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EFFICACY OF METHOTREXATE VERSUS CYCLOPHOSPHAMIDE IN THE TREATMENT OF "NON-RENAL" WEGENER'S GRANULOMATOSIS

Short title:

NORAM (NON-Renal Wegener's granulomatosis treated Alternatively with Methotrexate)

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Summary

Wegener's granulomatosis (WG) and microscopic polyangiitis (MP) are primary systemic vasculitides predominantly affecting small blood vessels. Their standard treatment with corticosteroids (CS) and cyclophosphamide (CYC) is usually effective at controlling active disease but continued treatment is necessary to prevent disease relapse. Due to the cumulative toxicity associated with CYC treatment, alternatives have been looked for. Methotrexate (MTX) has been used for more than 20 years in the treatment of rheumatic diseases with less toxicity than CYC and has recently been shown to have a favourable effect in WG. The present multicenter, randomised trial will examine whether substitution of oral CYC with oral MTX is equally efficient for induction and maintenance of remission with less adverse effects in 92 early cases of WG or MP with signs of systemic disease but without overt renal involvement. All patients will receive the same regimen of oral CS. All treatment will be tapered to a stop after 1 year unless there is grumbling or persistent disease. The trial ends after 18 months.

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 vasculitides (SV). This was itself a development from an existing EC/BCR study group concerned with the design and standardisation of solid phase assays for determination of anti-neutrophil cytoplasmic antibodies (ANCA, autoantibodies prevalent in systemic vasculitides) brought together in 1991. The aims of the ECSYSVASTRIAL study group include the design and standardisation of disease scoring and data collection methodology, the design and facilitation of therapeutic trials and the harmonisation and improvement of the treatment of these disorders within the EC.

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

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

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

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

The first 5 protocols form a continuum with partially shared treatment arms and inclusion and exclusion criteria covering the entire spectrum of WG and MP. Protocols 1-3 include three subsidiary protocols: SAVAS, RELANCA and VITAL. SAVAS looks at the role of nasal carriage of *Staph. aureus*, RELANCA at the relation between disease relapse and ANCA levels, while scoring of disease activity and extent, morbidity and function will be assessed using the VITAL protocol.

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

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

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1. Background

1.1. The diseases

With the introduction of c-ANCA (classical anti-neutrophil cytoplasm antibodies) (1) as a diagnostic tool for Wegener's granulomatosis (WG) (2) (see disease definitions in Appx. 6.5) it has been reported that the diagnosis is made up to 5 times more frequently than before (3). A number of these cases will be early cases with symptoms of systemic disease but still with normal kidney function and not yet with life threatening symptoms. Such cases will here be referred to as "non-renal" Wegener's granulomatosis (NRWG). In these early cases without renal involvement it may be difficult to differentiate between microscopic polyangiitis (MP) (2) (see disease definitions in Appx. 6.5) and WG. In cases without symptoms from the upper respiratory tract a diagnosis of MP may well be correct. In order to reach patients as early in the course of systemic disease as possible such cases will be included in the present study.

1.2. Treatment of "non-renal" Wegener's granulomatosis (NRWG)

Untreated, systemic WG and MP follow a progressive course with a fatal outcome due to vital organ failure but with the empirical introduction of corticosteroids and cytotoxic agents, five year survival increased from under 20 to over 60% (4,5). The combination of oral corticosteroids (OCS) and cyclophosphamide (CYC) developed by the National Institutes of Health (NIH), has become established as standard therapy for WG and MP, and is effective at controlling disease progression in up to 90% of patients (6,7). However, patients have a high cumulative exposure to drugs with a narrow therapeutic index and treatment-related morbidity and mortality rivals that caused by the underlying disease (6,8-11). The NIH regimen uses OCS and CYC for remission induction and then maintains CYC for a further 12 months while tapering OCS, following which time CYC is slowly tapered. More recently, attempts to reduce CYC-associated toxicity have tapered CYC once remission is reached or used pulsed intravenous CYC for the maintenance of remission (5,12-14). Due to the adverse effects of CYC, other treatment modalities have been looked for. Azathioprine has been used in the treatment of WG and MP for almost 30 years; it is less effective than CYC for the control of active disease, but several groups have found AZA to be of value in place of CYC during remission with relapse rates in follow-up studies being comparable to CYC (7,15,16.). Of other alternative remission agents to CYC such as methotrexate (MTX), chlorambucil, ciclosporin (17), intravenous immunoglobulin (18) or monoclonal antibodies, there has been less experience than with AZA. Patients with NRWG are presumed to represent either early cases or cases with a less severe disease course. It is therefore tempting to look for less aggressive treatment modalities than the standard treatment. Based on original observations at the Mayo Clinic (19), several groups have been - and are - examining the role of sulfamethoxazole/trimethoprim (S/T) treatment for initial phase WG. As the results of S/T treatment in cases with systemic disease have not been comparable to the effect of the standard treatment so far, this therapeutic possibility is not considered for the present study. Other treatment modalities have not been designed specifically for limited WG or early systemic NRWG.

1.2. Aims of NORAM

In order to create a base-line therapy for NRWG patients it is presupposed that recommendations for the standard OCS/CYC treatment, even with minor frequently used modifications such as a general lowering of OCS dosage and a termination of all treatment after a year, can not be changed until a new and less toxic treatment has proven to be equally effective. Based on the experience reported by Hoffman et. al. (20), that low-dose MTX was effective in cases previously unsuccessfully treated with OCS/CYC, and recent experience by Handrock et al. (21) who obtained maintenance of remission in 14 of 17 WG patients and successful induction of remission in 4 of 6 patients with moderate disease activity and minor organ involvement with low-dose MTX, it is here proposed that a base-line treatment of NRWG should be identified by examining to which extent treatment with MTX may substitute treatment with OCS/CYC in these patients in respect to arresting disease and maintaining the remission. Moreover, the adverse effects will be compared. This would then define the relevant

control treatment arm for future clinical trials of therapy for NRWG and serve as a basis for a harmonised approach to treatment in Europe.

2. Study Medications

2.1. Cyclophosphamide

Cyclophosphamide is an inactive pro-drug, converted by the mixed function oxidase system in the liver to the alkylating agents 4-hydroxy-cyclophosphamide and phosphoramidate mustard which alkylate guanine nucleotides, thus blocking cell division (22). Bioavailability after oral administration is greater than 75%, but there are large variations between individuals in the rate of production of active metabolites. A phenotypic variation in carboxylator activity affects the production of the inactive metabolite carboxyphosphoramide from 4-hydroxy-cyclophosphamide, which may influence efficacy and toxicity. The relation of renal and hepatic failure to the production and elimination of active metabolites has not been fully determined. Bladder toxicity is caused by renal excretion of the metabolite acrolein which can cause haemorrhagic cystitis and a markedly increased risk of bladder cancer (11). Other adverse effects include nausea and vomiting, myelosuppression, 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 lymphomas is increased tenfold; less common adverse-effects include pulmonary fibrosis, hepatitis and the syndrome of inappropriate ADH secretion.

2.2. Prednisolone

Prednisolone is a synthetic derivative of cortisone with widespread influences on metabolism and organ function. Desirable effects in WG and MP 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, avascular necrosis, subcapsular cataracts, skin fragility, myopathy, Cushingoid facies, hirsutism, alopecia, fat re-distribution, striae and growth retardation in children may occur (22). Of note in SV, has been the correlation of the cumulative OCS dosage with the total incidence of adverse-effects, and particularly with infections.

2.3. Methotrexate

Methotrexate (MTX) is a folic acid antagonist (23). The cytotoxic effect is mediated through binding of dihydrofolic acid reductase leading to an inhibition of the reduction of folic acid to tetrahydrofolate, which is essential for the biosynthesis of purine and pyrimidine. MTX easily penetrates to the tissues after oral administration with the highest concentrations obtained in the liver and the kidneys. However, crossing of the blood/brain barrier to the cerebrospinal fluid requires high dose, intravenous administration. Most MTX is excreted unchanged through the urine within 24 hours. Renal disease thus causes accumulation of MTX. In rare cases MTX may form complexes in the kidneys leading to renal damage. The plasma protein binding is about 50%. Thus large amounts of pleural effusions may lead to accumulation and delayed excretion of MTX. Adverse effects include myelosuppression occurring on day 7 - 14 after single dosage, infections due to immunosuppression, stomatitis, gastrointestinal disturbances with nausea, vomiting and diarrhea, pulmonary fibrosis and a reversible liver affection with increase of transaminases. An important pharmacologic interaction is the concurrent action of trimethoprim on folic acid synthesis. Moreover, salicylates, diphenhydantoin, barbiturates, benzodiazepines, tetracyclines, sulfonamides and p-aminobenzoic acid may displace MTX from serum albumin, causing increased free concentrations.

3. Hypothesis

Methotrexate is as effective as cyclophosphamide in inducing and maintaining remission of early, systemic, "Non-Renal" WG (WG with normal kidney function and without life-threatening symptoms or conditions considered to cause imminent permanent loss of organ function) with less adverse effects. As early cases of MP may mimic WG such cases will be included.

4. Study design

4.1. Nature

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

4.2. Rationale

Early, systemic WG and MP are potentially progressive disorders for which the standard treatment is a combination of OCS and CYC. This study will examine whether substitution of CYC with MTX is equally efficient for induction and maintenance of remission in early cases preventing these patients from progression of the disease and development of permanent organ damage.

4.3. Inclusion criteria

- 1) Active WG (or MP) with or without histological confirmation (see appendix 6).
- 2) Involvement of one or more organ systems compatible with WG and/or MP with symptoms of general malaise (two or more of the symptoms: fever, headaches, myalgias, arthralgias, tiredness, weight loss > 2kg/week, anorexia) in combination with ESR > 45 and/or CRP > twice upper normal limit **excluding** the conditions mentioned below.
- 3) Typical c-ANCA pattern by indirect immunofluorescence (IIF) and/or positivity in the PR3 ELISA or positivity in the MPO ELISA with or without p-ANCA (1). ANCA negative cases may be included if a biopsy classified as characteristic or compatible is obtained (see appendix 6).

4.4. Exclusion criteria

- 1) Active renal vasculitis with creatinine >150 micromol/l and/or biopsy proven necrotising GN, > 30 red blood cells per high powered field and/or red cell casts and/or proteinuria of > 2g/24hr).
- 2) The following **conditions considered to be life-threatening or causing imminent permanent organ failure/loss of function:**
 - i. severe haemoptysis associated with bilateral infiltrates. (Slight haemoptysis and/or extensive pulmonary nodules and/or bilateral infiltrates can be **included**).
 - ii. cerebral infarction due to vasculitis.
 - iii. rapidly progressive optic neuropathy or retinal vasculitis or orbital pseudotumour.
 - iv. massive gastro-intestinal bleeding.
 - v. heart failure due to pericarditis or myocarditis.
- 3) Disease only with cutaneous involvement (e.g. leukocytoclastic vasculitis)
- 4) Co-existence of another multi-system autoimmune disease, e.g. SLE, rheumatoid arthritis.
- 5) CYC, MTX or other cytotoxic agent unless started less than a week before.
- 6) OCS for more than one year before entry.
- 7) Concomitant treatment with sulfamethoxazole/trimethoprim.
- 8) Hepatitis B antigenemia with active virus replication (HBe-antigen-pos). Include HBe-ag.-neg. cases.
- 9) Positive anti-HCV antibodies.

- 10) Known HIV positivity (HIV testing will not be a requirement for this trial)
- 11) Bone marrow insufficiency (leucocytes < 3.000/microl, thrombocytes < 100.000/microl).
- 12) Previous malignancy (usually exclude unless agreed with trial coordinator)
- 13) Pregnancy or insufficient contraception.
- 14) Age under 18 or over 75 years.
- 15) Allergy to OCS, CYC or MTX.
- 16) Chronic alcohol abuse.
- 17) Liver disease with increase of transaminases more than 3-fold.
- 18) Folic acid depletion.
- 19) Previous episodes of necrotizing and/or crescentic glomerulonephritis.

4.5. End-points

4.5.1 The primary endpoint is successful induction of remission as defined in 6.6.3 within 6 months.

4.5.2 The secondary endpoints are:

- 1) Major relapses (6.6.4) necessitating a switch to induction OCS/CYC treatment (Appx. 4) or more aggressive treatment (e.g. Methylprednisolone bolus therapy or plasma exchange) in the observation period. Minor relapses (6.6.4) that can effectively be controlled by a transient, non-toxic increase in OCS are not considered an end-point.
- 2) Intolerance to trial medications and adverse effects. Adverse effects will be monitored (see appendix 7).

4.6 Interventions

4.6.1. Drug regimens (Appx. 1 + 2 + 3)

- 1) Patients will be randomized at entry into either receiving the standard OCS/CYC therapy (**CYC group**) or OCS with MTX instead of CYC (**MTX group**)
- 2) Relapse treatment to follow guidelines for relapse regimens (Appx. 4).
- 3) After one year, all medications will be tapered to a full stop unless disease is active or grumbling.
- 4) Sulfomethoxazole/trimethoprim must not be used during the first 12 trial months unless pneumocystis pneumonia is diagnosed (Appx. 3).

4.6.2. Evaluations (Appx. 5)

- 1) History and examination at entry, monthly for first 6 months then then three monthly until 18 months.
- 2) Blood drawn monthly for first year then two monthly.
- 3) WG patients to have nasal swabs monthly for at least 8 months after hospital discharge.
- 4) Scoring of BVAS 1 + 2 and SF-36 (24) and DEI (25) at 0,1,2,3,4,5,6,9,12,15 and 18 months.
- 5) Scoring of VDI (24) every 6 months.

4.7. Withdrawal

- 1) Patient's or patient physician's request.
The reason(s) for withdrawal must be noted in the Patient Record Book.

4.8. Adverse-effects

- 1) All drug-related adverse-effects (see appx. 7) will be recorded in the Patient Record Book and reported to the International Review Board.

- 2) Adverse-effects sufficient to withdraw a medication will be determined locally. Intolerance to CYC or MTX is and end-point of the study and will result in departure from the protocol (appx. 7) without withdrawing the patient from the study.
- 3) The presence or absence of major adverse-effects will be determined and recorded at each evaluation.

4.9. Statistical analysis

4.9.1. Stratification

- 1) Patients will be stratified prior to randomisation according to presence of upper respiratory tract symptoms (presumed to represent WG) and those without (presumed to represent MP).
- 2) Cases with diagnostic uncertainty will be discussed with the trial co-ordinator.

4.9.2. Power

Accepting a difference in efficacy of <10%, with predicted remission rates of 90% after 6 months in both groups requires 92 patients to confirm equivalence in a one tailed design (Randomised clinical trial, SAMPLE.SIZ freeware program) with a power of 0.8 and type 1 error of 0.05. The actual remission rates evaluated half way will serve to calculate the exact patient number needed.

4.10. Ethical Considerations

WG and MP are progressive disorders responsive to treatment, but there is a wide variation in both the choice of drugs and their doses between different centres in the EU. The trial committee has by consensus agreed on an established or standard protocol based on that developed at the NIH in the 1970s using oral corticosteroids (OCS) and cyclophosphamide (CYC) (4). This "standard regimen" will then be compared in a randomised fashion to the use of methotrexate (MTX) which has recently been reported to be efficient in non-life threatening cases for inducing and maintaining remission (20,21). Entry into the study should not require additional tests or clinic attendances above normal practise, apart from the drawing of an additional 10 ml of blood and nasal swabs (Appx. 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.

4.11. International Review Board

An International board consisting of 3 members will be consulted annually to review the incidence and severity of adverse events, the conduct of the study and communication of the study's results.

4.12. Duration

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

4.13. Co-ordination

- 1) NORAM organisers will act as national co-ordinators.
- 2) International and DK co-ordination by Niels Rasmussen, Copenhagen, Denmark.
- 3) Clinical Trials Assistant (CTA) to be appointed.
- 4) Study data will be recorded by the investigator in Patient Record Books.
- 5) Following exit from the study, Patient Record Books will be reviewed by the CTA and local investigator before being sent with the saved sera for central analysis.
- 6) Records of patient registration will be maintained both locally and centrally.

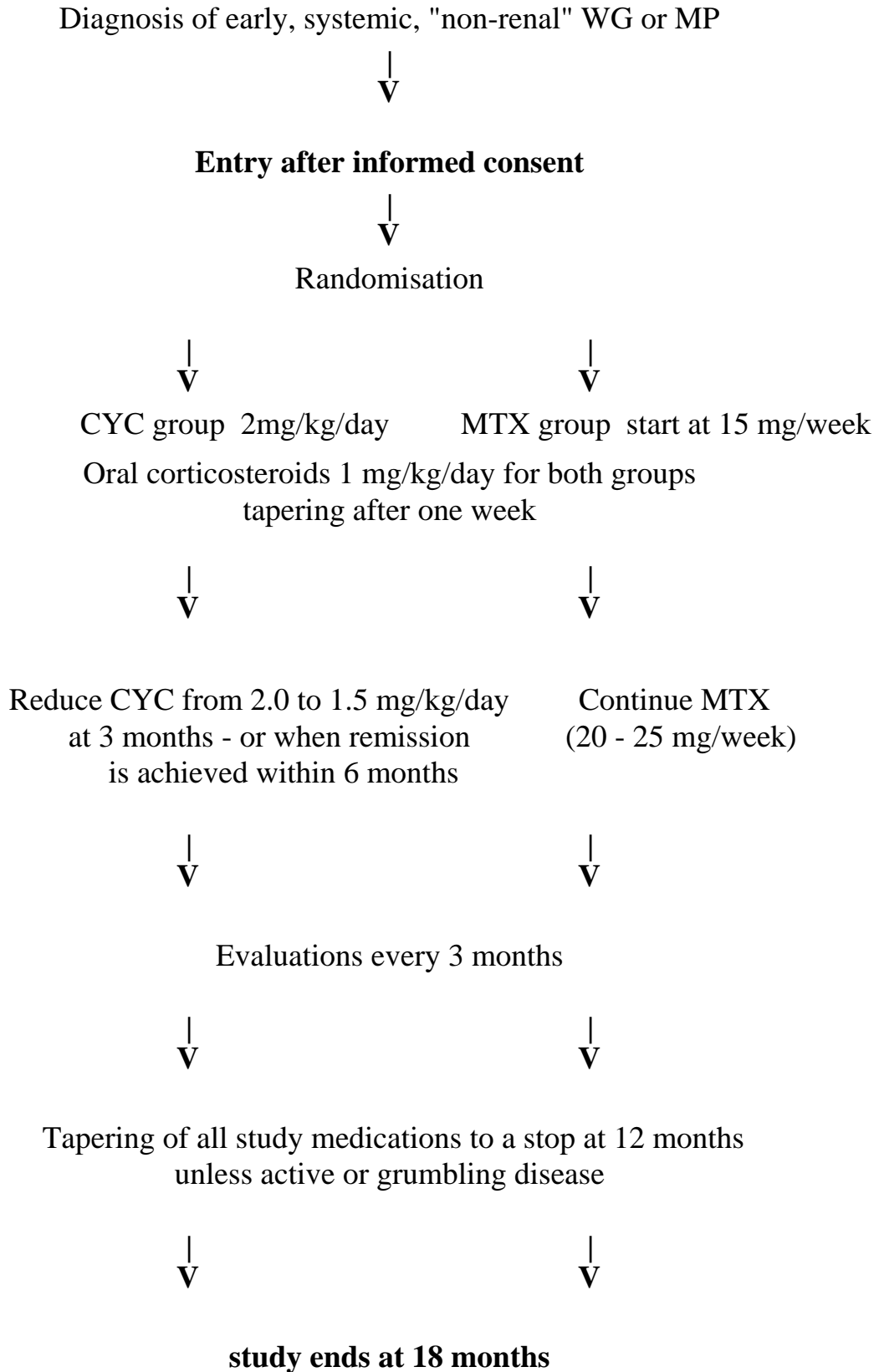
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NORAM

6.1. Appendix 1

Trial Overview



6.2. Appendix 2 Drug Regimens

6.2.1. Induction and remission treatment in CYC group and MTX group

time from entry	prednisolone mg/kg/day	cyclophosphamide mg/kg/day CYC	methotrexate mg/week MTX
0	1 \pm 12.5% *	2	15
1 week	0.75 etc.	2	15
2 weeks	0.5	2	15
4 weeks	0.4	2	17.5
6 weeks	0.33	2	17.5
8 weeks	0.28	2	20
10 weeks	0.25	2	20 - 22.5
12 weeks	0.25 = 15 mg/day	1.5	20 - 25
3 months	for a 60 kg person	1.5	20 - 25
4 months	12.5 mg/day	1.5	20 - 25
5 months	10 etc.	1.5	20 - 25
6 months	7.5	1.5	20 - 25
7 months	7.5	1.5	20 - 25
8 months	5	1.5	20 - 25
9 months	5	1.5	20 - 25
10 months	2.5	1.0	20 - 22.5
10 mths + 1 week	2.5	1.0	20
10 mths + 2 weeks	2.5	1.0	17.5
10 mths + 3 weeks	2.5	1.0	15
10 mths + 4 weeks	2.5	1.0	12.5
10 mths + 5 weeks	2.5	1.0	10
10 mths + 6 weeks	2.5	1.0	7.5
10 mths + 7 weeks	2.5	1.0	5
10 mths + 8 weeks	2.5	1.0	2.5
12 months	0	0	0

* See table on calculated steroid dose in mg/day for different weight groups!

6.3 Appendix 3 Notes for drug regimens

6.3.1. Cyclophosphamide

- 1) Maximum dose is 150 mg daily
- 2) Round dose down to nearest 25mg
- 3) Age > 60 years, reduce dose by 25mg
- 4) Administer dose in the morning and maintain good hydration
- 5) Patients initially intolerant of oral medication may receive 75% of the oral dose by daily injection.
- 6) **Check full blood count (FBC) and WBC differential: weekly for first month two-weekly for second month, monthly for first year**
- 7) Stop CYC if white blood cell count (WBC) < $4 \times 10^9/l$ and restart with dose reduced by at least 25mg/day when WBC > $4 \times 10^9/l$ on 2 consecutive tests or $>5 \times 10^9/l$ on one test.
- 8) If leucopenia is severe (< $1 \times 10^9/l$), or prolonged (< $4 \times 10^9/l$) for > 2 weeks, recommence drug at 50 mg daily and increase to target dose 50 mg less than previous dose as weekly WBC permits. For severe leucopenia, consider fungal and pneumocystis prophylaxis.
- 9) 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 25 mg daily if further fall of $> 0.5 \times 10^9/l$.
- 10) Withdraw CYC for CYC-induced hemorrhagic cystitis. MESNA for bladder protection is not feasible with oral CYC.
- 11) Withdraw CYC for CYC-induced increasing transaminase rise.

6.3.2. Prednisolone

- 1) Maximum dose in first week is 80mg/day
- 2) Round dose to nearest 5 mg above 20 mg/day and to nearest 2.5 mg below 20 mg/day
- 3) The dosage of alternate days may not vary by more than 5 mg
- 4) Patients initially intolerant of oral medication may receive IV hydrocortisone or methylprednisolone in an equivalent dose
- 5) Use either prednisone or prednisolone, avoid enteric coated or soluble forms
- 6) A flexibility in prednisolone dose of $\pm 12.5\%$ from the protocol dose will be allowable in the first 12 weeks while $\pm 25\%$ will be allowable after 3 months (see prednisolone chart). Refer bigger changes in prednisolone dosage to trial co-ordinator.
- 7) Minimum dose in first 3 months is 12.5 mg/day

6.3.3. Methotrexate

- 1) MTX is given orally although parenteral administration gives a more precise uptake. Parenteral administration may, however, be used if oral medication is not tolerated.
- 2) In case of gastrointestinal disturbances (nausea, vomiting, diarrhoea) the weekly dosage may be given late in the afternoon or divided and given one half in the morning and one half in the evening on the same day. Additionally, metoclopramide may be given.
- 4) **Check folic acid monthly for first year then two monthly.**
- 3) If transaminases rise > 3-fold of the normal range or leucocytopenia < 3000/microl and/or thrombocytopenia < 100.000/microl occur (lasting more than 4 weeks and being ascribable to MTX treatment only), folic/folinic acid should be administered orally on the day after MTX treatment in an equal dose. If the condition is not reversed within 4 weeks, reduce MTX and folic/folinic acid to 50%. If this is not effective either, stop MTX and folic/folinic acid. If the disease is in remission and the condition is reversed within 4 weeks, MTX and folic/folinic acid may be restarted in original dosage.

6.3.4. Prophylaxis (suggested only):

- 1) Peptic ulceration: ranitidine or omeprazole once a day (not cimetidine) for > six months.
- 2) Fungal infection: oral fluconazole, nystatin or amphotericin, for 12 weeks
- 3) Osteoporosis: follow local practice.
- 4) Oral ulcers in MTX group: Folic/folinic acid in dose equal to MTX dose on the day after MTX.
- 5) Pneumocystis carinii: monthly aerosolised pentamidine.

6.3.5. Treatment of complications

- 1) Pneumocystis pneumonia: sulfamethoxazole/trimethoprim according to local practice, stop MTX if in MTX group, continue with CYC if necessary. Omit for allergy to S/T and use pentamidine spray instead.
- 2) Anemia due to folinic acid depletion: treat with folic/folinic acid as necessary.

6.4. Appendix 4 Guidelines for changes of drug regimens for relapse (non-obligatory)

6.4.1 Major relapse

- 1) CYC 2mg/kg/day (stop MTX if from MTX group)
- 2) OCS 45 mg/day, reduce to 20mg/day by four weeks
- 3) When remission achieved return to regimen for CYC group at 3 month point for all relapses
- 4) If life threatening disease progression occurs or no remission can be achieved after two months follow local preference .
- 5) All changes in drugs and doses to be recorded in the Patient Record Book
- 6) If major relapse occurred on MTX do not return to MTX but maintain CYC or alternative according to local practise.

6.4.2. Minor relapse

- 1) Maintain MTX or CYC dose as per protocol.
- 2) Increase OCS to 30 mg/day then reduce by 5mg/day each week until the appropriate point on the protocol is reached.
- 3) If progression of disease occurs during the first month of increased OCS treatment and/or this treatment is ineffective after one month, treat as major relapse (see 6.4.1).
- 4) After 12 months in the protocol CYC or MTX should not be restarted. If increase of OCS to 30 mg/day is ineffective treat as major relapse (see 6.4.1) or follow local practice.

6.5. Appendix 5 Study Evaluations

notes for Minimum information required for the study. Additional tests (see **drug regimens**) or more frequent intervals to follow local practise.

- 6.5.1. Entry**
BVAS 1, VDI, SF-36 (=VITAL) and DEI score.
FBC and WBC differential
ESR, CRP, ANCA (IIF, PR3, MPO ELISA)
creatinine and creatinine clearance (isotope study or 24 hr collection)
ALT or AST, alkaline phosphatase, albumin, glucose
Complement C3, Complement C4.
Folic acid if in MTX group
ANA, rheumatoid factor, cryoglobulins
dipstick urine analysis and urine microscopy
24 hr protein excretion
chest X-ray
sinus X-ray (CT-scan or MR scan preferred if available)
5ml serum saved
nasal swab
- 6.5.2. Monthly for first year then two monthly.**
5ml serum saved
nasal swab (not obligatory after eight swabs)
- 6.5.3. Monthly for first 6 months then three monthly for remaining duration of study.**
BVAS 1 and 2, SF-36 (=VITAL) and DEI score
ESR, CRP
FBC and WBC differential
dipstick urine analysis and urine microscopy
creatinine
alkaline phosphatase, albumin, ALT or AST,*
glucose*
*only abnormal values are recorded
- 6.5.4. Every 6 months.**
VDI
- 6.5.5. At the end of the study at 18 months.**
chest X-ray
sinus X-ray (CT-scan or MR scan preferred if available)

6.6. Appendix 6 Disease Definitions

6.6.1. Wegener's granulomatosis (WG)

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 specificity for proteinase3 (PR3-ANCA) by ELISA, is found in over 90% of untreated patients with generalised WG; some studies have found a minority of cases to have ANCA with specificity for myeloperoxidase (MPO-ANCA) instead of PR3-ANCA. In WG with disease limited to the respiratory tract, ANCA positivity is less frequent.

For the purposes of this study, a diagnosis of WG requires the presence of chronic inflammation, with a history of at least four weeks and not attributable to another cause, supported by a characteristic histology on biopsy and/or detectable C-ANCA by IIF, or PR3-ANCA or MPO-ANCA by ELISA. WG is a clinico-pathological syndrome where confidence in the diagnosis often requires 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.

A characteristic or compatible histology for non-renal biopsies is defined by an inflammatory exudate dominated by PMN's with at least one of the following findings:

1. necrotising vasculitis affecting small to medium-sized vessels
2. epithelioid cell granulomas and
3. giant cells,

after exclusion of other causes.

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

6.6.2 Microscopic polyangiitis

MP is characterised by a vasculitis predominantly affecting small vessels. Renal involvement is usual and reflected by a necrotising glomerulonephritis. Granulomata are absent. Arteritis of medium-sized arteries may also occur (2). MP is associated with MPO-ANCA or PR3-ANCA; a minority of MP patients is ANCA negative or recognise other ANCA antigens.

For the purposes of this study, patients may be entered in the category of MP if they have a chronic inflammatory process with nongranulomatous vasculitis of small vessels (i.e. capillaries, venules or arterioles) which does not involve the upper respiratory tract.

6.6.3. 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.

6.6.4. 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 Appendix 7 Adverse effects

6.7.1. Intolerance of trial therapies

- 1) Persistent leucopaenia (total WBC < 4 x 10⁹/l for a period of 3 weeks, or recurring at a dose of 50 mg/day CYC or 15/week of MTX)
- 2) Persistent liver affection (increase in transaminases > 3 fold for a period of 3 weeks, or recurring at a dose of 50 mg/day CYC or 15/week of MTX)
- 3) 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)

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 will be noted:

- 1) Bleeding
- 2) Infection; site/organism to be noted
- 3) Leucopaenia: total WBC < 4 x 10⁹/l; duration and consequences to be noted
- 4) Alopecia or skin changes sufficient to concern the patient
- 5) Cataracts, new and/or progressing
- 6) Avascular necrosis or pathological fractures
- 7) Newly presenting diabetes
- 8) Peptic ulceration
- 9) Psychological disturbance
- 10) Malignancy
- 11) Amenorrhea and infertility
- 12) Pulmonary fibrosis
- 13) Hypertension, new and/or progressing. The number of agents required to treat it will be noted.

6.7.3. Adverse effects score

This will be developed based on:

- 1) Influence on study medications
- 2) Influence on quality of life (decreased capability for work and/or social life).
- 3) Influence on survival and/or organ function.

6.8. Patient Information and Consent

Brief description of the purpose and the procedures of the study

You are suffering from a form of inflammation of the blood vessels or vasculitis. The standard treatment for this condition consists of a combination of tablets which controls the disease but which must be continued to prevent the disease from coming back. These tablets frequently cause side-effects, especially infection, which can be serious. In this study we plan to compare the standard treatment combination with another treatment combination which is reported to be effective for controlling the disease but with less side-effects. Both types of treatment have been in use for more than 20 years in different hospitals but have never been compared. We would like to compare them to see whether they are equally effective and which has the least side-effects.

The side-effects associated with these treatments include lowering of the blood count, increased susceptibility to infection, hair loss, nausea, bladder irritation, high blood pressure, infertility, foetal damage and an increased risk of cancer. You will receive either the standard treatment or the new treatment by blind allocation. You will remain in the study for one and a half years in total.

When you are taking the tablets, it is our normal practice to watch you closely with regular examinations and blood checks, which will initially take place every week, then less frequently as your condition improves. In addition to the usual blood tests we require, for the purposes of research, an additional small quantity of blood at each visit and at 8 visits also nasal swaps to control for infection . It is essential that women of child-bearing age use efficient contraception to prevent pregnancy during the study.

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

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

.....

The details of this study have been explained to me by

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

Signed (patient) Date

Signed (investigator) Date

Signed (witness) Date

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