the usual significance threshold of 5%).

Statistical analyses will be conducted in the Department of Biostatistics of Cochin Hospital (Pr Coste) with a SAS software version 8.

5. Ethical Considerations

- 1) Ethical approval will be sought by local Ethics Committees in each country. Approval received in one country will be circulated among all study centres to facilitate accordance of local approval.
- 2) Patients will be entered only after they have given written, informed consent.
- 3) Details of patients' identities will be restricted to the local investigator.
- 4) Data will be coded prior to computer entry. Study databases will be independent of computer networks. Confidentiality of patient data will be respected.
- 5) Participation in this study should not require additional tests or clinic consultations above normal practice, except for the (optional) 10-ml blood sample drawn at inclusion.

6. Trial Coordination

Prof. Loïc Guillevin in Paris will coordinated the trial in cooperation with an international Steering Committee. The trial coordinators are available to give advice on patient management and drug administration. The principal coordinator will register and randomize patients and dispatch a patient record book. A clinical trial assistant (CTA) will be appointed depending on the funding of the trial. The trial administration office (TAO) will be informed of each inclusion and will receive a copy of each report form.

6.1. Trial organisation

- 1) Patient registration forms will be faxed or e-mailed to the principal coordinator.
- 2) The principal coordinator will register and randomize patients and dispatch a patient record book (3 copies of each page in English and French).
- 3) Patient activity will be monitored by data returns every trimester from study centres.
- 4) Trial data will be entered into the database by the principal coordinator.

- 5) The principal coordinator will submit reports every trimester on trial progress to the Trial Management Subcommittee.
- 6) Participating centres will be visited by the principal investigator at least once during the trial.
- 7) Records of patient registration will be maintained both locally and centrally.
- 8) A copy of all documents will be dispatched to the TAO (in the UK). All the recorded data will be transmitted to the TAO to be included in the central database.

6.2. Data collection

- 1) Patient record book: BVAS, HAQ-DI and SF-36, laboratory variables, and adverse effects will be entered. At the end of every trimester data will be forwarded by surface mail.
- 2) For the purpose of central ANCA testing, optionally collected serum samples will be shipped to a central serum bank: 10 ml of sera to be taken at entry, at 0, ½, 1, 3, 6, 9, 12, 15, 18, 24, 30 and 36 months and at relapse. Sera will be batched and shipped frozen to the serum bank.

6.3. Independent review board

- 1) An Independent Review Board is appointed (to be chosen).
- 2) Trial coordinators will submit annual reports by the Independent Review Board concerned with recruitment rate, adverse effects and data returns.
- 3) Once 50% of patients have been recruited, end-point data will be reviewed (participating physicians will be blinded to the outcome) and will hopefully allow early identification of unexpected variations of responses between arms.

6.4. Finances

- 1) Financial support will be sought locally.
- 2) Administrative costs will be covered by the coordinators.
- 3) No additional medical costs should be incurred by participation into the trial.

6.5. Trial duration

- 1) A total of 5 years: 36 months per patient; 24 months for recruitment. Trial launch in July 2005.

Appendix 1. Study Medications

A.1.1. Cyclophosphamide

CYC is an inactive pro-drug, converted by the mixed-function oxidase system in the liver into the alkylating agents 4-hydroxy-cyclophosphamide and phosphoramidate mustard, which alkylate guanine nucleotides, thereby blocking cell division. Bioavailability after oral administration is greater than 75%, but the production rates of active metabolites vary widely between individuals. The relationship of renal and hepatic failure with the production and elimination of active metabolites has not been fully determined. Bladder toxicity is caused by renal excretion of the metabolite acrolein, which can cause haemorrhagic cystitis and thus sharply raise the risk of bladder cancer. Other adverse effects include nausea, vomiting, myelosuppression with neutropenia, infections, alopecia and infertility. Permanent ovarian failure occurs in over 50% of the women exposed for 1 year and is age-related; male infertility has been less well studied. Leukaemia and lymphoma incidences are increased 10-fold with prolonged administration; less common adverse-effects include pulmonary fibrosis, hepatitis and the syndrome of inappropriate anti-diuretic hormone (ADH) secretion.

A.1.2. Azathioprine (AZA)

After hepatic conversion to 6-mercaptopurine, AZA cytotoxic effects are mediated by diminished purine synthesis, incorporation of purines into DNA, and impaired endonuclease repair activity of DNA polymerase. The drug is well absorbed after oral administration and elimination requires hepatic metabolism by xanthine oxidase; AZA interacts strongly with xanthine-oxidase inhibitors, such as allopurinol. Lymphocyte functions are affected, B-cells more than T-cells, and the cellular component of the inflammatory response is suppressed. The major adverse effects are nausea and vomiting, dose-dependent myelosuppression and reversible, cholestatic, hepatic toxicity. Furthermore, dose-dependent increases of skin cancers and lymphomas are seen following administration for > 2 years after organ transplantation.

A.1.3. Prednisone/Prednisolone

Prednisone is a synthetic derivative of cortisone with widespread influence on metabolism and organ function. Desirable effects in SNV affect the suppression of acute and chronic inflammatory disease processes and immune-cell functions. The major short-term adverse-effects of OCS are salt and water retention, hypertension, hyperglycaemia, central nervous system stimulation, peptic ulceration and immunosuppression. While such effects are reversible, when OCS use is prolonged additional adverse-effects including osteoporosis, subcapsular cataracts, skin fragility, myopathy, cushingoid facies, hirsutism, alopecia, fat redistribution, striae cutis distensae. Notably in SNV, the cumulative OCS dose has been correlated with the total frequency of adverse-effects, particularly infections [7].

Appendix 2. Drug regimens

A.2.1. Prednisone

Arm A

One to 3 methylprednisolone pulse(s): 15 mg/kg/day

Then prednisone:

- from D4: 1 mg/kg/day (× 3 weeks with 3 pulses on D1, 2, 3)
- from D22: 0.75 mg/kg/day (× 3 weeks)
- from D43: 0.5 mg/kg/day (× 2 weeks)
- from D57 (start week 9): 0.42 mg/kg/day (× 4 weeks)
- from D85 (start week 13): 0.33 mg/kg/day (× 4 weeks)
- from D113 (start week 17): 0.29 mg/kg/day (× 4 weeks)
- Start of the 6th month (M6, W21, D141): 0.25 mg/kg/day (× 4 weeks)
- Start of the 7th month (M7, W25, D169): 0.21 mg/kg/day (× 12 weeks)
- from the 10th month (M10, W37, D253) to the 12th month included: 0.17 mg/kg/day (× 12 weeks)
- then reduce 1 mg/month to 5 mg/day, dose to be maintained for 8 weeks.
- then reduce 1 mg every 2 months until complete discontinuation of treatment.

Arm B

Only one methylprednisolone pulse can be given initially: ≤ 500 mg.

Prednisone at an initial dose: 1 mg/kg/day for 21 days (another pulse can be envisaged during these first 21 days).

Then reduce 5 mg/week until 30 mg/day.

30-mg/day dose maintained for 3 weeks.

Then reduce 2.5 mg every 5 days until 15 mg/day.

From 14 mg/day of prednisone, reduce 1 mg every 10 days until complete discontinuation.

Only patients with CSS can receive prolonged steroid therapy (prednisone: 5 to 7 mg/day) to control asthma.

Arm A				Arm B			
Days	Duration	Dose/day (mg)	Total dose (mg)	Days	Duration	Dose/day (mg)	Total dose (mg)
1 to 21	3 week	60	1260	1 to 21	3 week	60	1260
22 to 42	3 week	45	945	22 to 28	1 week	55	385
43 to 56	2 week	30	420	28 to 34	1 week	50	350
57 to 84	4 week	25	700	35 to 41	1 week	45	315
85 to 112	4 week	20	560	42 to 48	1 week	40	280
113 to 140	4 week	17.5	490	49 to 55	1 week	35	245
141 to 168	4 week	15	420	56 to 76	3 week	30	630
169 to 253	12 week	12.5	1050	77 to 81	5 days	27.5	137.5
254 to 338	12 week	10	840	82 to 86	5 days	25	125
339 to 366	4 week	9	252	87 to 91	5 days	22.5	112.5
367 to 394	4 week	8	224	92 to 96	5 days	20	100
395 to 442	4 week	7	196	97 to 101	5 days	17.5	87.5
443 to 470	4 week	6	168	102 to 106	5 days	15	75
472 to 499	8 week	5	280	107 to 116	10 days	14	140
500 to 555	8 week	4	224	117 to 126	10 days	13	130
556 to 611	8 week	3	168	127 to 136	10 days	12	120
612 to 667	8 week	2	112	137 to 146	10 days	11	110
668 to 723	8 week	1	56	147 to 156	10 days	10	100
				157 to 166	10 days	9	90
				167 to 176	10 days	8	80
				177 to 186	10 days	7	70
				187 to 196	10 days	6	60
				197 to 206	10 days	5	50
				207 to 216	10 days	4	40
				217 to 226	10 days	3	30
				227 to 236	10 days	2	20
				237 to 246	10 days	1	10
Total duration		Total dose		Total duration		Total dose	
723 days 26 months	104 weeks	8305 mg		247 days 8.8 months	36 weeks	5152,5 mg	

CS dose in arm A and arm B. Example for an inclusion weight of 60 kg.

Notes:

- 1 Prednisone/Prednisolone may be administered as an intravenous pulse of 15 mg/kg/day (maximal: 1 g/d) on the first 3 consecutive days in arm A. Prednisolone may be administered as a single intravenous pulse: not to exceed 500 mg in arm B.
- 2 If remission is not achieved by 3 months, consider changing from pulse to oral daily CYC.

A.2.2. Failure to achieve remission by 3 months

1. The trial coordinators should be informed.
2. For failure to control progressive disease activity during the remission-induction period: (rising serum creatinine or progression of disease activity in other vital organs), additional treatment is recommended with i.v. methylprednisolone, 15 mg/kg/day for 3 days (maximum 1 g/day) and/or to follow local practices. Preliminary data also suggest that any patient who fails on pulse CYC may do better on continuous oral CYC. In addition, plasma exchanges may be used. All patients should remain in the trial for the purposes of data follow-up even if they withdraw from the trial drug regimen.
3. Trial data collection should continue and the patient remains in the trial.

A.2.3. Side effects

Leucopenia

1. Stop immunosuppressant if white blood cell (WBC) count $< 4 \times 10^6/L$. When WBC count returns to $> 4 \times 10^6/L$, restart with immunosuppressant dose lowered by at least 100 mg/pulse for CYC and 25 mg for AZA. Monitor weekly for 1 month.
2. If severe ($< 1 \times 10^6/L$ or prolonged ($< 4 \times 10^6/L$ for > 2 weeks), restart immunosuppressant at half dose, increasing to target dose as weekly WBC counts permit.
Consider: *Pneumocystis carinii* prophylaxis, fungal prophylaxis; test for CMV infection and treat when present.
3. For falling WBC ($< 6 \times 10^6/L$ and decline of $> 2 \times 10^6/L$ over previous count), check again 1 week later and lower dose as above.

A.2.4. Prophylaxis

1. Peptic ulcer (suggested only): ranitidine or omeprazole, not cimetidine or misoprostol, for at least 6 months.
2. Fungal infection (suggested only): only if needed.

3. *Pneumocystis carinii* (in both arms if CD4⁺ lymphocyte count < 300/mm³): sulfamethoxazole–trimethoprim 400/40 mg/day or monthly aerosolised pentamidine (9).
4. Haemorrhagic cystitis in both arms: mesna during CYC therapy at the same dose as CYC.
5. Osteoporosis in both arms: oral calcium and vitamin D₃, and bisphosphonate, unless contraindicated or not tolerated.
6. Tuberculosis: rifampicin (10 mg/kg/day) + isoniazid (4 mg/kg/day) for 3 months, or isoniazid alone (4 mg/kg/day) for 9 months, if rifampicin is contraindicated. Indications: no history of treated tuberculosis or recent contact with an infected individual. Increase the OCS dose by 30% with rifampicin.

A.2.5. Drug regimen changes in case of rising ANCA titre

Some centres consider it unethical to lower immunosuppressive drug doses when ANCA titres rise because an imminent relapse is suspected. Therefore, an option to postpone dose reduction under these conditions is included in the protocol.

Definition of ANCA-titre rise:

1. An ANCA-titre rise is defined as: conversion from negative to positive (any positive value for indirect fluorescence titres)
2. A rise in indirect fluorescence titres by at least 3 titre points (example: from 1:16 to 1:128 or higher)
3. A rise of at least 50% for ELISA optical density (OD) readings (PR3-ELISA for C-ANCA, MPO-ELISA for P-ANCA) by.

If an ANCA-titre rise is observed:

- Option to postpone the next dose-reduction step for OCS and AZA or mycophenolate mofetil (MMF) suggested by the protocol by 4 weeks.
- If no relapse occurs and if the ANCA titres do not rise further (definition: see above), dose reduction can proceed.

A.2.6. Drug-regimen changes for relapse (non-obligatory guidelines)

Major relapse

1. Use pulse or oral CYC at 2 mg/kg/day [8] and stop AZA if relapse occurred during maintenance therapy.
2. Increase OCS to 0.5 mg/kg/day, then lower to 20 mg/day by 4 weeks.
3. Once remission is achieved, follow the OCS + CYC regimen starting at the 3-month point.
4. If remission is not achieved after 2 months, follow local practices.

Minor relapse

1. Increase AZA to 3 mg/kg/day.
2. Increase OCS to 0.5 mg/kg/day then reduce to 15 mg/day over 1 month.
3. Once remission is achieved, return to previous regimen starting at the 3-month point.

Relapsing patients will remain in the study and all changes in drugs and doses are to be recorded in the patient record book.

Appendix 3. Study Evaluations

Minimum information required for the study. Additional tests should follow local practices.

A.3.1. Entry

1. **VITAL Scores:** BVAS, vasculitis damage index, (VDI), Short-form 36 (SF-36) and HAQ-DI.
2. **Haematology**
 - a) Full blood count (FBC): haemoglobin (Hb), white cell count (WBC), neutrophil, lymphocyte and platelet counts
 - b) ESR or CRP
3. **Biochemistry**
 - a) Serum creatinine and creatinine clearance
 - b) ALT, AST, alkaline phosphatase, albumin, glycated haemoglobin (such as Hb_{A1c}), glycaemia, cholesterolaemia, CPK, LDH, blood calcium, phosphataemia.
 - c) C-reactive protein (CRP).
4. **Immunology**
 - a) IgG, IgA and IgM levels.
 - b) ANCA (IIF, PR3 and MPO ELISA).
 - c) Hepatitis Bs Ag (if positive, check HBeAg), anti-hepatitis C antibodies, anti-CMV antibodies.
 - d) Optional: ANA, anti-GBM-antibodies, rheumatoid factors, cryoglobulins, complement C3, C4).
5. **Other**
 - a) 10 ml of serum saved (optional).
 - b) Urinalysis for red cells, proteinuria and cytobacteriology
 - c) Chest and sinus X-rays.

A.3.2. On D1, D15 and D29, then every 3 or 4 weeks until remission, then every 3 or 6 months depending on the trial arm and disease severity:

- BVAS, VDI, SF-36, HAQ-DI
- FBC: Hb; WBC, neutrophil, lymphocyte and platelet counts.
- ESR, CRP, ANCA, ALT, AST, CPK, LDH, glycaemia
- creatinine, creatinine clearance (24-hour protein, if proteinuria present),
- Urinalysis for red cells, proteinuria, glycosuria and cytobacteriology
- 10 ml of serum saved (optional)

Note:

1. VITAL is a composite of BVAS, VDI, HAQ-DI and SF-36 functional assessment score. BVAS and VDI have been validated, and BVAS will help define remission and relapse in this study. The disease extension index (DEI) score will be computed from the BVAS data.

2. Should new macroscopic haematuria occur, cystoscopy should be performed. Consider cystoscopy for new microscopic haematuria. If haemorrhagic cystitis is confirmed, surveillance cystoscopy should be performed every 6 months.

A.4. Disease definitions

A.4.1. Wegener's granulomatosis

Systemic WG is characterised by granulomatous inflammation of the respiratory tract, together with necrotizing vasculitis affecting small- to medium-sized vessels; necrotizing glomerulonephritis is common and reflects renal involvement. A C-ANCA pattern by IIF (predominant specificity for PR3 by ELISA) is found in over 90% of untreated patients with generalised WG; some studies have found a minority of cases to have ANCA targeting myeloperoxidase (MPO-ANCA). In WG with disease localised to the respiratory tract, ANCA positivity is less frequent.

For the purposes of this study, a diagnosis of WG requires the presence of chronic inflammation, lasting at least 4 weeks and not attributable to another cause, supported by characteristic histology on biopsy and/or detectable C-ANCA by IIF or PR3-ANCA by ELISA. WG is a clinical–pathological syndrome, for which confidence in the diagnosis might require prolonged observation; the diagnosis may therefore be qualified by the terms, ‘suspected’, ‘probable’ or ‘definite’. When the diagnosis is in doubt, the trial coordinator should be consulted. Characteristic or confirmatory histology for non-renal biopsies requires the exclusion of other causes and an inflammatory infiltrate, predominantly neutrophils, with at least one of the following:

1. necrotizing vasculitis affecting small- to medium-sized vessels
2. epithelioid granulomata
3. giant cells

Systemic WG requires the involvement of an extrarespiratory tract organ (*e.g.*, kidney, skin, nervous system) in addition to respiratory tract disease. General constitutional symptoms (*e.g.*, fever, headache, myalgias, arthralgias, fatigue, weight loss of > 2 kg) themselves do not constitute extrarespiratory involvement but indicate that the disease is active and systemic. Disease involving only one non-vital organ (usually the upper respiratory tract) with fewer than 2 general symptoms is defined as localised.

A.4.2. Microscopic polyangiitis

MPA is characterised by vasculitis predominantly affecting small vessels. Renal involvement is common and manifests as necrotizing glomerulonephritis. Granulomata are absent. Medium-sized vessel arteritis may also be seen. MPA is mostly associated with MPO-ANCA, less often with PR3-

ANCA; a minority of MPA patients are ANCA-negative or recognise other ANCA autoantigens. For the purposes of this study, PR3–C-ANCA-positive patients may be classified as MPA when a chronic inflammatory process with non-granulomatous vasculitis of small vessels (*i.e.* capillaries, venules, arterioles or small arteries) is present.

A.4.3. Kidney-limited vasculitis

Isolated pauci-immune necrotizing, crescentic glomerulonephritis, typically known as idiopathic rapidly progressive glomerulonephritis (idiopathic RPGN) has many features suggesting that it represents a kidney-limited form of WG or MPA, including the presence of circulating anti-MPO or anti-PR3 antibodies.

A.4.4 Polyarteritis nodosa

AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA (1990)

For classification purposes, a patient shall be said to have polyarteritis nodosa if at least 3 of these 10 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 82.2% and specificity of 86.6%.

- Weight loss > 4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness or leg tenderness
- Mono- or polyneuropathy
- Diastolic arterial pressure > 90 mm Hg
- Renal insufficiency (BUN > 400 mg/l or creatininaemia > 15 mg/l)
- Serological hepatitis B markers (HBs antigen or anti-HBs antibody) or virus replication
- Arteriographic abnormalities (aneurysms and/or visceral artery occlusions)
- Small- or medium-calibre artery containing granulocytes with or without mononuclear leucocytes in the artery wall

A.4.5 Churg–Strauss syndrome

AMERICAN COLLEGE OF RHEUMATOLOGY CRITERIA (1990)

For classification purposes, a patient shall be said to have Churg–Strauss syndrome if at least 4 of these 6 criteria are present, yielding a sensitivity of 85% sensitivity and specificity of 99.7%.

- Asthma
- Blood eosinophilia > 10%
- Mono- or polyneuropathy
- Non-fixed pulmonary infiltrations
- Paranasal pain or abnormality
- Extravascular eosinophils in biopsy

A.4.6. Remission

Full clinical remission is indicated by complete absence of disease activity, as assessed by the BVAS. Partial remission is defined as partial improvement or – in the case of smouldering disease – an unchanged status within the last 6 weeks. Absence of renal disease activity: stable or falling creatinine/microhaematuria and the absence of red cell casts. Absence of pulmonary disease activity: resolution of pulmonary opacities; size reduction of existing lesions unless attributable to scarring; no new lesions. Normal C-reactive protein supports the diagnosis of complete remission. ANCA are ignored for the purpose of this study.

A.4.7. Relapse

1. A major relapse is defined as the recurrence or new appearance of major organ involvement, such as the following, if they are attributable to active vasculitis:
 - a) Serum creatinine increase of > 30% or creatinine clearance reduced by > 25%, within a 3-month period or histological evidence of active, focal, necrotizing glomerulonephritis. Biopsy is strongly recommended for recurrent haematuria or an unexplained creatinine rise.
 - b) Clinical, radiological or bronchoscopic evidence of pulmonary haemorrhage or granulomata. Biopsy may be appropriate for undiagnosed opacities.
 - c) Threatened vision, *e.g.* orbital granuloma increasing in size or retinal vasculitis.

- d) Marked subglottal or bronchial stenosis.
 - e) New multifocal lesions on brain MRI suggestive of cerebral vasculitis.
 - f) Motor mononeuritis multiplex.
 - g) Gastrointestinal haemorrhage or perforation.
2. A minor relapse is defined as enhanced disease activity of less severity than initially, such as the following, if they are attributable to active vasculitis:
- a) Ear, nose and throat (ENT): epistaxis, crusting, pain, onset or progression of deafness, active nasal ulceration or proliferating mass seen during nasal endoscopy.
 - b) Mouth ulcers.
 - c) Rash.
 - d) Myalgias, arthralgias, arthritis.
 - e) Episcleritis or scleritis.
 - f) Pulmonary symptoms, *e.g.* cough, wheeze, dyspnoea, without or with minor radiological changes.
3. Relapse is confirmed by:
- a) Exacerbation of at least 2 constitutional symptoms (malaise, weight loss, fever or night sweats).
 - b) CRP rise.
4. If in doubt, contact a trial coordinator.

Note:

A rising ANCA titre may precede relapse. These patients should be monitored more closely.

A.5 References

1. Gayraud M, Guillevin L, le Toumelin P, et al.: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; 44: 666-75.
2. Mouthon L, Le Toumelin P, Andre MH, Gayraud M, Casassus P, Guillevin L: Polyarteritis nodosa and Churg-Strauss angiitis: characteristics and outcome in 38 patients over 65 years. *Medicine (Baltimore)* 2002; 81: 27-40.
3. Guillevin L, Lhote F, Gayraud M, et al.: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore)* 1996; 75: 17-28.
4. Machin D, Campbell M, "Statistical tables for the design of clinical trials.," Blackwell Scientific Publications, Oxford, 1987.
5. Glasziou PP, Simes RJ, Gelber RD: Quality adjusted survival analysis. *Stat Med* 1990; 9: 1259-76.
6. Cole BF, Gelber RD, Goldhirsch A: Cox regression models for quality adjusted survival analysis. *Stat Med* 1993; 12: 975-87.
7. Jarrousse B, Guillevin L, Bindi P, et al.: Increased risk of *Pneumocystis carinii* pneumonia in patients with Wegener's granulomatosis. *Clin Exp Rheumatol* 1993; 11: 615-21.
8. Guillevin L, Cordier JF, Lhote F, et al.: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. *Arthritis Rheum* 1997; 40: 2187-98.

P.1. CORTAGE – Summary of Practical Procedures

Potentially suitable?

- An untreated patient ≥ 65 years old with newly diagnosed or active WG, MPA, RLV, PAN or CSS
 - Informed consent given
 - Patient may be entered within 1 month after starting therapy if treated according to protocol
-

Ready to enter?

- Fax or e-mail registration form to principal coordinator office for randomization
 - BVAS, VDI, SF-36, HAQ-DI and baseline laboratory data
-

Entry

- Your patient will be registered and randomly assigned to one of two arms
 - Start induction treatment (OCS with or without CYC according to protocol)
 - Option to use plasma exchanges in severely ill patients (alveolar haemorrhage and/or creatininaemia $> 500 \mu\text{mol/l}$) during the first 2 weeks of induction treatment according to local practices.
-

Remission induction phase

- Clinical (BVAS, HAQ-DI, SF36), biological evaluation on D15, D29 and every 3 or 4 weeks
 - Continue CYC until 3 (and up to 6) months until remission achieved. Maximum 6 pulses in arm B
 - If no remission by 6 months: withdraw from trial drug regimen and follow local practices
-

Remission-maintenance phase

- AZA: 2 mg/kg/day in both arms. Duration: 18 months. If AZA is contraindicated or not tolerated, prescribe MMF (2 g/day) or methotrexate (0.25 mg/kg/week).
-

End of the study: 5 years (3 years for each patient)

- Complete termination record; send data to trial database

Coordination:

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P2. Patient Information Sheet used in France

This information sheet should be adapted to legislation in each participating countries and translated in to local language(s).

SYSTEMIC NECROTIZING VASCULITIDES IN THE ELDERLY.

COMPARISON OF TWO TREATMENT STRATEGIES: STEROIDS WITH OR WITHOUT IMMUNOSUPPRESSANTS (CORTAGE)

Dear Sir or Madam,

Your doctor has proposed that you participate in a clinical and therapeutic trial concerning the vasculitis with which you are afflicted, *i.e.*, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome, or polyarteritis nodosa.

To help you can decide whether or not to participate in this study, here is some information about these diseases.

Vasculitis is an inflammation of the blood vessels. The inflammatory reaction occurs mainly around blood vessels and preferentially affects nerves, skin, joints, the digestive tract, the lungs and, sometimes, other sites, like the nasal sinuses, the heart, *etc.* ...

The involvement of several organs defines a systemic form of the disease. The precise cause of the disease is often unknown; sometimes it is caused by a virus. However, we do know that the 'trigger' induces a deregulation of the immune system.

The severity of this disease justifies the use of corticosteroids and sometimes immunosuppressants.

Because systemic necrotizing vasculitides are known to have a high risk of treatment side effects, particularly in patients over 65 years old, the aims of this study are to optimize the treatment by evaluating the efficacy of a new strategy based on lower doses of steroids and immunosuppressants.

Regardless of the arm to which you will be assigned, your doctor will prescribe medications to protect your bones and vessels.

The data collected during the course of this trial will be stored in a computerized database to which only the coordinating physicians, trial investigators and their medical associates will have access. Your personal data cannot be transmitted to anyone and all statistical analyses will be conducted with complete respect of the confidentiality of your medical records, as stipulated in the French Law on Informatics and Liberty (enacted 6 January 1978, modified 1 July 1994). You have the right to access the information concerning you and to rectify it at any time through the intermediary of you physician, as stipulated by Article 40 of the above-cited law.

The Ethics Committee of Aulnay-sous-Bois Hospital has approved this trial and, in accordance with the French law, the study promoter, Assistance Publique–Hôpitaux de Paris, has procured the necessary insurance to cover its civil responsibility, in accordance with the law of 20 December 1988, as modified by the law of 25 July 1994.

You are by all means free not to participate. You have the right to withdraw from the study at any time without specifying your reasons.

Your decision will in no way affect the quality of care that you will be given and you incur no legal or moral responsibility vis-à-vis the investigators and their study. The confidentiality of these data will be fully respected.

P3. Patient's Consent Form

I, the undersigned, _____

Born _____

Living at _____

– Declare that the objectives, the conditions of the therapeutic study on systemic necrotizing vasculitides and its duration have been clearly explained to me, as were the constraints and foreseeable risks, including the premature termination of the trial. I was given a copy of the Patient's Information Sheet. I was given the opportunity to ask all the questions I considered necessary to inform me. I was also told that the Ethics Committee of the Aulnay-sous-Bois Hospital had approved this study.

– Know that I can refuse to participate in this study or withdraw my consent to participate at any time, without running any risk of incurring any prejudice concerning all subsequent treatment of my disease.

– Accept, by signing this form, to participate freely with full knowledge of the facts in the clinical and therapeutic study conducted by Doctor _____.

Date: _____

Doctor's signature

Patient's signature