

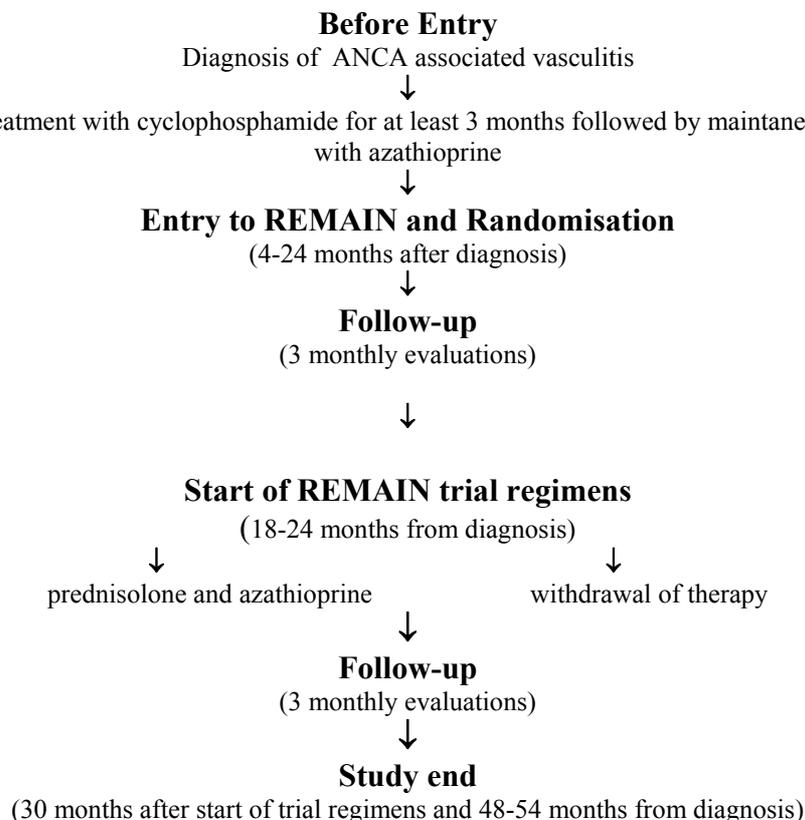
CLINICAL TRIAL PROTOCOL: **REMAIN**

Randomised trial of prolonged remission-maintenance therapy in systemic vasculitis (Version 4.2: January 2006)

Summary

The primary ANCA-associated vasculitides, Wegener's granulomatosis and microscopic polyangiitis, are progressive, multisystem, autoimmune diseases which respond to immunosuppressive therapy. Their initial treatment has been standardised in recent European trials. REMAIN aims to improve the management of the next phase of these conditions, when the major difficulty is to balance the risks of organ damage due to recurrent disease with the adverse effects of immunosuppressive drugs. The effects of a low toxicity maintenance regimen will be compared with the effect of withdrawal of therapy. The maintenance regimen will comprise low dose prednisolone and azathioprine, and has been used safely in several European centres during the last ten years. Patients with ANCA associated vasculitis who have been treated with conventional induction protocols will be entered 4 to 24 months after the onset of therapy. They will be randomised to receive either azathioprine and prednisolone until 48 months from the onset of therapy or to discontinue by 24 months. The study will last until 48 months from the onset of therapy with 3 monthly evaluations. The primary end-point of relapse rate, and secondary end-points of cumulative morbidity scores, decline in renal function, and adverse-effects of therapy will be compared; 128 patients, still remaining in the study at the start of the REMAIN trial regimens, will be required.

Trial Overview



1. Introduction to the trials

1.1. ECSYSVASTRIAL

The ECSYSVASTRIAL project started in January 1994 under the European Community (EC) BIOMED-1 concerted action programme. It aimed to design and standardise disease scoring and data collection methodology, facilitate therapeutic trials and harmonise the treatment of vasculitis within the EC. A first wave of clinical trials for ANCA-associated systemic vasculitis (AASV), (Wegener's granulomatosis, WG, microscopic polyangiitis, MP, and their renal-limited variant, renal-limited vasculitis, RLV), was launched in 1995, based on the extent and severity of disease (NORAM, early systemic disease; CYCAZAREM, generalised disease; MEPEX, severe renal disease). Two subsequent protocols have subsequently been developed to examine IV cyclophosphamide (CYCLOPS) and this study.

2. Aims of REMAIN

The aims of REMAIN are to determine whether prolonged maintenance therapy, using low dose prednisolone and azathioprine, reduces long-term morbidity in vasculitis by reducing the relapse rate, when compared with cessation of therapy in the second year.

3. Study design

3.1. Hypothesis

Prolonged maintenance therapy with low-dose prednisolone and azathioprine reduces long-term morbidity in systemic vasculitis, by reducing the frequency of relapse, when compared with cessation of therapy in the second year.

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

1. Previous diagnosis of WG, MP or its renal-limited variant, in accordance with the Chapel Hill consensus criteria [2] (appendix 6).
2. Remission within 12 months from commencement of therapy and at time of entry 4-24 months from commencement of therapy
3. ***Either***
 - a) Previous entry in CYCAZAREM, MEPEX or CYCLOPS studies [1]
 - or***
 - b) previous treatment with a non-trial drug regimen, comprising:
 - i) Oral corticosteroids from diagnosis.
 - ii) Cyclophosphamide for at least 3 months .
 - iii) Azathioprine substituted on cessation of cyclophosphamide.

3.3. Exclusion criteria

1. Age under 18.
2. Pregnancy.
3. Previous malignancy (usually exclude unless agreed with trial coordinators).
4. Hepatitis Be antigenaemia or detectable anti-HCV antibody.
5. Known anti-HIV positive (HIV testing is not a requirement for this trial).
6. Previous life-threatening relapse.
7. Allergy to study medications (excluding prophylactic agents).
8. Established on renal replacement therapy.

3.4. Interventions

1. At entry, patients will be randomised to continued treatment or early withdrawal limbs.
2. Drug regimens (appendix 3):
 - a) Both limbs: azathioprine and prednisolone from cessation of cyclophosphamide
 - b) Continued limb continues treatment at least until 30 months after start of REMAIN trial regimen

- c) Withdrawal limb discontinues all treatment 4 months after start of REMAIN trial regimen
- d) Relapse will be treated according to guidelines for treatment of relapse. Data collection will continue to four years (appendices 4 and 6).
- e) Patients who experience minor relapse after randomisation and who have not been in stable remission for at least six months at 24 months after commencement of therapy are unable to start of REMAIN trial regimes and have to be excluded from the study.
- f) Patients who permanently discontinue azathioprine or prednisolone between randomisation and 24 months from commencement of therapy should be excluded from the study.

3.5. Evaluations (appendix 4):

- a) History, examination and blood tests at 3 monthly intervals.
- b) Disease activity (VITAL) scoring [1]:
 - i) Birmingham Vasculitis Activity Score (BVAS) at 3 monthly intervals [3,4].
 - ii) Vasculitis Damage Index (VDI) at entry, and after 12, 24 and 30 months in the study [5].
- c) GFR will be measured at start of REMAIN trial regimens, and after 12, 24 and 30 months after the start.

3.6. End-points

- 1. Primary end-point is relapse rate.
- 2. Secondary end-points:
 - a) Rise in cumulative morbidity score during 30 months of study (VDI and SF-36).
 - b) Fall in GFR during 30 months of study.
 - c) Adverse effects of therapy.

3.7. Adverse-effects

- 1. The presence of adverse-effects will be actively sought.
- 2. All adverse-effects will be recorded on standardised forms.
- 3. Adverse-effects sufficient to withdraw a medication will be determined after discussion with the trial co-ordinator.

3.8. Withdrawal

Patients may withdraw from the trial at their or their physician's request without explanation; where possible the reason for withdrawal will be noted in the Patient Record Book.

4. Statistical analysis

- 1. Data will be collected to allow retrospective analysis according to duration of previous cyclophosphamide therapy, previous treatment with methylprednisolone, diagnosis and ANCA specificity.
- 2. **Power:** Based on a 1-tailed design, with a significance of 5% and a power of 80, 116 patients will be required to demonstrate a 20% lower relapse rate in the maintenance therapy group (assuming relapse rates of 10% in the maintenance group and 30% in the withdrawal group). 128 patients will be recruited to allow for a 10% rate of loss to follow-up.

5. Ethical Considerations

- 1. Low relapse rates have been achieved in a single centre with the use of long-term low dose maintenance therapy, without an excess of severe complications [6]. However, this policy has not been tested systematically and there is concern about the use of long-term immunosuppression. This trial selects patients who are at risk of major morbidity if this pattern of disease recurs. This trial uses doses of immunosuppression which are lower than those used to prevent renal transplant rejection; oral steroids are discontinued at approximately three years from diagnosis. The trial protocols have been agreed by consensus, and are based on protocols used in experienced centres.
- 2. Approval for the study will be sought from local ethical committees.
- 3. Details of patients' identities will be restricted to the local investigator only.

4. Data will be coded prior to any computer entry and study databases will be independent from computer networks. Confidentiality of patient data will be respected.
5. Participation in this study should not require additional tests or clinic attendances above normal practice, apart from the drawing of an additional 10ml of blood and nasal swabs (appendix 4).

6. Trial administration

The EUVAS group has overall responsibility for the trials. The Trial co-ordinators are available to give advice on all aspects of patient management and drug administration.

6.1 Trial administration office (TAO)

1. Patient registration forms can be send by e-mail to dj106@cam.ac.uk or by regular mail to the TAO (for address see last page).
2. The trial office will register and randomise patients and dispatch a Patient Record Book.
3. Trial data will be entered by the trial office into the central database.

6.3. Independent Review Board

1. An Independent Review Board will receive annual reports from the trial co-ordinators to the concerned with recruitment rate, adverse effects and data returns.
3. After 50% of patients have been recruited there will be a review of primary end-point data, which will be blinded to the participants, and will allow early identification of unexpected variations in therapeutic response between limbs.

6.5. Finances

1. Trial administrative costs will be provided EUVAS.
2. There will be no contribution to other medical costs which should not be influenced by participation into the trial.

Appendix 1. Background

A.1.1. The diseases

The primary systemic vasculitides are multisystem autoimmune disorders of unknown cause which are potentially fatal and often result in long-term morbidity and incapacity. The presence of circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA) has helped to define those systemic vasculitides predominantly affecting small blood vessels, Wegener's granulomatosis (WG) and microscopic polyangiitis (MP), as ANCA-associated vasculitides (AASV) [2,7,8]. This grouping is supported by similarities in histological appearance and response to therapy of these syndromes; also, the existence of early and organ-limited forms, 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 [2]. They have been presumed to have an autoimmune basis due to their association with ANCA, the abnormal behavior of immune reactants in the circulation and at sites of injury, and by their response to immunosuppressive medication [9,10]. However, no immunogenetic predisposition has been clearly demonstrated, and in some cases these diseases have been causally linked with certain drugs, infections, or occupational exposures.

A.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 has increased from under 20 to over 60% [11-14]. 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 [13,14]. Their limitations are: firstly, disease remission may only be partial or despite absence of objective vasculitic activity the restoration of health is delayed or incomplete; secondly, 25-40% of patients relapse within the first two years, as therapy is reduced, and many pursue a chronic, grumbling course; thirdly, this combination of drugs has a narrow therapeutic index and treatment-related morbidity and mortality rivals that caused by the underlying disease [14]. Of particular concern has been the late damage resulting from high cumulative exposure to steroids and cyclophosphamide such as osteoporosis, infertility and cancer. Rather than risk the toxicity of continuing cyclophosphamide, some groups have elected to discontinue therapy once the patient is in established remission, and hope to diagnose relapse early and treat it aggressively [14]. Others have chosen to use a maintenance regimen of lower toxicity in the hope of preventing relapse [6] or reducing its severity. Each strategy carries potential advantages. The first approach may avoid side-effects from continuing immunosuppressive drugs, although this may be negated if high dose therapy is required for recurrent disease. The second approach may reduce the organ damage associated with relapse. A direct comparison has not been performed.

Appendix 2. Study Medications

A.2.1. Azathioprine

After hepatic conversion to 6-mercaptopurine, the cytotoxic effects of azathioprine (AZA) are mediated by the impairment of purine synthesis and incorporation of purines into DNA, and impairment of the endonuclease repair activity of DNA polymerase [15]. 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, particularly lymphomas and skin cancers, has been observed with prolonged administration after organ transplantation.

A.2.2. Prednisolone

Prednisolone is a synthetic derivative of cortisone with widespread influences on metabolism and organ function. Desirable effects in vasculitis relate to the suppression of acute and chronic inflammatory 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 re-distribution and striae may occur [15]. Of note in vasculitis, has been the correlation of the cumulative OCS dosage with the total incidence of adverse-effects, and with infections.

Appendix 3. Drug Regimens

A.3.1. Drug doses and schedule

Patients may enter REMAIN between 3 and 24 months from onset of therapy. Drug doses should be aligned with those in the respective limb.

Both limbs until start of REMAIN trial regimens

Months from diagnosis	New doses (permitted ranges)	
	Prednisolone mg daily	Azathioprine mg/kg daily
6	10	2
9	10	2
12	10	1.5-2
15	7.5-10	1.5
18	5-7.5	1-1.5
(21)	(5)	(1)
(24)	(5)	(1)

Continued treatment limb:

Months from Start of trial regimens	New doses (permitted ranges)	
	Prednisolone mg daily	Azathioprine mg/kg daily
0	7.5 (5-7.5)	1
3	5	1
17	4	1
18	3	1
21	2	1
22	1	1
23	0	1
30	0	1
Study end		

Withdrawal limb:

Months from Start of trial regimens (months)	New doses (permitted ranges)	
	Prednisolone mg daily	Azathioprine mg/kg daily
0	5	0.75
1	4	0.75
2	3	0.75
3	2	0
4	1	0
5	0	0
30	0	0
Study end		

A.3.2. Notes for drug regimens

A.3.2.1. Azathioprine

1. maximum dose is 200mg.
2. round dose down to nearest 25mg (may vary alternate day dosage, e.g, 100 and 150mg).
3. age > 60 years, reduce dose by 25%, > 75 years by 50%.
4. Check full blood count (FBC) and ALT or AST (for hepatotoxicity):
 - a) two-weekly for one month.
 - b) two monthly for first year, then three monthly.

A.3.2.2. Leucopaenia

1. Stop AZA if white blood cells (WBC) < $4 \times 10^9/L$.
2. Restart with dose reduced by 25% when WBC > $4 \times 10^9/L$. Monitor FBC weekly for 4 weeks.
3. If severe (< $1 \times 10^9/L$) or prolonged (< $4 \times 10^9/L$ for > 2 weeks), restart AZA at 50mg/day, increasing to target dose as weekly WBC permits. *Pneumocystis carinii* pneumonia and fungal prophylaxis are recommended, G-CSF may be considered.
4. For falling WBC (< $6 \times 10^9/L$ and fall of > $2 \times 10^9/L$ over previous count), reduce dose by 25%.
5. AZA reductions/discontinuation for aplastic anaemia, selective lymphopaenia, neutropaenia or thrombocytopenia, and severe hypogammaglobulinaemia should be discussed with trial coordinators.
6. If leucopaenia recurs at AZA dose 50mg daily, discontinue AZA permanently.

A.3.2.3. Prednisolone

1. Round dose to nearest 5mg above 20mg, and nearest 2.5mg below 20mg.
2. Single daily dose (may vary alternate day dosage by up to 5mg).
3. Use either prednisone or prednisolone, avoid enteric coated or soluble forms.
4. Variability in daily prednisolone dose from regimen of $\pm 25\%$ is permitted.

A.3.2.4. Prophylaxis (suggested only):

1. Prophylaxis against osteoporosis follows local practice, but is strongly advised.
2. Prophylaxis against *pneumocystis carinii* may be considered in high-risk patients, using either three times weekly cotrimoxazole or monthly inhaled pentamidine, according to local practice.
3. Patients should be warned about the increased risk of skin cancer attributable to immunosuppressive drugs, and advised to avoid prolonged sun exposure, and either cover exposed skin or use high-protection-factor sun block.

A.3.3. Changes to drug regimens for relapse

These are non-obligatory guidelines. Additional or alternative regimens may follow local practice. Relapsing patients should remain in the trial with protocol departures (drugs and doses etc) noted in the Patient Record Book.

A.3.5.1. Major relapse (appendix 4)

1. Increase, or start, cyclophosphamide at 2mg/kg/day
2. Increase prednisolone to 0.5mg/kg/day, reduce to 20mg/day by four weeks
3. If ineffective after 2 months, or if life-threatening, follow local preference or discuss with trial co-ordinator
4. On completion of 3 months of cyclophosphamide revert to AZA 2mg/kg and continue at this dose until the end of the study

A.3.5.2. Minor relapse

1. Prednisolone 0.5mg/kg/day; tapered according to local practice.
2. AZA 1.5mg/kg daily. Continue at this dose until the end of the study.
3. If ineffective after 1 month, change cytotoxic as for major relapse.

Appendix 4. Study Evaluations

This is the data required for analysis of the trial. Monitoring for adverse effects (eg FBC for cytotoxic monitoring, liver function monitoring in patients on azathioprine) may require more frequent blood sampling and should follow local practice.

A.4.1. At start of trial regimen and retrospective data from the time of diagnosis when available

1. VITAL Scores¹:
 - a) Birmingham Vasculitis Activity Score: (BVAS) [3].
 - b) Vasculitis Damage Index: (VDI) [4].
2. Haematology:
 - a) Full blood count (FBC): Hb, WBC, neutrophil, lymphocyte and platelet counts.
 - b) ESR.
3. Biochemistry:
 - a) Serum creatinine.
 - b) GFR: creatinine clearance or isotope scan (preferred method).
 - c) ALT or AST, alkaline phosphatase, albumin, glycated haemoglobin (such as HbA1c).
 - d) C-reactive protein (CRP).
 - e) 24 hour urine protein.
4. Immunology:
 - a) ANCA (IIF, PR3 and MPO ELISA).
 - b) Hepatitis BsAg (if positive, check HBeAg), Hepatitis C Antibody.
5. Other:
 - a) Urine dipstick.
 - b) Pathology report from time of diagnosis

A.4.2. 3 monthly

1. BVAS
2. FBC: Hb, WBC, neutrophil, lymphocyte and platelet counts.
3. ESR, Serum creatinine and CRP.
4. ANCA, urine dipstick.

A.4.4. Additionally, at 12, from diagnosis, and at 12, 24 and 30 months after start of trial regimens

1. VDI.
2. GFR (by creatinine clearance or isotope scan (use same method as at entry)).
3. HbA1c.
4. AST or ALT.

Note:

1. 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 [3-5]. BVAS and VDI have been validated and BVAS will contribute to definition of remission and relapse in this study. The disease extension index (DEI) score will be computed from the BVAS data. However, SF-36 will not be evaluated in this study.

Appendix 5. Disease Definitions

A.5.1. Vasculitis syndromes

Patients who did not participate in the MEPEX and CYCAZAREM studies should have a clinical diagnosis in one of these categories, together with evidence of necrotising glomerulonephritis at presentation. Diagnosis of WG, MP or RLV in the majority of patients entering REMAIN will have been made at the time of entry to MEPEX or CYCAZAREM, according to criteria stipulated in the protocols of those trials. The characteristics of these syndromes are outlined below:

A.5.2. 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. 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 >2 kg) 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 two constitutional symptoms is defined as localised disease.

A.5.3. Microscopic polyangiitis

MP is characterised by a vasculitis predominantly affecting small vessels. In contrast to WG, granulomata are absent, and inflammation of the upper respiratory tract and/or lung nodules are absent. Renal involvement is usual and is reflected by a necrotizing glomerulonephritis. Arteritis of medium-sized vessels may also occur. 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).

A.5.4. Renal-limited vasculitis

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

A.5.5. 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. The absence of pulmonary activity is indicated by reduction in size of radiological opacities. Diagnosis of complete remission is supported by a normal CRP.

A.5.6. Relapse

1. Major relapse requires the recurrence or new appearance of major organ involvement such as the following, if they are attributable to active vasculitis:
 - a) an increase in serum creatinine of >30% or reduction in creatinine clearance of >25%, within a period of three months or histological evidence of active, focal, necrotizing glomerulonephritis. Biopsy is strongly recommended for recurrent haematuria or unexplained rise in creatinine.
 - b) clinical, radiological or bronchoscopic evidence of pulmonary haemorrhage or granulomata. Biopsy may be appropriate for undiagnosed opacities.
 - c) threatened vision, e.g. increasing orbital granuloma or retinal vasculitis.
 - d) significant subglottic or bronchial stenosis.
 - e) new multifocal lesions on brain MR suggestive of cerebral vasculitis.
 - f) motor mononeuritis multiplex.
 - g) gastro-intestinal haemorrhage or perforation.
2. Minor relapse requires the recurrence of disease activity of less severity, such as as the following, if they are attributable to active vasculitis:
 - a) ENT: epistaxis, crusting, pain, new deafness, active nasal ulceration or proliferative mass at nasal endoscopy.
 - b) mouth ulcers.
 - c) rash.
 - d) myalgia, arthralgia, arthritis.
 - e) episcleritis or scleritis.
 - f) pulmonary symptoms without or with minor radiological changes, e.g. cough, wheeze, dyspnoea.
3. Relapse is supported by:
 - a) exacerbation of at least two constitutional symptoms (new malaise, weight loss, fever or night sweats).
 - b) rise in CRP.
4. If in doubt, contact a trial co-ordinator.

Appendix 6. References

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P1. REMAIN - Summary of Practical Procedures

Potentially suitable ?

- male or female, 18 years or over with WG, MP or RLV
- cyclophosphamide for at least three months from diagnosis
- now on Azathioprine and in remission 4-24 months from diagnosis
- informed consent given

Ready to enter ?

contact trial office for randomisation dj106@cam.ac.uk

Entry

- your patient will be randomised to either the treatment or withdrawal limbs
- Continue treatment and adjust drug doses to appropriate regimen. Start filling in patient record book.

Follow - up (every 3 months)

- every 3 months score BVAS and laboratory data.
- every 12 months after start of REMAIN trial regimen and study end, score VDI, check AST or ALT, HbA1c and GFR

End of the study (48 months)

- complete termination record
- data to trial database

Flow chart for visits

Time point after diagnosis (retrospective if available when included later than 6 months)	Visit	Blood tests	BVAS	VDI
0 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
6 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
9 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
12 months	x	FBC, creatinine, CRP, ESR dipstick, ANCA, ASTor ALP, HbA1c, GFR	x	x
15 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
18 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
(21 months)	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
start of trail regimen	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
Time point after start of trial regimes				
3 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
6 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
9 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
12 months	x	FBC, creatinine, CRP, ESR dipstick, ANCA, ASTor ALP, HbA1c, GFR	x	x
15 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
18 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
21 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
24 months	x	FBC, creatinine, CRP, ESR dipstick, ANCA, ASTor ALP, HbA1c, GFR	x	x
27 months	x	FBC, creatinine, CRP, ESR, dipstick, ANCA	x	
30 months (Trial end)	x	FBC, creatinine, CRP, ESR dipstick, ANCA, ASTor ALP, HbA1c, GFR	x	x

P2. Patient Information Sheet (This may be modified to meet local requirements)

Randomised trial of prolonged remission-maintenance therapy in systemic vasculitis (REMAIN)

We would like to ask you to participate in a research project. You should not take part if you do not wish to do so. We know that you may have already taken part in one trial of vasculitis treatment. If you do decide to take part, please let us know beforehand if you have been involved in any other study in the last year. If you decide not to take part, your treatment will not be affected by your decision. You are free to withdraw at any stage without giving an explanation and without affecting your subsequent treatment.

You have already received treatment for a form of inflammation of the blood vessels, called "vasculitis". We know that a proportion of patients (around a third) will relapse in the first few years after diagnosis of vasculitis and that this relapse can sometimes cause irreversible damage to the parts of the body it affects. It is uncertain whether it is better to continue drug treatment to try to prevent relapse, or to come off the drugs while there is no sign of recurrence, in order to avoid any side-effects. In this study, which will last 2½ years, we plan to compare the two approaches. Both have been in use for more than ten years in different hospitals, and we would like to compare them to see which approach will keep patients fitter. Which of these two plans you follow will be decided randomly.

If you are selected to continue on treatment, we will continue the prednisolone and azathioprine, which you are already taking for your vasculitis. The dose of the two drugs will be lowered, and the azathioprine will continue throughout the 2½ years of the study. The prednisolone will be tailed off gradually after one year in the study. If you are selected instead to come off treatment, the prednisolone and azathioprine will be tailed off during the first six months of the study. We cannot guarantee to stop or reduce any other medication which you may be taking.

The side-effects which can occur with continuing treatment include increased risk of infection, nausea, thinning of the skin and bones, mood changes, high blood pressure, an increased risk of cancer, cataracts, inflammation of the liver, and diabetes, although the doses we will use will minimise these risks. There are also risks to your health if relapse occurs, including damage to the kidneys, lungs, nose and sinuses, eyes, and nerves, although not all of these will affect everyone who relapses.

It is our normal practice to give you regular examinations and blood checks. These are usually every 2-3 months. In addition to the usual tests, we require, for the purposes of research, an additional small quantity of blood (5ml).

You should not take part in this study if you know you have HIV infection. If you have previously had treatment for cancer, you must discuss this with us before entering the study. You should not take part if you are pregnant and you should not breast-feed during the study. Women of child-bearing age must use efficient contraception to prevent pregnancy during the study. Details of your case will be stored in coded form on computer, but will not be available to anyone not directly involved in this trial.

In the event of an emergency please contact.....

P3. Consent form

(This form may be replaced to meet local requirements)

REMAIN clinical trial

(Randomised trial of prolonged remission-maintenance therapy in systemic vasculitis)

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.)

P4. REMAIN TRIAL PATIENT REGISTRATION

Copy, complete and fax this form to register patients for entry into REMAIN.
A reply will be faxed within 48 hours.

Centre details

From Dr		<input type="text"/>
Centre		<input type="text"/>
FAX		<input type="text"/>
Date	dd/mm/yy	<input type="text" value="/ /"/>

Patient details

Date of entry	dd/mm/yy	<input type="text" value="/ /"/>
Date of birth	dd/mm/yy	<input type="text" value="/ /"/>
Sex	M/F	<input type="text"/>

Please send this form by e-mail (or by regular mail to the address below):

dj106@cam.ac.uk

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Vasculitis Clinic
Box 118
Addenbrookes Hospital
Cambridge CB22QQ
UK

Tel +44-(0)1223 217259
e-mail dj106@cam.ac.uk

P5. CONTACT DETAILS

REMAIN CO-ORDINATORS

(Major organisational decisions, medical discussions)

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EUVAS

(Project management, study group co-ordination)

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