

International Mycophenolate mofetil Protocol to reduce outbreaks of vasculitides

(IMPROVE)

Mycophenolate mofetil versus azathioprine
for maintenance therapy in
ANCA associated systemic vasculitis

Summary

The primary, ANCA-associated systemic vasculitides (AASV), including Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) and renal limited vasculitis (RLV), are progressive, multisystem, autoimmune diseases which respond to immunosuppressive therapy. Their treatment with corticosteroids and cytotoxic drugs has been standardised in a first wave of studies (ECSYSVASTRIAL project), but limitations of such regimens include a high relapse rate and appreciable treatment-related toxicity. The present trial, IMPROVE, aims to reduce the relapse rate by administering mycophenolate mofetil (MMF) for the maintenance of remission. The potential benefit of using MMF in this way for AASV has been demonstrated in a preliminary, uncontrolled study. Patients with previously untreated "generalised" AASV will be randomised to receive either MMF or standard treatment with azathioprine (AZA) once remission has been induced with cyclophosphamide and prednisolone. MMF and AZA will be continued for 42 months while prednisolone dose is being tapered and finally stopped in both limbs. In the last 6 months, the patients will not receive any immunosuppressive drugs. The study will last 48 months. The primary end-point is the disease-free period, taken as the period of time from remission until relapse or study end; secondary end-points are adverse effects, cumulative damage and immunosuppressive drug exposure. 160 patients are required.

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1. Trial Overview

Entry and randomisation

Active, ANCA positive WG, MPA, RLV; > 18, < 75 years; previous treatment (according to protocol) no longer than 1 month



Induction regimen = OCS + CYC (daily oral or pulse)
(0-3 (up to 6) months)



Remission treatment as randomised
(stratification by WG vs. MPA/RLV and oral daily vs. pulse CYC)
(3 – (up to) 6 months)



OCS + MMF



OCS + AZA



Evaluations
(every 3 months)



stop MMF
(42 (up to 45) months)

stop AZA
(42 (up to 45) months)



Study end
(48 (up to 51) months)



2. Aims of IMPROVE

Because AASV patients (especially WG patients) are known to have a high risk of relapse, the aims of IMPROVE are to optimise the treatment of the remission phase by comparing the efficacy of AZA (standard treatment) with the new drug MMF in preventing relapse. Preliminary data indicate that relapse rates are lower with MMF compared to AZA, whereas long-term toxicity of both drugs seems to be favourable as compared to CYC. Therefore patients will be randomised to receive either treatment with AZA and OCS or “test“ treatment with MMF and OCS. For the induction treatment, daily oral or bolus CYC plus OCS were chosen for all patients because these are the most effective treatments for these disorders, and the major adverse-effects of short-term CYC are mostly reversible.

3. Study design

3.1 Hypothesis

MMF is more effective than azathioprine for the maintenance of remission in AASV patients (50% fewer relapses) and has the same rate of adverse effects.

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

- 1) **A new diagnosis of WG, MPA or renal-limited vasculitis (RLV)** (appendix 5). Patients may be entered within one month after start of therapy if treated according to protocol ¹
- 2) **ANCA positivity** (appendix 5). ANCA positivity requires PR3-ANCA or a typical cANCA pattern by indirect immunofluorescence (IIF), preferably confirmed by anti-PR3 ELISA. MPO-ANCA determined by ELISA requires demonstration of pANCA, and pANCA by IIF requires confirmation by anti-MPO ELISA ². Optionally, central review of ANCA serology can be performed.
- 3) **Age 18 to 75 years**

Notes:

- 1 Histological confirmation of the diagnosis should be sought
- 2 If indirect immunofluorescence is not available locally, MPO-ANCA must be confirmed as pANCA in a reference laboratory. If MPO ELISA is not available locally, pANCA must be confirmed as MPO ANCA in a reference laboratory.

3.3. Exclusion criteria

- 1) Any cytotoxic drug within previous year, unless started within one month of entry
- 2) Co-existence of another multi-system autoimmune disease, e.g. SLE
- 3) Replicating hepatitis B and C, known HIV positivity (HIV testing will not be a requirement for this trial)
- 4) Active tuberculosis
- 5) Failure to achieve remission by six months
- 6) Failure to control progressive disease with induction protocol
- 7) Previous malignancy (usually exclude unless agreed with trial co-ordinator)
- 8) Pregnancy or inadequate contraception
- 9) Age below 18 and above 75 years*
- 10) Endstage renal failure unless active extrarenal disease requires treatment (temporal dependency of hemodialysis is not an exclusion criterion)
- 11) Inability for informed consent*

* After discussion with the trial administrator, patients less than 18 years may be incorporated on separate application to the appropriate local ethic committee.

3.4. Interventions

3.4.1. Drug regimens

- 1) All patients will receive an induction regimen of OCS (optionally bolus of 1g/d on first 3 days), optionally plasmapheresis, and daily oral or bolus CYC for 3 months (see also A.3.1.).
- 2) Following achievement of remission, patients will be randomised at three months to receive either the standard (OCS+AZA) or test (OCS+MMF) regimens.
- 3) Patients not in remission at three months may be entered when remission is achieved if this occurs before six months.

3.4.2. Evaluations (see also A.4.)

- 1) Study assessments will be performed at 0,1½,3,6,9,12,18,24,30,36,42, and 48 months and at the time of relapse.
- 3) Birmingham Vasculitis Activity Score (BVAS) will be done at 0,1½,3,6,9,12,18,24,30,36,42, and 48 months and at relapse. Short form-36 patient functional questionnaire (SF-36) and the Vasculitis Damage Index (VDI) will be done at 0 months, at the beginning of remission treatment, at months 12,24,36, at relapse and at study end. Disease Extension Index (DEI) (6) will be computed from the BVAS (5).
- 4) Optionally, blood will be drawn at 0,1½,3,6,9,12,18,24,30,36,42, and 48 months and at relapse for central ANCA testing (the clinical value of ANCA levels is an associated aim of this study).

3.5. End-points

- 1) The primary end-point is disease free period. The disease free period is the period from commencement of MMF or AZA until first relapse (major or minor relapse; definition: A.5.5.) or study end.
- 2) Secondary end-points are:
 - i. relapse rate
 - ii. intolerance of study medications and adverse effect rates
 - iii. cumulative exposure to OCS, MMF and AZA
 - iv. cumulative Birmingham vasculitis activity score (BVAS), vasculitis damage index (VDI) and Shortform 36 (SF 36) rates
 - v. cumulative ANCA and CRP levels
 - vi. change in renal function as measured by rate of change of reciprocal creatinine plots from remission to study end.
 - vii. Cost effectiveness (optional, see 7.).

3.6. Adverse-effects

3.6.1. Adverse effects reporting

- 1) The presence of the common adverse effects will be actively sought and will be recorded on standardised forms in the patient record-book.
- 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 co-ordinator.

3.6.2. Intolerance of trial therapies

This includes persistent leucopenia (total WBC < 4 x 10⁹/l for a period of 4 weeks, or recurring at a dose of 50mg CYC/AZA or 1g MMF.) or refractory CMV infection under therapy with MMF.

If AZA is definitely not tolerated, the patient is allowed to be switched to MMF (2g/d) and shall be further observed within the study. Patients intolerant of MMF can be switched to AZA (dose as specified above) and shall be observed within the study. However, their further follow up will be analysed separately from the other patients of their group.

3.7. Withdrawal

- 1) Patient or patient physician's request without explanation. Where possible, reason for withdrawal to be noted in the Patient Record Book.
- 2) Patients not achieving remission within a prolonged induction phase of 6 months are considered as failures and will be withdrawn from the trial. Their further treatment will follow local practice.
- 3) Patients who develop end stage renal failure will be withdrawn from the trial unless extrarenal disease necessitates further immunosuppressive treatment.
- 4) Changes to the treatment regimen dictated by physician and patient choice (drug intolerance, relapse etc.) shall not result in withdrawal from the trial but should be recorded in the Patient Record Book.

4. Statistical analysis

- 1) Patients will be stratified at entry by diagnosis (WG vs. MPA/RLV) and by induction therapy (daily oral CYC vs. bolus CYC).
- 2) The combined outcome measure of the remission rate and the early relapse rate, deemed the "disease free period", (DFP), will be used. DFP is taken from time of remission to the time of relapse. Based on the preliminary data from the CYCAZAREM trial, we assume for AZA a relapse rate of 20% of the WG patients in 15 months (= 0.16 relapses per patient per year). For the MPA patients, we assume a relapse rate of 8% in 15 months (= 0.05 relapses per patient per year).

Under the hypothesis that MMF halves the relapse rate as compared to AZA by 50% in both WG and MPA, we expect 0.26 relapses per patient to occur under MMF in WG and 0.081 relapses per patient in MPA within the 39 months of the remission phase of the study. Under AZA, we expect to observe 0.52 relapses per patient in WG and 0.163 relapses in the MPA group. An interim analysis will be performed after 24 months. With a significance level of 0.05, a power of 0.8 and a one-sided design, 160 patients are needed (assuming a loss of patients of 10 %).

- 3) An interim analysis will be performed when all patients have been included and 50% of the patients have been observed for 2 years.

5. Ethical Considerations

- 1) IMPROVE aims to reduce relapse rate in AASV through the use of MMF for the maintenance of remission. The control limb will be treated with standard maintenance regimen designed by consensus based on the results of a previous randomised trial (CYCAZAREM).
- 2) Ethical approval will be sought by local ethic committee in Mannheim. The approval will be circulated among all study centers to obtain local ethical approval.
- 3) Patients will only be entered after they have given written, informed consent.
- 4) Details of patients identities will be restricted to the local investigator.
- 5) Data will be coded prior to computer entry. Study databases will be independent from computer networks. Confidentiality of patient data will be respected.
- 6) Participation in this study should not require additional tests or clinic attendances above normal practice, apart from the (optional) drawing of 10 ml of blood (at 0,1½,3,6,9,12,15,18,24,30,36,42,48 months and at relapse) and completion of SF 36 questionnaire (at entry, start of remission treatment, relapse and at study end).

6. Trial administration

Co-ordination by Prof. F.J. an der Woude and Wilhelm Schmitt in Mannheim in co-operation with an international steering committee. The trial co-ordinators are available to give advice on patient management and drug administration. Trial administration in conjunction with the AVERT trial administration office (TAO). The TAO will register and randomise patients and dispatch a patient record book. Clinical Trials Assistant (CTA) to be appointed depending on the funding of the trial.

6.1. Trial administration office (TAO)

- 1) Patient registration forms (P.4) will be faxed to the TAO.
- 2) TAO will register and randomise patients and dispatch a Patient Record Book.
- 3) Patient activity will be monitored by 3-monthly data returns from study-centers.
- 4) Trial data will be entered by the TAO into the central data base.
- 5) The TAO will submit threemonthly reports on trial progress to the trial management subcommittee.

- 3) Participating centres will be visited by the CTA at least once during the trial.
- 4) Records of patient registration will be maintained both locally and centrally.

6.2. Data collection

- 1) Patient Record Book (PRB): BVAS, VDI and SF-36, laboratory variables, and adverse effects by entry into the PRB. Three monthly postal returns of data.
- 2) For the purpose of central ANCA testing, serum samples collected optionally will be shipped to a central serumbank: 10 ml of sera to be taken at entry, at 1½,3,6,9,12, 15,18,24,30,36,42, and 48 months and at relapse. Sera will be batched and shipped frozen to the serumbank.

6.3. Independent international review board

- 1) An Independent Review Board is appointed (Prof. Cameron (London, UK), Prof. Donker (Amsterdam, The Netherlands), and Prof. Koch (Hannover, Germany).
- 2) Annual reports will be submitted by the trial co-ordinators to the Independent Review Board 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 identifications of unexpected variations in therapeutic response between limbs.

6.4. Finances

- 1) Financial support will be sought locally, for example by ROCHE's national branches (concerning the costs of MMF) or by other sources.
- 2) The administrative costs will be covered by the co-ordinators.
- 3) There will be no contribution by other medical costs which should not be influenced by participation into the trial.

6.5. Trial duration

- 1) 75 months totally: 48 months (up to 51 months) per patient; 24 months for recruitment. Trial launch in Spring 2002.

7. Drug Dosis Calculator

A computer program integrated into MS word is available that provides all the doses of the medications depending on the weight, age, and renal function of a patient, and the dates when the doses have to be reduced during the trial. For further information, please contact Wilhelm Schmitt (address at the end of the protocol).

Appendix 1. Background

A.1.1. The diseases

Following the widespread introduction of ANCA testing, the primary systemic vasculitides Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) appear to be more frequent than was previously thought (1). Their annual incidence exceeds 20 per million per year (2), and they are the most common cause of rapidly progressive glomerulonephritis. Also, the existence of early and organ-limited forms of these diseases, such as renal-limited vasculitis (RLV), is clearly recognised (1). These entities are frequently associated with ANCA, and are therefore categorised as ANCA-associated systemic vasculitides (AASV) (1). cANCA directed against proteinase 3 (PR3-ANCA) are mainly associated with Wegener's granulomatosis. pANCA reactive with myeloperoxidase (MPO-ANCA) are more often found in cases of MPA. Although these diseases share many features concerning histology, serology as well as responsiveness to treatment, preliminary data from multinational trials such as the CYCAZAREM study indicate that WG is associated with an increased risk of relapse compared to MPA.

A.1.2. Their treatment

Untreated generalised WG and MPA follow a progressive course with 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% (16-18). Although unsupported by controlled study, the combination of oral corticosteroids (OCS) and cyclophosphamide (CYC) has become established as standard therapy for WG, MPA, and RLV, and is effective at controlling disease progression in up to 90% of patients (4,7,8). Alternatively, intermittent pulses of CYC instead of the oral daily administration have been employed (9-10). Furthermore, the use of plasmapheresis during the first days of induction treatment may be of benefit in severely ill cases.

To prevent relapses of AASV, immunosuppressive drugs are usually maintained together with gradually tapered doses of OCS for at least 12 months after induction of remission. Nevertheless, in WG and MPA relapses occur in up to 45% within the first 4-5 years (11). Also, CYC is associated with a high toxicity (11-14,16). This dilemma has stimulated the current search for less toxic drugs. Besides a favourable side-effect profile, such drugs need to have sufficient immunosuppressive potency to maintain remission of AASV. For the maintenance of remission, azathioprine has recently been shown to be as effective as CYC when started three months after the beginning of induction therapy with CYC and OCS (CYCAZAREM trial). Nevertheless, especially in WG patients relapse rates in both groups remained unacceptably high at about 20% in 15 months.

A.1.3. Mycophenolate mofetil as an alternative for maintenance therapy

Mycophenolate Mofetil (MMF) appears to be an excellent candidate for maintenance therapy of AASV because it has a strong immunosuppressive potency combined with a rather low toxicity (17-19). For prophylaxis of renal allograft rejection it is clearly superior over AZA (18,20).

Encouraged by preliminary experience with MMF in 4 AASV-patients (20), 11 patients with severe generalised disease (9 WG, 2 MPA) were entered into a pilot-study for the maintenance of remission after a standard induction therapy with oral CYC and OCS: During a 15 months course of MMF (2g/d) and low dose OCS only one of 11 patients (WG) relapsed in the 14th month of maintenance therapy. Drug-related adverse effects were transient and did include abdominal pain, respiratory infection, diarrhoea, leucopenia and a CMV-colitis (21). Long-term treatment with MMF in these diseases is attractive because of its putative low-toxicity. Of course, long-term experience in a high number of patients treated with MMF is still not available and it may be argued that a carcinogenic potential may only reveal itself after years. The overall frequency of malignancies in the transplant studies in which MMF was combined with other immunosuppressive drugs was as low as 1% (22-24). In patients treated for rheumatoid arthritis no malignancies occurred (25). Important data on long-term safety come from the experience in psoriasis patients with mycophenolic acid, the active compound of MMF, in the 70s. The safety data of 85 patients who were treated with mycophenolic acid for up to 13 years in comparatively high dosage showed no increased malignancy rate (26-27). Therefore the role of MMF will have to be clarified further and compared to AZA maintenance therapy in randomised trials.

Appendix 2. Study medications

A.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 (28). Bioavailability after oral administration is greater than 75%, but there are large variations between individuals in the rate of production of active metabolites. 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 (12). Other adverse effects include nausea, vomiting, myelosuppression with neutropenia, infections, 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.

A.2.2. Azathioprine (AZA)

After hepatic conversion to 6-mercaptopurine, the cytotoxic effects of AZA are mediated by the impairment of purine synthesis, incorporation of purines into DNA, and impairment of the endonuclease repair activity of DNA polymerase (28). 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. Furthermore, there is a dose-dependent increase in skin cancers and lymphomas following administration for more than two years after organ transplantation.

A.2.3. Mycophenolate mofetil (MMF)

Mycophenolic acid, the active metabolite of the pro-drug MMF reversibly inhibits inosine monophosphate-dehydrogenase (IMDH), a key-enzyme of „de novo“ purine synthesis (16,17). Lymphocytic proliferation and function relies almost exclusively on „de novo“ purine-synthesis, whereas most other cells can also use the salvage pathway. MMF is a potent immunosuppressive drug for prophylaxis and treatment of renal transplant rejection in combination with OCS and Cyclosporine A (22-24). For prophylaxis of renal allograft rejection it is clearly superior over AZA (22,24). The most common side effects, gastrointestinal pain and diarrhoea, are probably due to the metabolite mycophenolic acid glucuronide, which accumulates in renal failure (25). Therefore, dose reduction is recommended in patients with a creatinine clearance below 25 ml/min. Other major side-effects include leucopenia and more tissue-invasive and prolonged post-transplant

cytomegalovirus infections. MMF was predicted to cause no mutagenicity or carcinogenicity because it does not interfere with DNA-replication and this prediction has so far not been refuted by clinical experience.

A.2.4. 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 re-distribution, striae and growth retardation in children may occur (28). Of note in SV, has been the correlation of the cumulative OCS dosage with the total incidence of adverse-effects, and particularly with infections.

Appendix 3. Drug regimens

A.3.1 Induction treatment - both groups

Free choice (stratified) for oral daily administration of CYC or CYC pulse treatment.

time from entry (weeks) ¹	Prednisolone (mg/kg/day)	plus either	Cyclophosphamide (oral) (mg/kg/day) ²	or	Cyclophosphamide (pulse) (mg/kg) ²	Puls no.
0	1		2		15 i.v.	1
1	0.75		2			
2	0.5		2		15 i.v.	2
4	0.4		2		15 i.v.	3
7	0.3		2		15 i.v. or 3x5 p.o. ³	4
10	0.28		2		15 i.v. or 3x5 p.o. ³	5
13 ⁴	0.25		2		15 i.v. or 3x5 p.o. ³	6

Notes:

1. Optionally, prednisolone may be administered as a bolus of up to 1g/d i.v. on 3 consecutive days during the first two weeks of treatment. Plasma exchange may be performed in severely ill patients during the first 2 weeks of induction treatment according to local practice.
2. Please note dose reduction for cyclophosphamide for age > 60 years and impaired renal function.
3. The first 3 pulses are given at intervals of 2 weeks and must be given i.v.. If it is decided to give the subsequent pulses orally, which is recommended, the dose of CYC should be divided over 3 days giving 5 mg/kg each day. If it is decided to give the subsequent pulses i.v., the entire dose of CYC (15 mg/kg) can be given on one day.
4. If remission is not achieved by 3 months, continue 2mg/kg/day of oral daily cyclophosphamide or 3 weekly pulses until remission is achieved (maximum: 3 further months = 6 months in total). Consider changing from pulse to daily cyclophosphamide if remission is not achieved within first 3 months.

A.3.2. Failure to achieve remission by 6 months

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

A.3.3. Remission treatment : OCS+MMF * randomised against OCS + AZA¹

Time from entry (months)	Action	Prednisolone (Pred) (mg/day)	Plus Either	Mycophenolate mofetil (MMF) (g/day)	or	Azathioprine (AZA) (mg/kg/day)
3	Reduce Pred, start MMF/AZA	15		2		2
4	Reduce Pred	12.5		2		2
5	Reduce Pred	10		2		2
6	Reduce Pred,	7.5		2		2
12	Reduce Pred and MMF/AZA	5		1.5 ²		1.5 ²
18	Reduce Pred and MMF/AZA	2.5		1 ²		1 ²
24	Stop Pred	0		1		1
42	Stop MMF/AZA	0		0		0
48 ³	Study end	0		0		0

Notes:

- 1 optionally, the drop of medication may be delayed independently of the clinical status if ANCA titer rises (definition: see A.3.4.8.)
- 2 prolonged induction treatment (up to 6 months) results in prolonged remission treatment (up to 27 months)
- 3 in case of prolonged induction treatment (up to 6 months instead of 3 months), the observation time will extend up to 51 months

A.3.4. Notes for drug regimens

A.3.4.1. Daily oral cyclophosphamide

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%, > 70 years by 50%.
4. Administer dose in the morning and maintain good hydration.
5. Check full blood count (FBC):
 - a) weekly for first month.
 - b) two-weekly for second and third month.
 - c) monthly thereafter.
6. Extra caution in the presence of renal failure (dose reduction by 20% is recommended if creatinine clearance < 25 ml/min).
7. Mesna is optional. The dose is the same as the cyclophosphamide dose, either from the I.V. vial orally or in form of tablets.

A.3.4.2. Pulsed cyclophosphamide

Pulsed CYC dose reductions for renal function and age		
Age (years)	Creatinine ($\mu\text{mol/l}$)	
	150-300	> 300
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
> 60 and < 70	12.5 „ „ „	10 „ „ „
> 70	10 „ „ „	7.5 „ „ „

1. Reductions for renal function and age according to table above.
2. Maximum CYC pulse is 1.2g.
3. Dissolve cyclophosphamide in water for injection, then dilute in saline 0.9% 500 ml and administer as i.v. drip over one hour.
4. Mesna is optional and will be administered orally in the same dose in mg as CYC in mg either from i.v. vials or in the form of tablets on days when CYC is administered. (If it has to be administered i.v., reduce mesna dose to 60% of the CYC dose).
5. Prevention of emesis: the choice of antiemetic drugs to cover the CYC pulses should follow local practice. Ondansetron is suitable for this indication.
6. Check FBC on day of pulse or previous day. If WBC prior to pulse < $4 \times 10^9/\text{L}$, then postpone pulse until WBC > $4 \times 10^9/\text{L}$, while checking WBC at least weekly. Reduce dose of pulse by 25%. With any further episodes of leucopenia, make equivalent dose reduction .
7. Check FBC between days 10 and 14 after a pulse. If the leucocyte nadir (i.e. the lowest leucocyte count between two CYC pulses) is < $3 \times 10^9/\text{L}$, even if the WBC just previous to the next pulse is > $4 \times 10^9/\text{L}$, then reduce the dose of the next pulse by:
 - a) leucocyte nadir 1 - $2 \times 10^9/\text{L}$ reduce CYC dose of last pulse by 40 % of previous dose.
 - b) leucocyte nadir 2 - $3 \times 10^9/\text{L}$ reduce CYC dose of last pulse by 20 % of previous dose.

A.3.4.3. 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%
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.
5. discuss withdrawal of AZA for adverse effects with co-ordinator

A.3.4.4. Mycophenolate mofetil (MMF)

1. maximum dose is 2g/day. Optionally, treatment can be started with 1g/d and increased to 1.5 g/d after one week with a further increase to 2 g/d after another week (introduction slowly reduces incidence of GI side effects and improves tolerance).
2. check full blood count (FBC):
 - weekly for first month
 - two-weekly for second month
 - monthly for first year
3. Age > 60 years, reduce dose by 25%
4. if 2g/d is not tolerated due to GI problems, reduce to 1g/d and increase to 1.5g/d after 4 weeks and to 2 g after a further 4 weeks. If this is not tolerated continue with 1g/d.
5. if creatinine clearance below 25 ml/min, dose reduction to 1 g/d is recommended. If renal function is reduced, always consider dose reduction in case of side effects.
6. Infections: mild bacterial or viral infections: continue MMF and treat with antibiotics or antiviral drugs. Severe infections: interrupt MMF and treat infection. When infection is controlled, resume MMF in a dose reduced to a maximum of 1.5 g/d.
7. Determination of free mycophenolic acid (MPA) is recommended, especially in cases of reduced renal function and infections. MPA determination (plasma sample) should be performed during the first week and at 3 month under MMF. Central MPA determination in Göttingen, Germany is recommended (see P5).
8. discuss withdrawal of MMF for adverse effects with co-ordinator

A.3.4.5. Leucopenia

1. Stop CYC/AZA/MMF if white blood cells (WBC) < 4 x 10⁶/L. Restart with CYC/AZA dose reduced by at least 25mg and MMF dose reduced by at least 500 mg when WBC > 4 x 10⁶/L. Monitor weekly for one month.
2. If severe (<1 x 10⁶/L or prolonged (< 4 x 10⁶ /L for > 2 weeks), restart CYC/AZA at 50mg/day or MMF at 1g/day, increasing to target dose as weekly WBC permits. Consider: pneumocystis carinii prophylaxis, fungal prophylaxis and in the case of MMF monitoring of pp65 for active CMV infection
3. For falling WBC (< 6 x10⁶/L and fall of > 2 x 10⁶/L over previous count), re-check in one week and reduce dose by 25mg or MMF 500 mg if further fall of > 0.5x10⁶/L

A.3.4.6. Prednisolone

1. maximum dose in first week is 80 mg/day (optionally bolus of 1g/d i.v. on first 3 days)
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 ± 12.5% from the protocol will be allowable in the first 12 weeks and ± 25% thereafter (larger variations from regimens should be discussed with trial co-ordinator)
7. minimum dose in first three months is 10 mg/day

A.3.4.7. 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 carinii (suggested only during induction phase):
sulfamethoxazole/trimethoprim (S/T) 480mg three times a week or monthly aerosolised pentamidine during induction phase. Prophylaxis is to be avoided during maintenance phase, as use of S/T may have an impact on relapse rate and may cause a bias.
4. hemorrhagic cystitis (suggested only):
oral mesna during cyclophosphamide therapy in the same dose as clophosphamide
5. osteoporosis (suggested only):
oral calcium and vitamin D, biphosponate recommended in high risk groups.

A.3.4.8. Changes in drug regimes in case of rising ANCA titer

Some centers regard it to be unethical to reduce immunosuppressive drugs in case of a rising ANCA titer because imminent relapse is suspected. Therefore, an option to postpone dose reduction under these conditions is included in the protocol.

Definition of rise in ANCA titer:

1. a rise in ANCA titer is defined as a) a conversion from negative to positive (any positive value for indirect fluorescence titers)
2. a rise in indirect fluorescence titers by at least 3 titer points (example: from 1:16 to 1:128 or higher)
3. a rise in ELISA readings (PR3-ELISA for cANCA, MPO-ELISA for pANCA) by at least 50%.

If a rise of the ANCA titer is observed:

- Option to postpone the next step of dose reduction of GC and AZA or MMF suggested by the protocol by four weeks.
- If no relapse occurs and if the ANCA titers does not show a further rise (definition: see above), the dose reduction must then be performed.

A.3.5. Changes to drug regimens for relapse (non-obligatory guidelines)

Major relapse

1. Use CYC at 2mg/kg/day (stop AZA/MMF)
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

Minor relapse

1. Increase AZA to 2mg/kg/day or MMF to maximal 2 g/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

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

Appendix 4. Study Evaluations

Minimum information required for the study. Additional tests to follow local practice.

A.4.1. Entry

1. VITAL Scores¹: (Birmingham Vasculitis Activity Score (BVAS), Vasculitis Damage Index (5), (VDI) (3), Short form 36 score (SF-36) (4).
2. Haematology
 - a) Full blood count (FBC): haemoglobin (Hb), white cell count (WBC), neutrophil, lymphocyte and platelet counts.
 - b) ESR.
3. Biochemistry
 - a) Serum creatinine and GFR (creatinine clearance or isotope study).
 - b) ALT or AST, alkaline phosphatase, albumin, glycated haemoglobin (such as, HbA1c).
 - c) C-reactive protein (CRP).
4. Immunology
 - a) IgG, IgA and IgM levels.
 - b) ANCA (IIF, PR3 and MPO ELISA).
 - c) ANA, anti-GBM-antibodies, rheumatoid factor, cryoglobulin, complement C3, C4).
 - d) Hepatitis BsAg (if positive, check HBeAg), Hepatitis C Antibody, CMV antibodies.
5. Other
 - a) 10 ml serum saved (optional).
 - b) Urine microscopy for red cells and red cell casts.
 - c) Chest and sinus x-ray.

A.4.2. 1½, 3,6,9,12,18,24,30,36,42, and at study end at 48 months or at relapse

1. BVAS score (VDI and SF36 to be performed only at entry, at beginning of remission treatment, at months 12,24,36 and at study end or at relapse).
2. FBC: Hb, WBC, neutrophil, lymphocyte and platelet counts.
3. ESR, CRP, ANCA.
4. creatinine (24 hour protein if proteinuria present), GFR measured by creatinine clearance or isotope study at 12,24,36, 48 months and at relapse.
5. dipstick urinalysis and urine microscopy for red cell count and red cell casts ²
6. 10 ml serum saved (optional)

Note:

1. VITAL is a composite of the Birmingham Vasculitis Activity Score (BVAS), the Vasculitis Damage Index (VDI) (3), the Short-Form-36 (SF-36) functional assessment score (4). 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 (6).
2. If there is occurrence of new macroscopic haematuria, a cystoscopy should be performed. Consider cystoscopy for new microscopic haematuria. If haemorrhagic cystitis is confirmed, 6-monthly surveillance cystoscopies should be performed.

A.5. Disease Definitions

A.5.1. 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 (specificity for proteinase 3 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 not attributable to another cause, supported by characteristic histology on biopsy and/or detectable cANCA by IIF, or PR3-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 leukocytes 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.

A.5.2. Microscopic polyangiitis

MPA 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). MPA is mostly associated with MPO-ANCA, less often with PR3-ANCA; a minority of MPA patients are ANCA negative or recognise other ANCA autoantigens. For the purposes of this study, PR3-/cANCA positive patients may be entered in the category of MPA if they have a chronic inflammatory process with nongranulomatous vasculitis of small vessels (i.e. capillaries, venules, arterioles or small arteries).

A.5.3. Renal-limited vasculitis

Isolated pauci-immune necrotizing, 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 MPA, including the presence of circulating anti-MPO or anti-PR3 antibodies.

A.5.4. Remission

Full clinical remission is indicated by complete absence of clinical disease activity using the BVAS item list. Partial remission is defined as partial improvement or – in the case of smoldering disease – an unchanged status within the last weeks (6). Absence of renal disease activity: stable or falling creatinine / microhematuria and the absence of red cell casts. Absence of pulmonary disease activity: Resolution of pulmonary opacities; reduction in size of existing lesions unless attributable to scarring; no new lesions. Diagnosis of complete remission is supported by a normal C-reactive protein. ANCA is ignored for the purpose of this study.

A.5.5. 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 (15):
 - 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 the following, if they are attributable to active vasculitis (15):
 - 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.

Note:

A rising ANCA may signify relapse. Such patients should be watched more closely. Concerning the option to postpone dose reduction of immunosuppressive drugs in case of a rising ANCA titer see A.3.4.8.

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P.1. IMPROVE - Summary of Practical Procedures

Potentially suitable ?

- Newly diagnosed or untreated patient with active WG, MPA or RLV, age > 18 a, < 75 a
 - ANCA positive (cANCA, PR3ANCA, or pANCA positive for MPO)
 - informed consent given
 - patient may be entered within one month after start of therapy if treated according to protocol
-

Ready to enter ?

- fax or e-mail registration form to trial office for randomisation (P.4.)
 - score BVAS, VDI and SF-36 and baseline laboratory data
-

Entry

- your patient will be registered and randomised to one of two limbs :-
 - azathioprine (AZA) or mycophenolate mofetil (MMF) for the maintenance of remission
 - commence induction treatment (OCS and CYC [oral daily or bolus] according to protocol:
 - continuous oral (2mg/kg/day) or pulse (15mg/kg initially IV every 2 weeks)
 - OCS 1mg/kg/day (or bolus of 1g/d for the first 3 days)
 - option to use plasmapheresis in severely ill patients during the first two weeks of induction treatment according to local practice
-

Remission induction phase (minimum 3, maximum 6 months)

- at 1 ½ and 3 months score BVAS, VDI, SF-36, laboratory data, and nasal swab
 - continue CYC until 3 [and up to 6] months until remission achieved
 - if no remission by 6 months: withdraw from trial drug regimen and follow local practice
-

Remission maintenance phase (3 [up to 6] to 48 [up to 51] months)

- starts 3 months after remission achieved, latest 6 months from entry
 - patient to be **randomised to either AZA or MMF**
 - stop CYC
 - start AZA or MMF according to randomisation
 - taper prednisolone and AZA or MMF according to regimen
 - stop prednisolone at 24 months
 - stop AZA or MMF at 42 months
 - at months 6,9,12,15,18,21,24,27,30, 33,36,39,42 and 45 months and at the time of relapse: BVAS and laboratory data
 - VDI and SF-36 at entry, beginning of remission treatment, relapse or study end
-

End of the study (48 [up to 51] months)

- complete termination record; data to trial database

P.2. Clinical trial: Patient Information Sheet

(This may be modified to meet local requirements)

International Mycophenolate mofetil Protocol to reduce outbreaks of vasculitides (IMPROVE)

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 which control the disease but which must be continued to prevent the disease coming back. These drugs frequently cause side-effects which can be serious. After about three months of treatment, several hospitals now change the cyclophosphamide to an alternative drugs, two of them being mycophenolate mofetil and azathioprine. However, it is unclear which of these drugs is more effective in your condition, and which is safer. A direct comparison has never been performed.

This study will compare mycophenolate mofetil with azathioprine for 39 months, in decreasing doses; After that, your course will be followed within the study for a total of 48 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 at 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 will be taken at your visits, but this will not need an extra needle puncture. All patients will be given a combination of steroid and cyclophosphamide for the first three (to six) months to control the disease, and then will be selected to receive either mycophenolate mofetil or azathioprine tablets, on a random basis. Additionally, all patients will be given the same low dose steroids, which will be further decreased with time.

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. 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 twenty patients. It is essential that women of child-bearing age use efficient contraception to prevent pregnancy during the study.

The most important side effects of azathioprine are lowering of the blood count, increased susceptibility to infection, allergy, and elevation of liver enzymes. The most important side effects of mycophenolat mofetil are lowering of the blood count, increased susceptibility to infection, nausea, and diarrhoea.

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. 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. Tel.:

P.3. Consent form

(This form may be replaced to meet local requirements)

International Mycophenolate Mofetil Protocol to reduce outbreaks of vasculitides (IMPROVE)

The details of this study have been explained to me by

Dr.

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.)

Copy, complete and fax this form to register patients for entry into IMPROVE.
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"/>

Patient details

Date of entry	dd/mm/yy	<input type="text"/>
Date of birth	dd/mm/yy	<input type="text"/>
Date of first treatment	dd/mm/yy	<input type="text"/>
Sex	M/F	<input type="text"/>
Induction treatment:		
Cyclophosphamide:	Bolus/daily	<input type="text"/>
Diagnosis:	WG or MPA/RLV	<input type="text"/>

Please **Fax** this form to:

(44) (0)1223

Or **e-mail** to:

dj106@cam.ac.uk

Trial Administration Office:
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P.5.

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