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Title: Randomised trial of adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis: plasma exchange versus intravenous methylprednisolone.

Short title: MEPEX

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Summary:

Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) are primary systemic vasculitides associated with a necrotising glomerulonephritis. This may run a rapidly progressive course to dialysis-dependent renal failure within weeks and standard therapy for vasculitis consisting of oral corticosteroids and cyclophosphamide may be insufficient to restore adequate renal function.

This trial is designed to compare the efficacy of adjunctive methylprednisolone and plasma exchange in restoring renal function in 150 new patients with ANCA-positive WG or MP associated with severe glomerulonephritis. Patients will receive the same standard induction and maintenance therapy and will be randomised to receive additionally either 3 pulses of intravenous methylprednisolone or 7 plasma exchanges. Renal function at 12 months and the incidence of adverse effects will be compared in the 2 groups.

(See trial overview in appendix 1).

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 developed from an existing EC/BCR study group concerned with the design and standardisation of solid-phase assays for anti-neutrophil cytoplasmic antibodies (ANCA, autoantibodies prevalent in SV), brought together in 1991. The aims of the ECSYSVASTRIAL 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 in the treatment of these disorders within the EC.

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

1. early generalised SV without overt renal involvement (NORAM)
2. WG or MP with slight to moderate renal involvement or other threatened vital organ function (CYCAZAREM)
3. **WG or MP with severe renal involvement (MEPEX, this protocol)**
4. SV cases refractory to standard treatment (WARCRY)

These protocols form a continuum with partially shared treatment arms and inclusion and exclusion criteria covering the entire spectrum of systemic forms of WG and MP. Two other protocols are integrated in the first 3 protocols: SAVAS looks at the role of nasal carriage of *Staph. aureus* and RELANCA looks at the relationship between relapse and ANCA levels. Scoring of disease activity and extent will be assessed using the VITAL protocol.

Patients with other forms of SV like Churg-Strauss syndrome (CHUS) and polyarteritis nodosa (PAN) may be included in a multicentre study already designed by participants of the ECSYSVASTRIAL study group.

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

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Background

1.1 The diseases

Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) are syndromes of primary systemic vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCA) (appendix 6; [1,2]). WG and MP share many histological features, including a necrotising glomerulonephritis which often leads to rapidly progressing renal failure. 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 vasculitis, including the presence of circulating anti-MPO or anti-Pr3 antibodies, and is usually treated with a similar regimen. Common histological and serological features, and a similar response to treatment, have justified a common approach to the treatment of WG and MP.

1.2 Their treatment

Historically, untreated generalised WG and MP followed a progressive course with a fatal outcome due to vital organ failure [3]. With the empirical introduction of corticosteroids and cytotoxic agents, five year survival increased from under 20% to over 60% [1]. This medium-term improvement was due in part to the simultaneous development of dialysis and transplantation for patients with established renal failure. Unfortunately, dialysis-dependent renal failure is itself associated with premature death. Since recent data suggest that SV is becoming more common [4], and likely to contribute increasing numbers to renal replacement therapy programmes, adjunctive therapies to restore renal function in the initial illness are highly desirable.

Two main approaches have been used. The first is to add pulsed high-dose intravenous methylprednisolone (IVMeP) to standard regimens. In RPGN without anti-GBM antibodies, the addition of three pulses of IVMeP 30mg/kg to oral prednisolone permitted discontinuation of dialysis in 16/23 patients, in contrast to 0/9 of those not given the additional therapy, but given instead varying combinations of oral steroids and other agents [5]. In another study of patients with ANCA-associated glomerulonephritis lower doses (7mg/kg) were added to varying regimens of prednisolone and cyclophosphamide; in this study 6/12 patients were able to discontinue dialysis [6]. Others have reported using three doses of 1g with varying results [7-9].

The second approach is to add plasma exchange (PE). In a controlled study in patients with focal necrotising glomerulonephritis without anti-GBM antibodies [10], 10/11 dialysis-dependent patients randomised to receive at least five 4 litre exchanges in addition to oral steroids, cyclophosphamide and azathioprine discontinued dialysis, while only 3/8 patients in the control group did so. Patients with lesser degrees of renal impairment at presentation responded adequately with or without PE. A recent multicentre trial performed in Canada examined whether addition of ten exchanges, each of one plasma volume, to a regimen of intravenous methylprednisolone (three doses of 10mg/kg), prednisone and azathioprine, improved renal outcome in patients with idiopathic crescentic glomerulonephritis [11]. No difference in outcome was demonstrated in patients who were not dialysis-dependent at presentation. Of the 11 patients who initially required dialysis, 3/4 patients treated with plasma exchange and 2/7 patients in the control group were able to discontinue dialysis. Two other studies using PE in RPGN have not demonstrated a convincing value, but this may have been due in part to the studies' design. The earlier study [13] used immunosuppressive agents alone, and immunosuppressive agents with additional PE, sequentially in the same patients. The later study permitted patients in the drug-treated group to receive additional PE if the initial response to drugs alone was inadequate [14]. Furthermore, these studies included not only patients with idiopathic RPGN, and some patients with RPGN associated with vasculitis, but also a number with RPGN associated with other systemic diseases.

In these and other smaller studies, adjunctive therapies have not always been used in combination with an optimal or consistent cytotoxic regimen, and outcome has varied. The best results reported with each type of adjunctive therapy are similar (and probably best of all in the trial reported by Pusey et al [10]), but no large studies directly comparing the efficacy of PE and IVMeP have been performed. In a small uncontrolled series, of dialysis-dependent patients with RPGN, [12], 9/11 patients treated with plasma exchange survived with

independent renal function, compared to 5/9 treated without plasma exchange. 13/15 treated with IVMeP survived with independent renal function, compared to 1/5 treated without. 5/11 in the plasma exchange group achieved a creatinine < 150mmol/l, compared with 5/15 in the IVMeP group. This study did not demonstrate statistically significant differences, and interpretation of the results was complicated by the fact that many of the patients studied received both PE and IVMeP. Thus the question remains to be answered.

Since there is increasing *in vitro* evidence for a possible pathogenic role for ANCA, PE may confer particular benefit by removing circulating antibodies. It may also be associated with lower morbidity than IVMeP, since steroid dose has been particularly associated with infection in previous studies of vasculitis treatment [15]. Suggestions from early studies that PE is associated with increased infection risk have not been confirmed [16]. However, since PE is more expensive and less widely available than IVMeP, a formal comparison of the two adjunctive therapies is required before PE can be recommended as a superior therapy. Since a previous study has failed to demonstrate benefit of plasma exchange in addition to corticosteroids in CHUS and PAN [17], these syndromes need not be included in the comparison.

1.3 Aims of MEPEX:

The aims of MEPEX are to determine whether PE is indeed more effective than IVMeP in restoring renal function in patients with severe renal impairment due to necrotising glomerulonephritis, when used in conjunction with a standard cytotoxic regimen, to compare the adverse effects of the two types of adjunctive therapy, and subsequently to harmonise approaches to the treatment of severe renal vasculitis in Europe.

2 Study therapies

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 phosphoramidate mustard, which alkylate guanine nucleotides, thus blocking cell division [18]. 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 carboxyphosphoramidate 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 [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 /or lymphoma is increased tenfold; 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 [18]. 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, have been observed with prolonged administration after organ transplantation.

2.3 Prednisolone and methylprednisolone

Prednisolone and methylprednisolone are synthetic derivatives of cortisone with widespread effects on metabolism and organ function [18]. Desirable effects in systemic vasculitis relate to the suppression of acute and chronic inflammatory processes and immune cell function.

The major unwanted effects of corticosteroids in the short term are salt and water retention, hypertension, hyperglycaemia, central nervous system stimulation, peptic ulceration and immunosuppression. While these effects respond to reduction or withdrawal of the drug, if their use is prolonged additional effects including osteoporosis and avascular necrosis, subcapsular cataracts, skin fragility, myopathy, Cushingoid facies, hirsutism, alopecia, fat re-distribution, striae and growth retardation in children may occur. IVMeP delivers a higher dose of corticosteroid, increasing the dose-related side-effects, notably hypertension and salt and water retention. Of note, in systemic vasculitis, has been the correlation of the cumulative steroid dosage with the total incidence of adverse effects, and particularly with infections [15].

2.4 Plasma exchange

Plasma exchange is a technique combining plasmapheresis - the separation of plasma from blood cells by centrifugation or filtration- and its replacement by a colloid solution [20]. Optimal efficiency requires exchange of 100-150% of the plasma volume (40ml/kg), and the usual exchange volume is 3-4l in an adult. Prerequisites for treatment are vascular access (typically either peripheral veins or dual lumen central venous catheters) and anticoagulation (using heparin or acid citrate dextrose). In this study, sterile human albumin solution will be used as the replacement colloid. Fresh frozen plasma may be given at the end of the exchange to replenish clotting factors in patients at risk of bleeding (see appendix 2). The most common complications of plasma exchange include complications of vascular access (risks to which dialysis-dependent patients are already exposed), transient hypotension, and minor allergic reactions to replacement fluids. Hypocalcaemia may occur when citrate anticoagulation is used. More serious, but rare, complications include cardiac ischaemia and arrhythmias due to inadvertent volume depletion in susceptible patients, non-cardiogenic pulmonary oedema probably associated with plasma replacement, viral infection transmitted in unpasteurised blood products, and bleeding due to clotting factor depletion. In a study of 7538 exchanges in 887 patients, the incidence of side-effects was 16.8%, although discontinuation of plasma exchange was required in only 4% [21]; three deaths occurred, and all were related to the administration of fresh frozen plasma. Although early studies suggested a significant increase in infective complications in patients undergoing plasma exchange, this has not been confirmed in recent studies [16].

3 Hypothesis

Plasma exchange is superior to pulsed methylprednisolone in securing renal recovery in severe ANCA and vasculitis-associated glomerulonephritis.

4 Study design

4.1 Nature:

International, multicentre, randomised, prospective study, with informed consent and local ethics committee approval.

4.2 Rationale:

The ANCA-associated vasculitides, WG and MP, are associated with a necrotising glomerulonephritis which may run a rapidly progressive course to dialysis-dependent renal failure within weeks. Standard therapy for vasculitis consisting of oral corticosteroids (OCS) and cyclophosphamide (Cyc) is often insufficient to restore adequate renal function when renal dysfunction is already severe at presentation. Intravenous boluses of methylprednisolone (IVMeP) and intensive courses of plasma exchange (PE) have been shown to facilitate renal recovery from dialysis-dependence in 70% and over 90% of patients respectively, but the two therapies have not been directly compared. Since PE is more expensive and less widely available than IVMeP, a formal comparison of the two adjunctive therapies is required before PE can be recommended as a superior therapy.

4.3 Inclusion criteria:

- 1) New diagnosis of WG, MP or its renal-limited variant, in accordance with the Chapel Hill consensus criteria [2], with active vasculitis, as indicated by the presence of active necrotising glomerulonephritis on renal biopsy. See appendix 6.
- and*
- 2) ANCA positivity: either a typical C-ANCA pattern by IIF, and/or positivity in the Pr3 ELISA, or positivity in the MPO ELISA, with or without P-ANCA. (ANCA result will be confirmed by a nominated reference laboratory.)
- and*
- 3) Biopsy-proven necrotising and/or crescentic glomerulonephritis, in the absence of another defined glomerulopathy, with severe renal impairment defined by:
 - (i) oliguria (<400ml/24hr)
 - or*
 - (ii) intention to commence dialysis within 48 hours of admission
 - or*
 - (iii) creatinine \geq 500mmol/l.

Patients will be stratified at entry into oliguric/dialysis-requiring (groups i and ii: olig/dial) and patients with biochemical derangement only (group iii: 500+) since previous experience suggests that the response to therapy differs in these categories [10].

In order to commence therapy as quickly as possible, patients may be entered on the basis of strong clinical suspicion and intention to treat as ANCA-associated glomerulonephritis, before confirmation by biopsy, and before the result of an immunoassay performed in a reference laboratory has been obtained. Patients with necrotising glomerulonephritis who prove later not to meet the ANCA criteria and patients with a firm clinical diagnosis but no histological confirmation will continue in the protocol but will be analysed separately. Patients without necrotising and/or crescentic glomerulonephritis or with another form of glomerulonephritis will be withdrawn.

4.4 Exclusion criteria:

- 1) Age under 18 or over 80.

- GBM on
- 2) Inadequate contraception in women of child-bearing age.
 - 3) Pregnancy.
 - 4) Previous malignancy (usually exclude unless agreed with trial coordinators).
 - 5) Hepatitis B antigenaemia or detectable anti-HCV antibody.
 - 6) Known anti-HIV positive (HIV testing is not a requirement for this trial).
 - 7) Diagnosis of Churg-Strauss syndrome, Henoch-Schönlein purpura, rheumatoid vasculitis, mixed essential cryoglobulinaemia, systemic lupus erythematosus, or the presence of circulating anti-GBM antibodies and linear IgG staining of the renal biopsy, with intent to treat as anti-GBM mediated nephritis.
 - 8) Life-threatening non-renal manifestations of vasculitis, including alveolar haemorrhage requiring mechanical ventilation within 24 hours of admission.
 - 9) On dialysis for > 2 weeks prior to referral.
 - 10) Significant baseline renal impairment: creatinine > 200mmol/l 1 year or more before presentation.
 - 11) A second clearly defined cause of renal failure (eg urinary tract obstruction. *Not* ATN).
 - 12) Previous episode of biopsy-proven necrotising and/or crescentic glomerulonephritis.
 - 13) IVMeP, PE or pulsed intravenous cyclophosphamide within the preceding year.
 - 14) More than 2 weeks' treatment with oral Cyc or azathioprine (Aza).
 - 15) More than 3 months' treatment with OCS.
 - 16) Allergy to study medications (excluding prophylactic agents).
 - 17) Previous IVMeP therapy which exceeds a single dose of 500 mg prior to referral to the participating centre.

4.5 End-points:

- 1) The primary endpoint is renal survival at 1 year.
- 2) Secondary endpoints:
 - i) Renal recovery to creatinine \leq 200mmol/l (at which level long-term preservation of renal function is likely).
 - ii) Adverse effects of treatment (see appendix 7).

4.6 Interventions

4.6.1 Drug regimens (appendix 2):

- 1) All patients will receive the same standard induction therapy and will be randomised at entry to receive either 3 pulses of IVMeP or a course of 7 PE treatments.
- 2) Patients in whom progression of life-threatening vasculitis occurs, during the induction phase despite ³ 2 weeks' therapy (*excluding* failure to regain independent renal function unless a repeat renal biopsy shows active necrosis) will have therapy modified according to local preference or will be entered into the refractory disease open study. Data collection will continue to one year.
- 3) Relapse, occurring after induction of remission (see appendix 6 for definition), will be treated according to guidelines for treatment of relapse (see appendix 4). Data collection will continue to one year.

4.6.2 Evaluations (appendix 5):

- 1) History and examination at entry, at 6 weeks, then at 3,6,9 and 12 months.
- 2) Blood drawn monthly for six months then at least every two months thereafter.
(The clinical value of laboratory parameters of disease activity is an associated aim of this study but treatment decisions will not be based on their levels. See RELANCA protocol.)
- 3) WG patients to have nasal swabs at presentation, monthly for the first six months then at least every two months thereafter, to a total of 8. (Follow-up swabs not to be taken during hospital admission or antibiotic therapy.)
(The relation of Staphylococcal carriage to disease relapse is an associated aim of this study, however results of nasal swabs will not affect patient management. See SAVAS protocol.)
- 4) VITAL score at entry, at 6 weeks, then at 3,6,9 and 12 months.
(VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS) I and II, the Vasculitis Damage Index (VDI) and the Short-Form-36 (SF-36) functional assessment. The Disease Extension Index (DEI) can be computed from VITAL.)
- 5) Characteristics of initial renal histology will be documented, and biopsies reviewed by a pool of pathologists.
- 6) GFR will be measured at 12 months and compared in the 2 groups.

4.7 Withdrawal:

At patient's or physician's request.

Reason for withdrawal is to be recorded in the record book.

4.8 Adverse effects:

- 1) See appendix 7 for details of effects to be reported. The presence or absence of these will be recorded in the patient record-book at each evaluation.
- 2) Adverse effects of therapy will be reported to the International review board.
- 3) Adverse effects sufficient to withdraw a medication will be determined. after discussion with the trial committee.

4.9 Statistical analysis:**4.9.1 Stratification:**

Prior to randomisation, patients will be stratified according to renal function: into those who are oliguric or dialysis-requiring (the olig/dial group), and those who are non-oliguric, do not require dialysis, but whose serum creatinine is > 500mmol/l (the 500+ group).

4.9.2 Power:

To detect a difference of 20% in renal survival (with renal survival 80% in PE group and 60% in IVMe group) with a power of 0.8 in a 1-tailed study and a type 1 error of 0.05, will require 137 patients. 150 patients will be recruited to permit a 10% rate of loss to follow-up.

4.10 Ethical considerations:

Glomerulonephritis associated with WG and MP often follows a rapidly progressive course which leads to irreversible renal failure unless adequately treated, with consequent morbidity and increased mortality. Published data suggests that addition of either plasma exchange or IVMe to conventional immunosuppressive regimens leads to the greatest chance of renal recovery. The best results, in small numbers of patients, have been reported using PE, but this a more expensive treatment than IVMe and less widely available, and so this trial is designed to test whether PE is a superior treatment before advocating its wider use. The trial protocols have been agreed by consensus, and are based on protocols used in experienced centres. Follow-up 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 (see appendix 5).

- 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 according to national regulations. Data will be coded prior to computer entry and the study database will be independent from any computer networks.

4.11 International review board:

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

4.12 Duration:

Three years: two years recruitment and one year follow-up.

4.13 Coordination:

International and UK coordination by Dr G Gaskin, Hammersmith Hospital, London.

MEPEX organisers will act as national coordinators.

Part-time clinical trial assistant (CTA) to be appointed.

Study data will be recorded by the investigator in the record-books.

Following exit from the study, record-books will be reviewed by the CTA and local investigator before being sent with the saved sera for central analysis.

Records of patient registration to be maintained both centrally and locally.

4.14 Budget:

Funding will be sought to cover trial administration costs (not the cost of drugs or infusions or plasma exchange disposables which will be met locally) from Baxter extra-mural grants programme. It is anticipated that costs will include the salary of a part-time CTA, the travelling expenses of trial coordinators and trial assistant to participating centres, the cost of data collection, data entry and analysis, and the cost of communications. These costs may be met in part by the ECSYSVASTRIAL budget.

	1 yr	2 yr	3 yr	4 yr	total (£)
Personnel (1/3 CTA)	8000	8000	8000	8000	32400
Data collection	500	500	500	500	2000
Data entry and analysis	2000	2000	2000	5000	11000
Investigator's meetings ¹	5000	5000	5000	5000	20000
Communications	200	200	200	200	800
IRB organisation	500	500	500	500	2000
Total	68200				

¹ One international meeting per year (3000) and one national meeting per year for countries with satellite centres (2000).

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6.1 Appendix 1 Overview of MEPEX

Diagnosis of ANCA-associated WG or MP with severe glomerulonephritis



Entry after informed consent

Stratification according to severity of renal dysfunction

Randomisation

olig/dial

500+



olig/dial

500+



IVMe x 3 pulses days 1-3
together with standard induction regimen (OCS + Cyc)

PE x7 within 14 days
together with standard induction regimen (OCS + Cyc)



Progressive OCS reduction
Change Cyc to Aza at 6 months (3 months if age <40)



Study ends at 12 months

6.2 Drug regimens (Appendix 2)

6.2.1. Standard therapy:

The OCS/Cyc/Aza regimen is summarised below:

Time from entry	Action	Prednisolone mg/kg	Cyclophosphamide	Azathioprine
			mg/kg daily	mg/kg daily
0	Start	1	2.5	0
1 week	Reduce P	0.75	2.5	0
2 weeks	Reduce P	0.5	2.5	0
4 weeks	Reduce P	0.4	2.5	0
6 weeks	Reduce P	0.33	2.5	0
8 weeks	Reduce P	0.28	2.5	0
10 weeks	Reduce P	0.25	2.5	0
3 months	Reduce C (Optionally change C to same dose A if age <40*)	15mg daily	1.5	(2.5*)
4 months	Reduce P	12.5mg daily	1.5	(2.5*)
5 months	Reduce P	10mg daily	1.5	(2.5*)
6 months	Change C to A	10mg daily	0	2
Dose at 12 mths		10mg daily	0	2

* denotes alternative for patients aged under 40

6.2.2 Adjunctive therapy:

- 1) Intravenous methylprednisolone, at a dose of 15mg/kg daily, days 1-3 (maximum daily dose 1g)
or
- 2) Plasma exchange, 7 treatments within first 2 weeks; 60ml/kg of plasma exchanged for 4.5% or 5% human albumin solution.

6.3 Notes on drug regimens (Appendix 3)

6.3.1 Cyclophosphamide and azathioprine

- 1) Starting dose of Cyc is reduced to 2mg/kg in patients aged over 60 yrs.
- 2) Dose is rounded down to the nearest 25mg.
(Only 50mg tablets of Cyc are available, and so, for example, 75mg daily would be given as 100mg and 50mg daily alternating.)
- 3) Maximum dose of Cyc 150mg daily in the first 3 months, 100mg daily in the following 3 months.
- 4) Patients initially intolerant of oral medication receive 75% of the dose of Cyc by daily intravenous injection.
- 5) A change from Cyc to Aza for maintenance may be made at 3 months if the patient is aged under 40 (when preservation of fertility is likely to be important). This is optional and should be noted in the record-book.
- 6) Oral Cyc should be given in the morning and a high fluid intake encouraged (if possible). Cyc should be discontinued in the presence of haemorrhagic cystitis.
- 7) Blood counts are performed at least weekly in the first month, 2-weekly in the 2nd month, and monthly thereafter.

6.3.2 Leucopaenia

- 1) Stop Cyc or Aza if total white blood cell count (WBC) less than $4 \times 10^9/l$. Restart with dose reduced by at least 25mg when $WBC > 4 \times 10^9/l$ on 2 consecutive tests, or $>5 \times 10^9/l$ on 1 test. Monitor WBC weekly for one month.
- 2) If leucopaenia is severe ($<1 \times 10^9/l$), or prolonged ($<4 \times 10^9/l$ for > 2 weeks), recommence drug at 50mg daily and increase to target dose 50mg less than previous dose as weekly WBC permits.
For severe leucopaenia, consider:
G-CSF (note concern over possible pro-vasculitic effect).
fungal prophylaxis
pneumocystis prophylaxis
nursing and food preparation according to local practice
- 3) For falling WBC ($< 6 \times 10^9/l$, and a fall of $>2 \times 10^9/l$ from previous count), recheck within 1 week and reduce dose by 25mg if further fall of $>0.5 \times 10^9/l$.
- 4) Cytotoxic reductions/discontinuation for aplastic anaemia, selective lymphopaenia, neutropaenia or thrombocytopaenia, and severe hypogammaglobulinaemia should be discussed with trial coordinators.

6.3.3 Prednisolone:

- 1) Use either prednisolone or prednisone; avoid enteric coated or soluble forms.
- 2) Give as a single daily dose.
- 3) Patients initially intolerant of oral medication may receive an intravenous steroid preparation in equivalent dose.
- 4) Maximum dose 80mg daily (first week).
- 5) Minimum dose in first 3 months is 12.5mg daily.
- 6) Flexibility of dose of $\pm 12.5\%$ will be allowed in the first 3 months, and $\pm 25\%$ from 3 months onward. If a greater variation in dose is being considered please discuss with trial coordinators.
- 7) After calculation for body weight and flexibility adjustment, dose will be rounded to the nearest 5mg above 20mg, and to the nearest 2.5mg below 20mg. A day to day variation in dose of up to 5mg is permitted to achieve calculated dose with available tablets.

6.3.4 Intravenous methylprednisolone:

- 1) Administered as an infusion in 100ml 0.9% saline over 30 minutes.

- 2) Volume depletion and hypokalaemia should be corrected prior to administration.
- 3) Dose of 15mg/kg is rounded to the nearest 100mg, to a maximum of 1g.

6.3.5

Plasma exchange:

- 1) Exchange may be performed using either a cyto centrifuge or plasma filter.
- 2) Anticoagulation may be either heparin (to a maximum dose of 10,000 units per exchange) or citrate, according to local practice.
- 3) Minimum exchange volume 3 litres; maximum 4 litres.
- 4) Fresh frozen plasma 300-500ml (or equivalent blood product) is administered at the end of the exchange in the presence of abnormal coagulation or bleeding, and may be administered as prophylaxis against bleeding due to clotting factor depletion within 5 days of a procedure which may induce bleeding (eg renal biopsy), according to local practice.
Use/omission under these circumstances is to be recorded in the patient record-book.
- 5) A 10ml blood sample for separation of plasma, drawn at the commencement of exchange, and a 20ml aliquot of the first 1000ml plasma removed are to be saved at -20°C for later quantification of ANCA removal, and comparison of cyto centrifuge and plasma filter methods.

6.3.5

Prophylaxis:

- 1) These guidelines apply to all patients.
- 2) Prophylaxis against peptic ulceration during the first six months is recommended using a once daily H₂ blocker (not cimetidine) or omeprazole but not misoprostol. Its use/omission is to be recorded in the record-book.
- 3) All patients should receive prophylaxis against fungal infection (oral fluconazole, or oral nystatin, or oral amphotericin, continued for 3 months).
- 4) Prophylaxis against osteoporosis follows local practice.
- 5) Patients with previous tuberculosis require prophylaxis according to local policy.
- 6) 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.

6.4 Changes to drug regimens for relapse or failure to recover independent renal function (Appendix 4)

These are non-obligatory guidelines.

6.4.1 Major relapse:

- 1) Change Aza to Cyc 2mg/kg/day or increase Cyc dose to this level
- 2) Increase OCS to 0.5mg/kg/day, reducing to 20mg daily by 4 weeks; reduce by 5mg daily per month until the doses of OCS and Cyc used approaching the 6 month point of the MEPEX protocol are achieved. These should be maintained until the end of the study.
- 3) If ineffective after 2 months, or if relapse life-threatening, follow local preference.

6.4.2 Minor relapse:

- 1) Increase in OCS to 0.5mg/kg/day; reduce dose by 5mg/week until the appropriate point on the protocol is reached.
- 2) Increase Aza to 2mg/kg if on lower dose.
- 2) If ineffective after 1 month, change cytotoxic as for major relapse.

All relapses, changes in drugs and doses are to be recorded in the record book, and patient data collected until the end of the study according to the protocol.

6.4.3 Failure to recover renal function:

In patients with renal-limited disease who remain dialysis-dependent, immunosuppressive therapy may be withdrawn after three months. A renal biopsy is strongly advised to exclude continuing disease activity before this decision is made. This action should be noted in the record book, and patient data collected until the end of the study according to the protocol.

Patients with extrarenal vasculitis should continue treatment according to the protocol.

6.5 Evaluations (Appendix 5)

These constitute the minimum information required for the study. Additional tests (eg FBC for cytotoxic monitoring) or more frequent attendances should follow local practice.

- 6.5.1 Entry:**
 VITAL score*
 Full blood count and white cell differential (FBC)
 C-reactive protein, ANCA (IIF, Pr3 and MPO ELISA performed at/confirmed by approved reference centre)
 Creatinine
 GFR, by creatinine clearance or isotope scan, within first 5 days
 AST or ALT, alkaline phosphatase, albumin
 Glucose
 Rheumatoid factor, ANA, DNA binding, anti-GBM, cryoglobulins, complement
 Hepatitis B and C serology
 dipstick urinalysis
 24 hour urine protein
 5ml serum saved
 Chest X-ray and sinus X-ray
 Renal biopsy
 Nasal swab for bacterial culture
- 6.5.2 Monthly for first 6 months and a minimum of 2-monthly for second 6 months:**
 5ml serum saved
 Nasal swab for bacterial culture
- 6.5.3 At 6 weeks, 3 months, 6 months, 9 months and 12 months:**
 VITAL scores*
 Full blood count and white cell differential (FBC)
 C-reactive protein
 Creatinine
 Glucose
 AST or ALT, alkaline phosphatase, albumin
- 6.5.4 Additionally at 1 year:**
 GFR, by creatinine clearance or isotope scan

* VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS) I and II, the Vasculitis Damage Index (VDI) and the Short-Form-36 functional assessment score. BVAS I has been validated in the UK, and international validation is in progress. The Disease Extension Index will be computed from data collected for VITAL.

6.6 Disease definitions (Appendix 6)

6.6.1 Wegener's granulomatosis

Generalised WG is characterised by granulomatous inflammation of the respiratory tract, together with necrotising vasculitis affecting small to medium-sized vessels; necrotising glomerulonephritis is common and reflects renal involvement [2]. A C-ANCA pattern by IIF, with anti-PR3 reactivity by ELISA, is found in over 90% of untreated patients with generalised WG; some studies have found a minority of cases to have anti-MPO instead of anti-PR3. In WG with disease limited to the respiratory tract, ANCA positivity is less frequent.

For the purposes of this study, a diagnosis of generalised WG requires the presence of an active necrotising glomerulonephritis, together with clinical, radiological or histological evidence of granulomatous inflammation in the respiratory tract, and detectable C-ANCA by IIF, or anti-Pr3 or anti-MPO ANCA by ELISA. A positive biopsy from the respiratory tract is not mandatory.

6.6.2 Microscopic polyangiitis

MP is characterised by a vasculitis predominantly affecting small vessels. Renal involvement is usual and reflected by a necrotising glomerulonephritis. Granulomata are absent. Arteritis of small or medium-sized arteries may also occur [2]. MP is associated with ANCA specific for MPO or Pr3; a minority of MP patients are ANCA negative or recognise other ANCA antigens.

For the purposes of this study, a diagnosis of generalised MP requires the presence of active necrotising glomerulonephritis, together with clinical, radiological or histological evidence of an extrarenal vasculitis, and detectable C-ANCA by IIF, or anti-Pr3 or anti-MPO ANCA by ELISA. A positive biopsy from an extra-renal site is not mandatory. The presence of granulomatous inflammation, or heavy immune deposition in glomeruli or vessel walls excludes this diagnosis.

6.6.3 Renal-limited vasculitis *or* Idiopathic rapidly progressive glomerulonephritis

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 MP or WG, including the presence of circulating anti-MPO or anti-Pr3 antibodies.

For the purposes of this study, a diagnosis of renal-limited vasculitis, or idiopathic rapidly progressive glomerulonephritis requires renal biopsy confirmation and a positive ANCA by the criteria outlined for generalised MP. Heavy immune deposition in glomeruli excludes this diagnosis.

6.6.4 Remission

Full clinical remission is indicated by complete absence of clinical disease activity using the item list of BVAS 1. 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.

6.7 Adverse effects (Appendix 7)

6.7.1 Intolerance of trial therapies:

This may include persistent leucopaenia (total WCC $< 4 \times 10^9/l$ for a period of ³ 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 coordinators should be contacted in case of difficulty in classification.

- Allergic reaction to plasma exchange replacement fluids
- Bleeding
- Vascular access complications during the first two weeks
- Thrombocytopenia
- Infection (site/organism to be noted)
- Leucopaenia (total WCC $< 4 \times 10^9/l$; duration and consequences to be noted).
- Haemorrhagic cystitis (cystoscopy should be performed in the presence of macroscopic haematuria or microscopic haematuria which is persistent and heavy or associated with abnormal urine cytology)
- Malignancy
- Amenorrhoea and infertility
- Nausea and vomiting
- Alopecia or skin changes sufficient to concern the patient
- Cataracts
- New or worsening osteoporosis, with or without pathological fracture
- Avascular necrosis
- Newly presenting diabetes
- Peptic ulceration
- New or exacerbated psychological disturbance
- Hypertension
- Liver dysfunction
- Drug-induced hypersensitivity reaction

6.9 Patient Information

Brief title of project

Randomised trial of adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis: plasma exchange versus intravenous methylprednisolone.

Explanation:

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. 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 are suffering from a form of inflammation of the blood vessels, called “vasculitis”, which has severely affected your kidneys. The standard form of treatment for this condition consists of a combination of tablets which, on their own, may not be powerful enough to make your kidneys recover. In this study we plan to compare two kinds of additional treatment which have been shown to improve the recovery of kidney function when added to the standard drugs. Both types of treatment have been in use for more than ten years in different hospitals, and we would like to compare them to see which is the best with fewest side-effects.

One of the treatments is called “plasma exchange”, which involves removing some of your own blood plasma and replacing it with a sterile purified protein solution. Like dialysis treatment, this involves putting a needle or a temporary plastic tube into your veins (using local anaesthetic) to pass your blood through a machine. It takes around two hours each treatment, and will be performed seven times in your first two weeks in hospital. The treatment is painless, although it can occasionally make you feel light-headed. The alternative treatment involves a daily infusion of steroids directly into a vein in your arm. This will be given on your first three days in hospital. Since you are likely to be in hospital for at least two weeks, these treatments will not usually prolong your hospital stay. Which of the two additional treatments you receive will be decided randomly. The side-effects which can occur with the standard and additional treatments include increased risk of infection, hair loss, nausea, bladder irritation, thinning of the skin and bones, mood changes, high blood pressure, infertility, foetal damage, an increased risk of cancer, cataracts, and diabetes, and also a risk of bleeding in the early stages of treatment. Many of these side-effects are due to the standard drugs.

You will remain in the study, continuing to take tablets, for 1 year. When you are taking these tablets, it is our normal practice to watch you closely with regular examinations and blood checks, which will take place initially each week, and then less frequently as your condition improves. In addition to the usual tests, we require each month, for the purposes of research, an additional small quantity of blood (5ml) and a swab taken from the nose.

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.....

6.10 Participant consent form

Title of Project

Randomised trial of adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis: plasma exchange versus intravenous methylprednisolone.

The participant or key carer should complete the whole of this sheet himself/herself.

(please cross out as necessary)

Have you been asked to consent for yourself or on behalf of someone else?

Self / Other

If your answer to the above is "other", please give the name of the person for whom you are consenting.

.....

Have you read the Information Sheet for Patients?

Yes / No

Have you had an opportunity to ask questions and discuss this study?

Yes / No

Have you received satisfactory answers to all of your questions?

Yes / No

Have you received enough information about the study?

Yes / No

Who have you spoken to?

Dr/Mr/Ms.....

Do you understand that you are free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting your future medical care?

Yes / No

Do you agree to take part in this study?

Yes / No

Signed..... Date.....

(NAME IN BLOCK LETTERS):.....