

ECSYSVASTRIAL

PROTOCOL

January 5th 1995

Randomised trial of cyclophosphamide versus azathioprine during remission in ANCA positive Systemic Vasculitis

(CYCAZAREM)

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(ECSYSVASTRIAL)

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Summary

Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) are primary systemic vasculitides predominantly affecting small blood vessels with heterogeneous clinical presentations. Their standard treatment with corticosteroids and cyclophosphamide is usually effective at controlling active disease, but continued treatment is necessary to prevent disease relapse, which exposes patients to the cumulative toxicities associated with these agents. Of alternative drugs for the maintenance of remission, azathioprine, which is safer than cyclophosphamide, has been in regular use by some centres for over 15 years. This trial is designed to compare the efficacy and safety of azathioprine to oral cyclophosphamide in the maintenance of remission in new patients with WG, MP, or renal-limited vasculitis with positivity for anti-neutrophil cytoplasm autoantibodies and threatened vital organ function. Patients will receive the same induction therapy with prednisolone and cyclophosphamide for three months, and if a stable remission is achieved, they will be randomised to receive azathioprine or continued cyclophosphamide, both combined with a reducing dose of prednisolone. After one year, cyclophosphamide will be stopped and all patients will continue on a tapering dose of azathioprine and prednisolone for a further six months. The control of disease activity and the incidence of adverse effects will be compared between the two groups. It is estimated that around 150 patients will be required.

ECSYSVASTRIAL

The ECSYSVASTRIAL study group was convened in January 1994 under the European Community (EC) BIOMED 1 concerted action programme to co-ordinate therapeutic trials in systemic vasculitis (SV). This was itself a development from an existing EC/BCR study group concerned with the design and standardisation of solid phase assays for determination of anti-neutrophil cytoplasm autoantibodies (ANCA, antibodies prevalent in SV) brought together in 1991. The aims of the ECSYSVASTRIAL study group include the design and standardisation of disease scoring and data collection methodology, the design and facilitation of therapeutic trials and the harmonisation and improvement of the treatment of these disorders within the EC.

An approach to the treatment of SV based on the extent and severity of disease has been developed by the ECSYSVASTRIAL study group. Four basic treatment protocols have been designed for WG and MP:

1. Early systemic WG or MP without overt renal involvement (NORAM)
2. **WG, MP or renal-limited vasculitis (RLV) with mild or moderate renal involvement or other threatened vital organ function (CYCAZAREM)**
3. WG, MP or RLV with severe renal involvement (MEPEX)
4. SV cases refractory to standard treatment (WARCRY)

Moreover ECSYSVASTRIAL members may participate in two supplementary, existing studies:

5. Non-systemic WG limited to the upper and/or lower respiratory tract (MAYO)
6. Classical polyarteritis nodosa and Churg-Strauss angiitis (CHUSPAN)

The first five protocols form a continuum with partially shared treatment arms and inclusion and exclusion criteria covering the entire spectrum of WG and MP. Protocols 1-3 include three subsidiary protocols: SAVAS, RELANCA and VITAL. SAVAS looks at the role of nasal carriage of Staph. Aureus, RELANCA at the relation between relapse and ANCA levels, while scoring of disease activity and extent, morbidity and function will be assessed using the VITAL protocol.

The MAYO and CHUSPAN studies were conceived and are co-ordinated by Ulrich Specks (Mayo Clinic, USA) and Loïc Guillevin (Bobigny, France) respectively. Further details about these studies may be obtained from the ECSYSVASTRIAL investigators or the trial co-ordinators.

The ECSYSVASTRIAL activities are co-ordinated by Niels Rasmussen, Copenhagen, Denmark.

Contents

1.	Background	
1.1.	The diseases	4
1.2.	Treatment of WG and MP	4
1.3.	Aims of CYCAZAREM	4
2.	Study drugs	
2.1.	Cyclophosphamide	5
2.2.	Azathioprine	5
2.3.	Prednisolone	5
3.	Hypothesis	6
4.	Study design	
4.1.	Nature	6
4.2.	Rationale	6
4.3.	Inclusion criteria	6
4.4.	Exclusion criteria	6
4.5.	End-points	7
4.6.	Interventions	7
4.7.	Withdrawal	7
4.8.	Adverse-effects reporting	7
4.9.	Statistical analysis	7
4.10.	Ethical considerations	8
4.11.	International Review Board	8
4.12.	Study duration	8
4.13.	Study co-ordination	8
4.14.	Budget	9
5.	References	10
6.	Appendices	
6.1.	Study overview	11
6.2.	Drug regimens	12
6.3.	Notes for drug regimens	13
6.4.	Guideline drug changes for relapse	14
6.5.	Evaluation regimens	15
6.6.	Disease definitions	16
6.7.	Adverse-effects scoring	17
6.8.	Patient information and consent	18

1. Background

1.1. The diseases

Following the widespread introduction of ANCA testing, the primary systemic vasculitides (SV), Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) appear to be more frequent than was previously thought (see definitions in Appendix 6). Also, the existence of early and organ-limited forms of these diseases, such as renal-limited vasculitis (RLV) is now clearly recognised. Their annual incidence exceeds 20 per million per year and they account for at least 5 % of the causes of end stage renal failure. The two diseases share many features of their histology, serology and response to treatment, pointing to similarities in their pathogenesis, which have justified a common approach to their management.

1.2. Their treatment

Untreated, generalised WG and MP follow a progressive course with a fatal outcome due to vital organ failure; but with the empirical introduction of corticosteroids and cytotoxic agents, five year survival was increased from under 20 to over 60% (2,3,5). Although unsupported by controlled study, the combination of oral corticosteroids (OCS) and cyclophosphamide (CYC) has become established as standard therapy for WG and MP, and is effective at controlling disease progression in up to 90% of patients (4,5). However, remissions may take several months to achieve and reduction or withdrawal of therapy is associated with disease relapse; consequently patients have a high cumulative exposure to drugs with a narrow therapeutic index and treatment-related morbidity and mortality rivals that caused by the underlying disease (4,6-8,19).

Such regimens use OCS and CYC for remission induction and maintain CYC for a further 12 months while tapering OCS, following which time CYC is tapered. More recently, attempts to reduce CYC-associated toxicity have tapered CYC once remission is reached, used pulsed intravenous (I/V) CYC or substituted less toxic alternatives to CYC, such as azathioprine (AZA), for the maintenance of remission (5,9-11). Several studies have compared oral to I/V CYC, but have differed in their conclusions, in particular the ability of I/V CYC to maintain remission (10,11). Azathioprine has been used in the treatment of WG and MP for almost 30 years; it is less effective than CYC for the control of active disease, but it has been of value in remission, and relapse rates in follow-up studies using CYC or AZA appear comparable (4,5,12,13). Of other alternative remission agents to CYC such as methotrexate, chlorambucil, cyclosporin, intravenous immunoglobulin or monoclonal antibodies, there has been less experience than with AZA, while the role of sulfamethoxazole/trimethoprim for localised WG is under evaluation (14-16).

1.4. Aims of CYCAZAREM

The aims of CYCAZAREM are to optimise the treatment of the remission phase of WG, MP and RLV by comparing "standard" treatment with CYC to a less toxic alternative (AZA); to harmonise approaches to the treatment of SV in Europe; and to assess the prognostic value of various clinical and laboratory indices for their management. OCS and oral CYC was chosen as the induction treatment for all patients because it is the most effective treatment for these disorders, and the major adverse-effects of short-term CYC are mostly reversible; as the long-term toxicity of azathioprine is both favourable to CYC and well-documented, it is planned to randomise patients to receive either continued "standard" treatment with OCS and oral CYC or "test" treatment with OCS and AZA.

2. Study Medications

2.1. Cyclophosphamide

Cyclophosphamide is an inactive pro-drug, converted by the mixed function oxidase system in the liver to the alkylating agents 4-hydroxy-cyclophosphamide and phosphoramide mustard, which alkylate guanine nucleotides, thus blocking cell division (17). Bioavailability after oral administration is greater than 75%, but there are large variations between individuals in the rate of production of active metabolites. A phenotypic variation in carboxylator activity affects the production of the inactive metabolite carboxyphosphoramide from 4-hydroxy-cyclophosphamide, which may influence efficacy and toxicity. The relation of renal and hepatic failure to 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 a markedly increased risk of bladder cancer (8,19). Other adverse effects include nausea and vomiting, myelosuppression with neutropaenia, infections due to immunosuppression alopecia and infertility. Permanent ovarian failure occurs in over 50% of women after one year's exposure and is age-related, male infertility has been less well studied. The incidence of leukaemia and lymphoma is increased tenfold with prolonged administration; less common adverse-effects include pulmonary fibrosis, hepatitis and the syndrome of inappropriate ADH secretion.

2.2. Azathioprine

After hepatic conversion to 6-mercaptopurine, the cytotoxic effects of azathioprine are mediated by the impairment of purine synthesis, incorporation of purines into DNA, and impairment of the endonuclease repair activity of DNA polymerase (17). The drug is well absorbed after oral administration and elimination requires hepatic metabolism by xanthine oxidase; an important drug interaction is with xanthine oxidase inhibitors, such as allopurinol. Lymphocyte function is reduced, B-cells more than T-cells, and there is suppression of the cellular component of the inflammatory response. The major adverse effects are nausea and vomiting, dose-dependent myelosuppression and reversible, cholestatic, hepatic toxicity. An increased incidence of malignancies has not been demonstrated for a treatment duration of up to one year, but there is a dose-dependent increase in skin cancers and lymphomas following administration for more than two years after organ transplantation.

2.3. Prednisolone

Prednisolone is a synthetic derivative of cortisone with widespread influences on metabolism and organ function. Desirable effects in SV relate to the suppression of acute and chronic inflammatory disease processes and immune cell function. 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, if the use of OCS is prolonged additional adverse-effects including osteoporosis, subcapsular cataracts, skin fragility, myopathy, Cushingoid facies, hirsutism, alopecia, fat redistribution, striae and growth retardation in children may occur (17). Of note in SV, has been the correlation of the cumulative OCS dosage with the total incidence of adverse-effects, and particularly with infections.

3. Hypothesis

Azathioprine is at least as effective as cyclophosphamide for the maintenance of remission in Wegener's granulomatosis, microscopic polyangiitis and renal-limited vasculitis and has fewer adverse effects.

4. Study Design

4.1. Nature

International, multicentre, unblinded, prospective, randomised study with informed consent and local ethical approval.

4.2. Rationale

WG, MP and RLV are progressive disorders for which the standard treatment is a combination of OCS and CYC. Following the induction of remission with OCS + CYC this study will examine whether substitution of AZA for CYC is equally effective for the maintenance of remission with fewer side-effects in a subgroup of patients presenting with progressive disease having either renal involvement and/or another presentation, which if untreated was likely to lead to permanent loss of organ function.

4.3. Inclusion criteria (1,2 and 3 are required)

- 1) A diagnosis of new or previously untreated WG, MP or RLV with or without histological confirmation (Appendix 6).
- 2) **Either**
 - i. elevated serum creatinine
 - ii. haematuria (> 30 red blood cells per high powered field)
 - iii. red cell casts
 - iv. proteinuria (> 1g/24hr)
- 3) **And/Or**

other conditions which are considered to be life-threatening, or in which there is imminent loss of vital organ function, attributable to active WG or MP, such as:

 - i. severe hypoxia or haemoptysis associated with bilateral lung infiltrates.
 - ii. cerebral infarction or cranial or peripheral motor neuropathy.
 - iii. rapidly progressive optic neuropathy or retinal vasculitis or orbital pseudotumour.
 - iv. massive gastro-intestinal tract bleeding.
 - v. heart failure due to pericarditis or myocarditis.
 - vi. other presentation after discussion with trial co-ordinator.
- 3) ANCA positivity; either typical CANCA pattern by indirect immunofluorescence (IIF) and/or positivity in the PR3 ELISA or positivity in the MPO ELISA with or without PANCA performed in an EC/BCR validated reference laboratory (18). ANCA negative cases may be included if the disease is confirmed histologically (Appendix 6).

4.4. Exclusion criteria

- 1) Any cytotoxic drug within previous year, unless started within two weeks of entry.
- 2) Co-existence of another multi-system autoimmune disease, e.g. SLE.
- 3) Hepatitis B antigenemia, only if HBe antigen positive.
- 4) Known HIV positivity (HIV testing will not be a requirement for this trial).
- 5) Serum creatinine >500umol/l.
- 6) Failure to achieve remission by six months.
- 7) Failure to control progressive disease with induction protocol.
- 8) Complete inability to tolerate CYC during first three months.
- 9) Previous malignancy (usually exclude unless agreed with trial co-ordinator).
- 10) Pregnancy.
- 11) Age under 18 or over 75 years.

4.5. End-points

- 1) Primary end-point is relapse rate (Appendix 6).
This will include both major and minor relapses.
- 2) Secondary end-points are:

- i. adverse effect rates
- ii. cumulative exposure to OCS,CYC and AZA

4.6. Interventions

4.6.1. Drug regimens

- 1) All patients will receive the same induction regimen for three months (Appendix 2).
- 2) Following achievement of remission, patients will be randomised at three months to receive either the standard (OCS+CYC) or test (OCS+AZA) regimens.
- 3) Patients not in remission at three months may be entered when remission is achieved if this occurs before six months.
- 4) Relapse treatment to follow guideline relapse regimens (Appendix 4).
- 5) After one year OCS+CYC patients will be switched from CYC to AZA and all patients will continue on tapering doses of OCS+AZA until the study end at 18 months.

4.6.2. Evaluations (Appendix 5)

- 1) Study assessments will be performed at entry, after 1½,3,6,9,12,15 and 18 months and at the time of relapse.
- 2) Blood drawn monthly for six months, then a minimum of two monthly thereafter.
(The clinical value of ANCA levels is an associated aim of this study but treatment decisions will not be based on their results.)
- 3) WG patients to have nasal swabs monthly for eight months.
(The relation of Staphylococcal carriage to disease relapse is an associated aim of this study, however results of nasal swabs will not influence treatment decisions.)
- 4) BVAS (activity) and SF-36 (function) scores at 0,1½,3,6,9,12,15 and 18 months and at relapse, VDI (damage) score at 0,6,12 and 18 months and at relapse, the Disease Extension Index (DEI) will be computed from the BVAS (11) (see Appendix 5).

4.7. Withdrawal

- 1) Patient or patient physician's request.
- 2) Reason for withdrawal to be noted in the Patient Record Book.

4.8. Adverse-effects (Appendix 7)

- 1) All adverse-effects will be recorded on standardised forms in the patient record-book.
- 2) The presence of the common adverse effects will be actively sought in the VDI score.
- 3) Adverse effects of therapy will be reported to the International review board.
- 4) Adverse effects sufficient to withdraw a medication will be determined after discussion with the trial co-ordinator.

4.9. Statistical analysis

Two statistical strategies will be adopted, a frequentist approach with which the organisers are familiar and which has guided the design of this protocol, and a Bayesian approach which is more experimental but is likely to be more flexible and to have other advantages outlined below. Should the latter approach prove successful during the course of the trial it will be used to determine the stopping point which may allow the trial to be completed with fewer patients.

Patients will be stratified at entry by diagnosis (WG or MP/RLV)

4.9.1. A frequentist approach

Given a predicted relapse rate of the standard (OCS+CYC) regimen of 25% and a range of equivalence between the two regimens of 20%; for a type I error of 0.05 and a type II error of 0.20, 146 patients will be required using log rank statistics in a 1-tailed test with an equivalence design.

4.9.2. A Bayesian approach

This approach recognises the subjective nature of deciding an alternative or null hypothesis such as in 4.9.1., the difference between the realistic (actual) difference and the clinically worthwhile difference, and the toxicities of the treatments. Due to a lack of existing data an accurate realistic difference between the two regimens can not be predicted, therefore a clinically worthwhile difference between the two regimens will be determined at the onset of the trial by circulating a standardised questionnaire

to the CYCAZAREM organisers. This exercise will be repeated after inclusion of 50 and 100 patients and will reflect the breadth of experience with the efficacy and safety of the two regimens. Interim analyses will be performed after inclusion of 50 and 100 patients from which the realistic difference between the two regimens may be extrapolated with increasing probability. The stopping rules and predicted patient requirements for the study will then follow from comparison of the realistic difference with the clinically worthwhile difference and discussion between the CYCAZAREM organisers according to an established methodology (21).

4.10. Ethical Considerations

WG, MP and RLV are progressive disorders responsive to treatment, but there is a wide variation in both the choice of drugs and their doses between different centres in the EU. The trial committee have by consensus agreed on a standard regimen (OCS+CYC), but acknowledge its toxicity. In an attempt to improve the treatment of SV, this trial plans to compare a less toxic alternative (OCS+AZA) to the standard. There is extensive experience with OCS+AZA and its efficacy in maintaining remission appears similar, but it has never been directly compared to OCS+CYC (5). Study entry will not require additional tests or clinic visits above normal practice, apart from an additional 10ml of blood and nasal swabs.

- 1) Patients will only be entered after they have given informed consent.
- 2) Approval for the study will be sought from local ethical committees.
- 3) Confidentiality of patient data will be respected. Data will be coded prior to any computer entry and study databases will be independent from computer networks.
- 4) Details of patients' identities will be restricted to the local investigator only.

4.11. International Review Board

An International board will be consulted annually to review the incidence and severity of adverse events, the conduct of the study and communication of the study's results.

4.12. Duration

48 months: 30 months for recruitment and 18 months for follow-up.

4.13. Co-ordination

- 1) In Cambridge by David Jayne.
- 2) Clinical Trials Assistant (CTA) to be appointed.
- 3) Study data will be recorded by the investigator in Patient Record Books and communicated every 3 months to the trial administration office.
- 4) Participating centres will be visited by either the national co-ordinator or CTA within three months of the first patient entry and annually thereafter.
- 5) Records of patient registration will be maintained both locally and centrally.

4.14. Budget

This will not include medical costs which will not be influenced by entry into the study.

	1 yr	2 yr	3 yr	4 yr	total (£)
Personnel 1/2 CTA	120000	120000	120000	12000	48000
Data collection	500	500	500	500	2000
record books					
VITAL scoring					
transmission of data					
collection of sera					
Sera analysis	500	500	500	500	2000
Investigator's meeting	3500	3500	3500	3500	14000
national per annum (x5)					
international per annum					
Communications	200	200	200	200	800
IRB organisation	500	500	500	500	2000
Data entry and analysis	1000	1000	1000	5000	8000
Total					76,800

5. References

1. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-192.
2. Walton EW. Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis). *Br Med J* 1958; 2: 265-270.
3. Leib ES, Restivo C, Paulus HE. Immuno-suppressive and corticosteroid therapy of poly-arteritis nodosa. *Am J Med* 1979; 67: 941-945.
4. Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; 98: 76-85.
5. Gaskin G, Pusey CD. Systemic Vasculitis. In: Cameron JS et al, eds. *Oxford Textbook of Clinical Nephrology*. Oxford: Oxford University Press, 1992: 612-636.
6. Cohen J, Pinching AJ, Rees AJ, Peters DK. Infection and immunosuppression: a study of the infective complications of 75 patients with immunologically mediated disease. *Q J Med* 1982; 51: 1-15.
7. Bradley JD, Brandt KD, Katz BP. Infectious complications of cyclophosphamide treatment for vasculitis. *Arthritis Rheum* 1989; 32: 45-53.
8. Hoffman GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: an analysis of 158 patients. *Ann Int Med* 1992; 116: 488-498.
9. Cohen Tervaert JW, Huitema MG, Hen, RJ, et al. Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet* 1990; II: 709-711.
10. Hoffman GS, Leavitt RY, Fleisher TA, Minor JR, Fauci AS. Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. *Am J Med* 1990; 89: 403-410.
11. Rheinhold-Keller E, Kekow J, Schnabel A et al. Influence of disease manifestation and ANCA titer on the response to pulse cyclophosphamide therapy in Wegener's granulomatosis. *Arthritis and Rheum* 1994; 37: 919-924.
12. Bouroncle BA, Smith EJ, Cuppage FE. Treatment of Wegener's granulomatosis with Imuran. *Am J Med* 1967; 42: 314-318.
13. Gordon M, Luqmani RA, Adu D, et al. Necrotizing vasculitis - Relapse Despite Cytotoxic Therapy. *Adv Exp Med Biol* 1994; 336: 477-482.
14. Allen NB, Caldwell DS, Rice JR, McCallum RM. Cyclosporin A therapy for Wegener's granulomatosis. *Adv Exp Med Biol* 1994; 336: 473-476.
15. Jayne DRW, Lockwood CM. ANCA anti-idiotype antibodies and the treatment of systemic vasculitis with intravenous immuno- globulin. *J Autoimmunity* 1993;6: 207-219.
16. DeRemee RA. The treatment of Wegener's granulomatosis with trimethoprim/ sulfamethoxazole: illusion or vision?. *Arthritis Rheum* 1989; 31: 1068-1073.
17. Azathioprine; cyclophosphamide; prednisolone. In: Dollery C, ed. *Therapeutic Drugs*. London: Churchill Livingstone, 1991: A181-A184; C366-C372; P199-P220.
18. Wiik A, Rasmussen N, Wieslander J. Methods to detect autoantibodies to neutrophilic granulocytes. In: *Manual of Biological Markers of Disease A9*. Amsterdam: Kluwer Academic Publishers, 1993: 1-14.
19. Stillwell TJ, Benson RC, DeRemee RA, et al. Cyclophosphamide-induced bladder toxicity in Wegener's granulomatosis. *Arthritis and Rheumatism* 1988;31:465-470
20. Luqmani RA, Bacon PA, Moots RJ et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. *Q J Med* 1994;87:671-678
21. Parmar MKB, Spiegelhalter DJ, Freedman LS et al. The CHART trials: Bayesian design and monitoring in practice. *Statistics in Medicine* 1994;13:1297-1312

6. Appendices

6.1. Appendix 1. Trial Overview

Previously untreated, progressive, WG or MP



Entry



Induction regimen = OCS + CYC

(0-3 months)



Randomisation if in Remission

(stratification by WG or MP)

(3 - 6 months)



OCS + CYC OCS + AZA



Evaluations

(every 3 months)



Switch CYC to AZA

(12 months)



Continue AZA



Study end

(18 months)

6.2. Appendix 2. Drug Regimens

6.2.1. Induction treatment - both groups

time from entry	prednisolone mg/kg/day	cyclophosphamide mg/kg/day
0	1	2
1 week	0.75	2
2 weeks	0.5	2
4 weeks	0.4	2
6 weeks	0.33	2
8 weeks	0.28	2
10 weeks	0.25	2
12 weeks	0.25	1.5

6.2.2. Remission treatment - OCS+CYC)

time from entry	prednisolone mg/day	cyclophosphamide mg/kg/day	azathioprine mg/kg/day
3 months	15	1.5	0
4 months	12.5	1.5	0
5 months	10	1.5	0
12 months	10	0	1.5
15 months	7.5	0	1.5
*			

6.2.3. Remission treatment - OCS+AZA

time from entry	prednisolone mg/day	azathioprine mg/kg/day
3 months	15	2
4 months	12.5	2
5 months	10	2
12 months	10	1.5
15 months	7.5	1.5
*		

* after 18 months, follow local practice

6.3. Appendix 3. Notes for drug regimens

6.3.1. Cyclophosphamide and Azathioprine

- 1) maximum dose is 150mg
- 2) round dose to nearest 25mg (may vary alternate day dosage, e.g. 100 and 150mg for 125mg dose)
- 3) age > 60 years, reduce dose by 25mg
- 4) administer dose in the morning and maintain good hydration
- 5) patients initially intolerant of oral medication may receive 75% of the oral dose by daily IV injection
- 6) CYC: check full blood count (FBC):
 - weekly for first month
 - two-weekly for second month
 - monthly for first year
- 7) AZA: check FBC and ALT or AST:
 - monthly for three months
 - then three monthly
- 8) discuss withdrawal of CYC or AZA for adverse effects with co-ordinator
- 9) MESNA for bladder protection is not feasible for oral CYC

6.3.2. Leucopaenia

- 1) Stop CYC/AZA if white blood cells (WBC) < $4 \times 10^9/L$.
Restart with dose reduced by at least 25mg when WBC > $4 \times 10^9/L$
Monitor weekly for one month.
- 2) If severe ($<1 \times 10^9/L$ or prolonged ($<4 \times 10^9/L$ for > 2 weeks)), restart CYC/AZA at 50mg/day, increasing to target dose as weekly WBC permits. Consider:
 - pneumocystis carnii prophylaxis
 - fungus prophylaxis
- 3) For falling WBC ($<6 \times 10^9/L$ and fall of $>2 \times 10^9/L$ over previous count), re-check in one week and reduce dose by 25mg if further fall of $>0.5 \times 10^9/L$

6.3.3. Prednisolone

- 1) maximum dose in first week is 80mg/day
- 2) round dose to nearest 5mg above 20mg, and nearest 2.5mg below 20mg
- 3) Single daily dose (may vary alternate day dosage by up to 5mg, e.g. 10mg and 15 mg for 12.5 mg dose)
- 4) patients intolerant of oral medication may receive any IV steroid at an equivalent dose as a daily injection
- 5) use either prednisone or prednisolone, avoid enteric coated or soluble forms
- 6) a flexibility in prednisolone dose of $\pm 12.5\%$ from the protocol will be allowable in the first 12 weeks and $\pm 25\%$ thereafter (larger variations from regimens should be discussed with trial co-ordinator)
- 9) minimum dose in first three months is 12.5mg/day

6.3.4. Prophylaxis

- 1) peptic ulceration (suggested only):
ranitidine or omeprazole, not cimetidine or misoprostol, for at least six months
- 2) fungal infection (suggested only):
oral fluconazole, nystatin or amphotericin, for 12 weeks
- 3) pneumocystis carnii (suggested only)
sulfamethoxazole/trimethoprim 480mg three times a week or
monthly aerosolised pentamidine

6.4. Appendix 4.

Changes to drug regimens for relapse

These are non-obligatory guidelines

Major relapse (Appendix 6)

- 1) Increase CYC to 2mg/kg/day (stop AZA if from AZA group)
- 2) Increase OCS to 0.5mg/kg/day, reduce to 20mg/day by four weeks
- 3) when remission achieved follow OCS+CYC regimen from 3 month point
- 4) if ineffective after two months follow local preference
- 5) if major relapse occurred on AZA do not return to AZA

Minor relapse

- 1) Increase CYC or AZA to 2mg/kg/day
- 2) Increase OCS to 0.5mg/kg/day then reduce to 15mg/day over one month
- 3) when remission achieved return to previous regimen at 3 month point
- 4) If ineffective after one month and in OCS+AZA regimen switch AZA to CYC.

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

6.5. Appendix 5. Study Evaluations

Minimum information required for the study. Additional tests or more frequent intervals to follow local practice.

6.3.1. Entry

VITAL score *
Hb, white cell count (WBC), neutrophil, lymphocyte and platelet counts
ESR, C-reactive protein (CRP), ANCA (IIF, PR3 and MPO ELISA)
creatinine, GFR (isotope study or 24hr urine collection)
ALT or AST, alkaline phosphatase, albumin
glucose
ANA, rheumatoid factor, anti-GBM, cryoglobulins, complement (C3 and C4)
Hep BsAg , Hep C Ab
chest and sinus X-ray
5ml serum saved
nasal swab for bacterial culture
urine microscopy for red cell count and red cell casts
dipstick urinalysis for protein (24hr quantification if present)

6.3.2. Monthly for first year

5ml serum save (at least two monthly after 6 months)
nasal swab for bacterial culture (stop after 8 swabs)

6.3.3. 1½, 3,6,9,12,15 months and at relapse

VITAL score (VDI only necessary at 0,6,12, 18 and relapse)
Hb, WBC, neutrophil, lymphocyte and platelet counts
ESR, CRP
creatinine (and GFR at 18 months only)
ALT or AST, alkaline phosphatase, albumin
glucose
dipstick urinalysis (and 24 hour protein at 18 months if proteinuria present)
5ml serum saved
urine microscopy for red cell count and red cell casts

6.3.4. Study end at 18 months

VITAL score
Hb, WBC, neutrophil, lymphocyte and platelet counts
ESR, CRP
creatinine, GFR
ALT or AST, alkaline phosphatase, albumin
glucose
dipstick urinalysis (and 24 hour protein if proteinuria present)
5ml serum saved
urine microscopy for red cell count and red cell casts

* VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS), the Vasculitis Damage Index (VDI), the Short-Form-36 (SF-36) functional assessment score. BVAS has been validated and will contribute to definition of remission and relapse in this study, validation of VDI is in progress (20). The disease extension index (DEI) score will be computed from data collected for VITAL (11).

6.6. Appendix 6. Disease Definitions

6.6.1. Wegener's granulomatosis

Generalised 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 (1). A CANCA pattern by IIF, with specificity for proteinase 3 (PR3-ANCA) by ELISA, is found in over 90% of untreated patients with generalised WG; some studies have found a minority of cases to have ANCA with specificity for myeloperoxidase (MPO-ANCA) instead of PR3-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, with a history of at least four weeks and not attributable to another cause, supported by characteristic histology on biopsy and/or detectable CANCA by IIF, or PR3-ANCA or MPO-ANCA by ELISA. WG is a clinico-pathological syndrome where confidence in the diagnosis may require a prolonged period of observation, the diagnosis may therefore be qualified by the terms, "suspected", "probable" or "definite". In cases of diagnostic doubt the trial co-ordinator should be consulted.

Characteristic or confirmatory histology for non-renal biopsies requires the exclusion of other causes and an inflammatory exudate dominated by polymorphonuclear leucocytes with at least one of the following:-

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

Generalised WG requires the involvement of an extra-respiratory tract organ (e.g. kidney, skin, nervous system) in addition to respiratory tract disease. Constitutional symptoms (e.g. fever, headache, myalgia, arthralgia, tiredness, weight loss of >2kg) themselves do not constitute extra-respiratory involvement but indicate that the disease is active and systemic. Disease only involving one non-vital organ (usually the upper respiratory tract) with less than 2 constitutional symptoms is defined as localised disease.

6.6.2. Microscopic polyangiitis

MP is characterised by a vasculitis predominantly affecting small vessels. Renal involvement is usual and is reflected by a necrotizing glomerulonephritis. Granulomata are absent. Arteritis of medium-sized vessels may also occur (1). MP is associated with MPO-ANCA or PR3-ANCA; a minority of MP patients are ANCA negative or recognise other ANCA autoantigens. For the purposes of this study, patients may be entered in the category of MP if they have a chronic inflammatory process with nongranulomatous vasculitis of small vessels (i.e. capillaries, venules, arterioles or small arteries).

6.6.3. Renal-limited vasculitis

Isolated pauci-immune necrotising and crescentic glomerulonephritis, typically known as idiopathic rapidly progressive glomerulonephritis (idiopathic RPGN) has many features to suggest that it represents a renal-limited form of WG or MP, including the presence of circulating anti-MPO or anti-PR3 antibodies.

6.6.4. Remission

Full clinical remission is indicated by complete absence of clinical disease activity using the BVAS item list. The absence of renal disease activity is indicated by stable or falling creatinine and the absence of red cell casts. Diagnosis of complete remission is supported by a normal C-reactive protein. ANCA is ignored for the purpose of this study.

6.6.5. Relapse

Major relapse requires the recurrence or first appearance of major organ involvement (e.g. lung, kidney, nervous system), of sufficient severity to require treatment with high dose OCS and CYC.

Minor relapse requires the recurrence of disease activity sufficient to warrant a transient increase in therapy, but which is not severe enough to be classified as a major relapse, and which does not threaten the function of vital organs.

Appendix 7. Adverse-Effects

6.7.1 Intolerance of trial therapies:

This includes persistent leucopaenia (total WBC < 4 x 10⁹/l for a period of 4 weeks, or recurring at a dose of 50mg Cyc or Aza.)

6.7.2 Adverse-effects of therapy:

These will be reported 3 monthly to provide information for the international review board's annual analysis.

In particular the presence/absence of the following potential complications of therapy will be noted, and the effect classified as mild, moderate, severe or life-threatening according to agreed guidelines. Other adverse events of unknown cause will also be documented. The trial co-ordinators should be contacted in case of difficulty in classification.

Infection

Drug-induced hypersensitivity reaction

Cataracts

New or worsening osteoporosis

Avascular necrosis

Newly presenting diabetes

Peptic ulceration

New or exacerbated psychological disturbance

Hypertension

Liver dysfunction

Nausea and vomiting

Alopecia

Leucopaenia

Thrombocytopaenia

Haemorrhagic cystitis

Malignancy

Amenorrhea and infertility

6.8. Appendix 8. Patient Information and Consent

Brief description of the purpose and the procedures of the study

You are suffering from a form of inflammation of the blood vessels or vasculitis. The standard treatment for this condition consists of a combination of prednisolone (a steroid) and cyclophosphamide tablets which control the disease but which must be continued to prevent the disease coming back. These tablets frequently cause side-effects which can be serious. In this study we will use this combination of tablets to control your disease and then, to stop the disease returning, we will continue the prednisolone at a lower dose and compare either continuing cyclophosphamide or, changing cyclophosphamide to an alternative tablet called azathioprine, which is safer over the longer-term but may be less effective. Both types of treatment have been in use for many years but they have never been directly compared to see which is the best with the fewest side-effects.

The side-effects associated with these treatments include lowering of the blood count, increased susceptibility to infection, hair loss, nausea, bladder irritation, high blood pressure, infertility, foetal damage and an increased risk of cancer. After entry into the trial you will receive prednisolone and cyclophosphamide tablets for three months, or until the disease is controlled, and will then either continue on the same tablets, at a lower dose, or the cyclophosphamide will be changed to azathioprine. The treatment will be continued for one year, when all patients will receive prednisolone and azathioprine in a slowly reducing dose. You will remain in the study for one and a half years in total.

When you are taking these tablets, it is our normal practice to watch you closely with regular examinations and blood checks, which will initially take place every week, then less frequently as your condition improves. In addition to the usual blood tests we require, for the purposes of research, an additional small quantity of blood at each visit. It is essential that women of child-bearing age use efficient contraception to prevent pregnancy during the study.

Details of your case will be stored in coded form on a computer, but will not be available to anyone not directly involved in this trial, the computer will not be connected to any computer networks.

You are free to withdraw from this study at any stage without giving an explanation and without affecting the care you receive from your doctors.

If you have any questions about your treatment or this study please contact:

..... Tel.....

The details of this study have been explained to me by

I fully understand what is involved and any questions I have about the study have been answered satisfactorily. I also understand that I may withdraw from the study without my care being affected.

Signed (patient) Date

Signed (investigator) Date

Signed (witness) Date

(The witness's duty is to make sure the patient understands what is involved. The witness may not be directly associated with this study, and should indicate his/her status.)

Comparison of cyclophosphamide to azathioprine in the treatment of vasculitis

Patient Information Sheet

Please consider participating in this project comparing two different drugs for the treatment of your condition. You are suffering from a form of inflammation of the blood vessels or vasculitis. The standard treatment for this condition consists of a combination of steroid and cyclophosphamide tablets which control the disease but which must be continued to prevent the disease coming back. These tablets frequently cause side-effects which can be serious. Several hospitals now change the cyclophosphamide to an alternative drug, azathioprine, after about three months of treatment. Azathioprine is safer than cyclophosphamide but is probably less effective at treating vasculitis.

This study will compare continuing cyclophosphamide for 12 months, to changing to azathioprine after three months; looking particularly at the number of patients in whom the disease returns and at the side effects. The study will not directly benefit your care but will help in the treatment of these diseases in the future.

As part of your routine care, we will perform a number of blood and urine tests and X-rays which will be repeated during the study, initially at weekly intervals, then less frequently. In addition to the usual blood tests we require, for the purposes of research, an additional small quantity of blood at your visits, but this will not need an extra needle puncture. All patients will be given a combination of steroid and cyclophosphamide tablets for the first three months and then will be selected to continue cyclophosphamide at a lower dose or receive azathioprine tablets, on a random basis. After 12 months, all patients will be given a low dose of azathioprine and steroids until the end of the study at 18 months.

The side-effects associated with these treatments include lowering of the blood count, increased susceptibility to infection, stomach irritation, difficulty sleeping, weight gain, hair loss, nausea, bladder irritation, thinning of the bones (osteoporosis) infertility, foetal damage and an increased risk of diabetes, high blood pressure and cancer. You will be regularly assessed by a doctor and by blood tests in order to reduce the chance and treat any side-effects, and will also receive tablets to lessen the risk of infection and stomach irritation. Milder side-effects, which will get better as the drug doses are reduced, occur in nine out of ten patients; while more serious side-effects, such as those needing a hospital admission, occur in about one in ten patients. It is essential that women of child-bearing age use efficient contraception to prevent pregnancy during the study.

Your personal medical information may be scrutinised by properly authorised persons but will be treated as strictly confidential. Details of your case will be stored in an anonymous form on a computer, but will not be available to anyone not directly involved in this trial, the computer will not be connected to any computer networks.

Non-participation in this study will not affect your treatment in any way and you are free to withdraw from this study at any stage without giving an explanation and without affecting the care you receive from your doctors.

If you have any questions about your treatment or this study please contact Dr