MTAC Clinical Trial protocol **June 2008**

Version 2

West London Renal and Transplant Unit

EudraCT Number 2008-001009-41

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Full trial name -Mycophenylate mofetil and tacrolimus vs tacrolimus alone for the treatment of idiopathic membranous glomerulonephritis

Abbrieviated trial name MTAC

Summary

Membranous nephropathy is a common cause of nephrotic syndrome in adults. It is difficult to treat and if persistent leads to end stage renal failure in a significant number of patients. It is currently treated in this institution with tacrolimus monotherapy. This is effective in the majority of patients in reducing proteinuria but the remissions are often partial and patients tend to relapse when the tacrolimus treatment is stopped. We propose to use mycophenylate mofetil in combination with tacrolimus with the aim of obtaining a more complete initial response to treatment, a decreased rate of relapse on withdrawal of therapy and less progression of renal failure.

Principal Investigators

Drs Megan Griffith Tom Cairns and Neill Duncan
Renal Unit
4th floor Ham House
Hammersmith Hospital
Du Cane Road
LondonW12 OHS

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1.Background

1.1 Membranous Glomerulonephritis

Idiopathic membranous nephropathy is the most common cause of nephrotic syndrome in Caucasian adults and up to 40% of patients eventually develop end stage renal failure (1). Historically used treatment regimes include high dose prednisolone, chlorambucil, and cyclophosphamide. Although these are effective in some patients there are significant side effects from the treatment hence the need to seek alternative immunosuppresive regimes. Cyclosporin is a well tolerated immunosuppresive agent used widely in transplantation, this has been shown to be effective in membranous nephropathy but there is a high incidence of relapse on withdrawal of therapy and long term risks of a decline in renal function due to nephrotoxicity (2). Tacrolimus is an alternative calcineurin inhibitor with less nephrotoxicity which has been shown to be very effective in the treatment of membranous nephropathy but there remains a high risk of relapse on withdrawal of therapy (3). Tacrolimus alone is the current standard therapy in this institution.

1.2 Mycophenylate Mofetil in membranous glomerulonephritis

Experimental models of membranous glomerulonephritis show that damage to the glomerular basement membrane by the deposition of immunoglobulin results in proteinuria (4). Mycophenylate mofetil (MMF) is an immuosuppressive agent which inhibits de novo purine nucleotide synthesis and the depletion of guanosine triphosphate (GTP) in lymphocytes and monocytes. Thus it selectively suppresses T and B lymphocyte proliferation and antibody formation, and is therefore likely to be effective in modifying this process. It has been used widely in other autoimmune diseases and has low toxicity (5). It has been shown to be effective in the treatment of membranous nephropathy when used in combination with high dose steroids (6,7,8). However there are significant side effects from the steroids and we wish to avoid these in our patients. MMF has been used in combination with tacrolimus in

transplantation, and this regime is better tolerated than those containing even low dose steroids (9). We hope that the addition of MMF to tacrolimus will result in improved remission rates from proteinuria for patients, improved preservation of renal function, will be well tolerated and will allow the eventual withdrawal of immunosuppressive agents without relapse thus avoiding the long term toxicity of ongoing treatment with these agents.

2. Aims of MTAC

To investigate if combining mycophenylate mofetil (MMF) with tacrolimus has a beneficial effect over tacrolimus therapy alone in the treatment of membranous glomerulonephritis. Tacrolimus alone is often effective in producing remission from heavy proteinuria but patients often relapse when the tacrolimus is withdrawn. We wish to investigate whether the addition of MMF will allow the subsequent withdrawal of tacrolimus without precipitating relapse. We will also study whether the addition of MMF to standard therapy with tacrolimus will be more effective in obtaining remission of proteinuria and preserving renal function

3.Hypothesis

When MMF is added to tacrolimus in the treatment of membranous glomerulonephritis, it is likely to improve the initial response to treatment and reduce the risk of relapse on stopping therapy.

4. Trial Design

This will be a randomized controlled trial in a single centre of tacrolimus alone vs tacrolimus and MMF therapy in 32 patients with heavy proteinuria secondary to

idiopathic membranous glomerulonephritis diagnosed by renal biopsy. We aim to recruit 32 patients 16 to each arm of the trial.

4.1 Eligibility

a) Inclusion criteria (requires all)

1 .Idiopathic membranous glomeulonephritis on renal biopsy

2.Proteinura – protein/creatinine ratio (PCR) >100units with hypoalbuminaemia or PCR >300 units with normal serum albumin despite 3 months treatment with maximum tolerated doses of ace inhibitors and angiotensin 2 antagonists; (or shorter if life threatening complications of nephrotic syndrome require institution of immediate immunosuppression.)

3. Male or female patients aged 18 to 80 years.

b) Exclusion Criteria

1 Hepatits B hepatitis C or HIV positive

2 Malignancy (all patients must have a CT chest abdomen and pelvis and other investigations if clinically indicated).

3. Untreated infection

4. Females who are pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception.

5. Any condition judged by the investigator that would cause the study to be detrimental to the patient.

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4.2 Trial Protocol

The research will be conducted via the glomerulonephritis clinc at Hammersmith Hospital. All patients with significant proteinuria secondary to membranous glomerulonephritis on renal biopsy will be considered for the trial. Patients will be screened for hepatitis B, C and HIV, and undergo CT chest, abdomen and pelvis to exclude viral and malignant causes for their membranous nephropathy (these are the

current standard investigations in all patients with membranous nephropathy.) All patients will be initially treated with maximum tolerated doses of ace inhibitors and angiotensin two antagonists for at least 3 months as is standard current treatment. Patients who remain significantly proteinuric (PCR>100units with hypoalbuminaemia or PCR >300 units with normal serum albumin) despite treatment with maximum tolerated doses of ACE inhibitors and angiotensin two antagonists will be randomised to receive tacrolimus monotherapy or tacrolimus in combination with mycophenylate mofetil therapy. The initial dose of tacrolimus will be 2mg twice a day and this would be titrated to achieve levels of 5-12 ng/ml. The initial dose of mycophenylate mofetil would be 500mg twice a day, and this would be titrated to achieve mycophenolic acid levels of 1.5-3.0 mg/L. Patients with a previous history of tuberculosis, or deemed at high risk due to Asian origin will receive isoniazid 150mg once a day and pyridoxine 50mg once a week.

Treatment will be initially for 1 year. Remission of proteinuria will be defined as complete if urinary PCR <30 units, and partial if urine PCR decreases by >50% but is still above 30 units. Patients not obtaining complete or partial remission after 1 year will be withdrawn from the trial and alternative therapies considered. When patients have been in remission for 12 months on treatment the tacrolimus will be withdrawn over 6 months. Those on MMF and tacrolimus will then have their MMF stopped prior to tacrolimus withdrawal over 6 months. Patients will be offered a renal biopsy prior to withdrawal of therapy. This will help predict relapse and show any evidence of tacrolimus toxicity which may help guide subsequent therapy in the case of relapse. Continuation in the trial is not dependent on undergoing renal biopsy. Patients will be followed for at least 3 years. Patients may withdraw from the trial at any point without any compromise to their clinical care.

4.3 Evaluations

The patients will initially be seen weekly until stable and then monthly until remission is achieved. They will then be reviewed 2-3 monthly for the rest of the trial depending on clinical need. Prior to entry all patients will have blood sent for hepatitis B

hepatitis C and HIV and have a CT scan of chest abdomen and pelvis to exclude malignancy.

At each clinic visit blood samples will be sent for full blood count, biochemical profile, drug level monitoring and selective proteinuria. Urine samples will be sent for PCR and selective proteinuria.

4.4 Withdrawal and treatment failure

Patients can be withdrawn at patient or physician request. The reason for withdrawal will be recorded in the patients records.

Patients not achieving remission at 1 year will be withdrawn from the trial and alternative treatments considered. They will remain under follow up in the clinic as is current standard practice.

4.5 End points

a) Primary Endpoints

Efficacy of MMF in preventing relapse of nephrotic syndrome on withdrawal of tacrolimus therapy. This will be initially measured at 6 months post withdrawal of tacrolimus therapy.

b) Secondary end points

The time to obtaining remission from proteinuria

The degree of remission of proteinuria obtained (complete or partial)

The rate of decline of renal function measured by the MDRD equation for glomerular filtration rate

4.6 Statistic Analysis

This will be carried out under the direction of Mr Bernard North -Statistics department Imperial College London. The sample size was based on the main outcome measure, time to relapse, and compared using a 1-sided log rank test assuming a 1% drop-out rate and a 50% relapse free survival rate in the tacrolimus group and a 95% relapse free survival rate in the tacrolimus and MMF group with an alpha level of 0.05 and 80% power. The NCSS PASS package was used. Hintze J (2004) Number Crunching Statistical Systems (PASS). The statistical analysis will be done by using a 1 sided log rank test.

4.7 Duration

5 years, with 24 months recruitment and 36 months follow up. Primary end points will be analysed when patients obtaining remission for 1 year have stopped tacrolimus therapy for 6 months. Secondary end point analysis of response to treatment will occur when patients have been on treatment for 12 months.

5. Adverse Events and Data Monitoring

It is anticipated that the treatment will be well tolerated as this regime has been extensively used in renal transplant recipients. All adverse events will be actively sort and recorded in the patients' notes. The data and progress of the trial will be reported to and monitored by the West London Renal and Transplant Glomerulonephritis Research Group at Hammersmith Hospital , on a monthly basis (appendix 2).

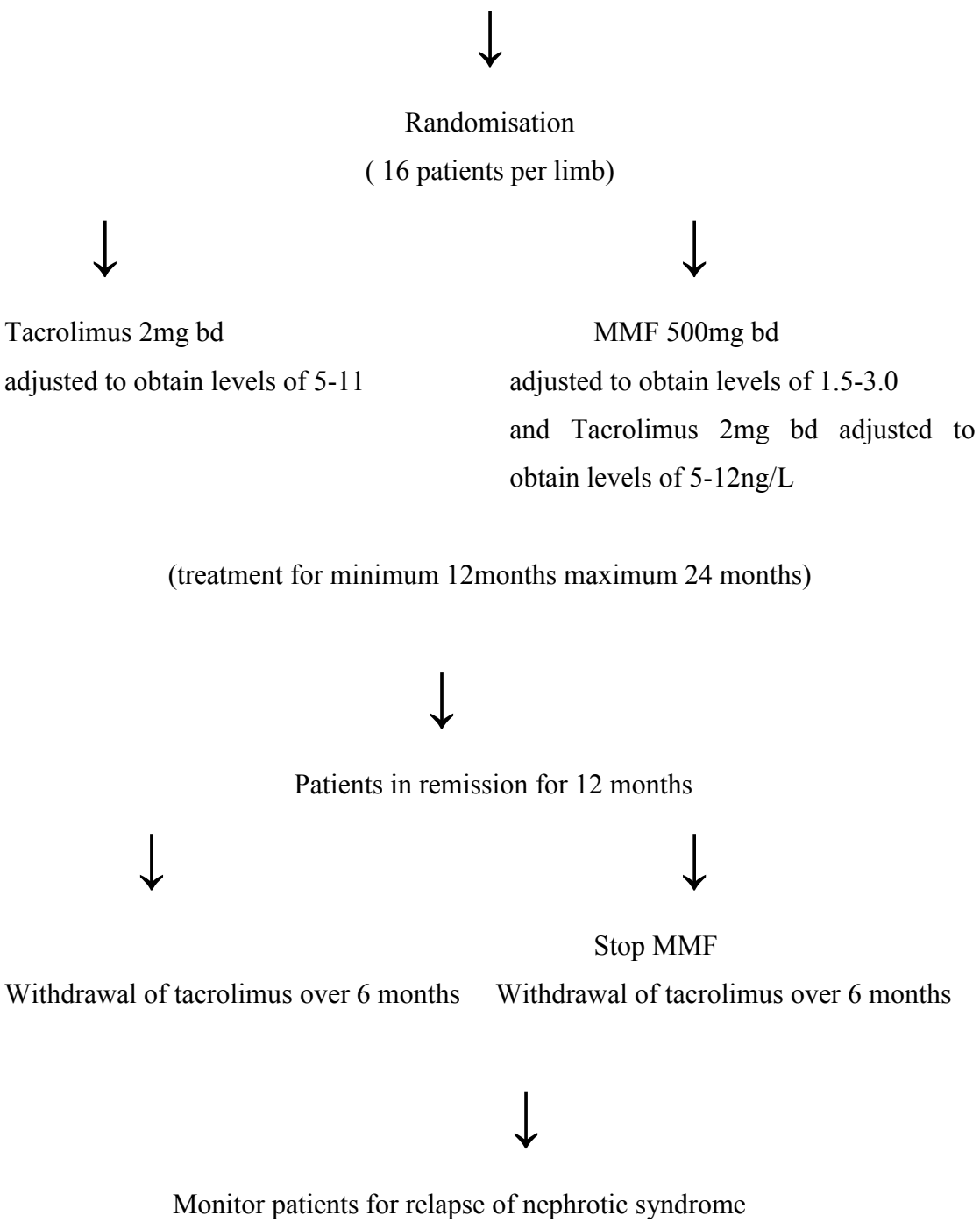
All Serious Adverse Events (SAE) and Suspected Unexpected Serious Adverse Drug Reactions (SUSADR) will be reported within 24 hours to the committee chairman Dr Liz Lightstone and to the sponsor, Dr Rodney Gale, i.e all events irrespective of their relation to study medications, that are either life threatening, result in hospitalization, result in death, result in persistent or significant disability or incapacity . The sponsor will report any such SAE or SUSAR to the regulatory authority in accordance with the European Directive 2001/20/EC.

6. Internal and External Review

The trial has been extensively reviewed, modified and approved by the West London Renal and Transplant Glomerulonephritis Research Group at Hammersmith Hospital. It has been externally reviewed and approved by Professor Patrick Maxwell, Professor of Medicine, The Rayne Institute, University College London WC1E 6JF.

Appendix 1

MTAC Trial Overview



Appendix 2: Membership of the Glomerulonephritis Research Group West London Renal and Transplant Unit Feb 2008

Professor Terry Cook	Consultant Pathologist
Dr Tom D Cairns	Consultant Nephrologist
Rania Betmouni	Renal Pharmacist
Prof Charles Pusey	Consultant Nephrologist
Dr Marie Conlon	Renal Registrar
Dr Liz Lightstone	Consultant Nephrologist
Dr Alan Salama	Consultant Nephrologist
Dr Megan Griffith	Consultant Nephrologist
Dr Frederick Tam	Consultant Nephrologist
Dr Ann Marie Habib	Renal Registrar
Sister Jane C Owen	Outpatient Sister
Dr Jeremy Levy	Consultant Nephrologist
Dr Gill Gaskin	Consultant Nephrologist
Dr Ruth Pepper	Renal Registrar

Appendix 3: References

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