MINTAC

Tacrolimus vs prednisolone for the treatment of nephrotic syndrome secondary to minimal change disease: A Randomised Control Trial

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Contents

STUDY SUMMARY

TITLE **Tacrolimus (prograf) vs prednisolone for the treatment of nephrotic syndrome secondary to minimal change disease: A Randomised Control Trial**

DESIGN Prospective randomised control trial

AIMS To compare the effectiveness of tacrolimus (prograf) vs prednisolone for the treatment of nephrotic syndrome secondary to minimal change disease

OUTCOME MEASURES

Primary outcome- proportion of patients achieving complete remission at 8 weeks

Secondary outcome- proportion of patients achieving complete remission at 16 and 24 weeks, prevention of relapse, nature and severity of side effects, change in glomerular filtration rate

POPULATION

52 patients (26 in each arm of the study)

ELIGIBILITY

All patients presenting to participating centres with nephrotic syndrome secondary to minimal change disease

TREATMENT

Tacrolimus (prograf) vs prednisolone

DURATION 5 years

TRIAL OVERVIEW MINTAC

Nephrotic syndrome secondary to idiopathic minimal change disease

↓

Randomise

↓

Tacrolimus (prograf) 0.05mg/kg bd (levels 6-12ng/ml)

Prednisolone 1mg/kg max 60mg od

↓

Achieval of complete remission

↓ ↓

Tacrolimus (prograf) maintenance for 3/12 tapered withdrawal over 1-2/12

Tapered steroid withdraw to give total course of at least 4/12

↓

Monitoring for relapse over 2 years

1. INTRODUCTION

1.1 BACKGROUND

Minimal change disease is a common cause of nephrotic syndrome in adults. Standard treatment is with high dose steroids which is often effective in controlling the nephrotic syndrome but has a high morbidity due to the side effects of the steroids. There is also a high relapse rate of up to 67% (1), therefore many patients require long term steroid therapy to control their disease which has significant morbidity and mortality. Some patients are or also become steroid resistant. There are studies showing the effectiveness of alkylating agents such as cyclophosphamide but the use of these drugs is limited by their toxicity, including increased rates of infection, cancers and infertility (2). Treatment with the calcineurin inhibitor cyclosporine has been shown to be effective, there have been concerns about the nephrotoxicity (3) of this agent although with careful monitoring this can be minimised (4).

1.2 RATIONALE FOR CURRENT STUDY

Tacrolimus (prograf) is a T-cell specific calcineurin inhibitor that shares similar immunosuppressive actions with cyclosporine A. It complexes with immunophilin FK506 binding protein and inhibits the phosphatase activity of calcineurin, resulting in decreased interleukin 2 transcription and inhibition of T-cell activation. Tacrolimus (prograf) is also capable of inhibiting the production of tumour necrosis factor – alpha and interferon-gamma by activated T-cells. In other glomerular diseases such as focal segmental glomerulosclerosis and membranous glomerulonephritis, prograf has been shown to be a very effective treatment for proteinuria. This may be due to the immunomodulatory effects on the underlying disease, but there may also be a direct effect of tacrolimus (prograf) on the podocyte, stabilising the actin cytoskeleton and therefore decreasing protein leak (5**).** Therefore tacrolimus (prograf) is likely to be effective in reducing proteinuria in minimal change disease.

Tacrolimus (prograf) has recently been shown to be an effective treatment for steroid resistant nephrotic syndrome in children with no significant effect on glomerular filtration rate (6). Studies in our own unit in patients with focal segmental glomerulosclerosis and membranous glomerulonephritis have also shown tacrolimus (prograf) to be a safe agent with no detrimental effect on glomerular filtration rate (7,8). It has also been shown to have a good side effect profile when used to allow the avoidance of steroids in transplantation (9). We have used tacrolimus (prograf) in our unit to treat relapsing minimal change disease in individual patients suffering from steroid toxicity with good effect, and have also used it as primary therapy in patients with steroid resistant nephrotic syndrome and for patients, in whom steroids were relatively contraindicated, again with good results in individual patients. To date there are no randomised trials comparing steroids with tacrolimus (prograf) in this group (10). This study aims to prospectively study if tacrolimus (prograf) is effective as treatment for minimal change disease compared with standard therapy with steroids, and whether it has advantages in terms of side effect profile and prevention of relapse.

2. AIMS OF MinTAC

To compare the effectiveness of tacrolimus (prograf) vs prednisolone for the treatment of nephrotic syndrome secondary to minimal change disease. The effectiveness of each treatment will be compared by the initial response rate (the proportion of patients achieving complete remission), the time taken to achieve complete remission, and the relapse rate post withdrawal of therapy, and the frequency, nature and severity of the side effects.

2.1 HYPOTHESIS

Tacrolimus (prograf) is not inferior to prednisolone in the treatment of nephrotic syndrome secondary to minimal change disease, has a preferable side effect profile and may decrease relapse rate.

3. STUDY DESIGN

This is a prospective open label randomised trial comparing tacrolimus (prograf) with prednisolone in the treatment of nephrotic syndrome secondary to minimal change disease There will be 52 patients randomised at a 1:1 ratio to each group (26 patients in each group).

The sample size has been calculated to assess non inferiority of tacrolimus (prograf) to prednisolone. The expected complete remission rate for patients treated with steroids at 8 weeks has been estimated at 60% (11), and tacrolimus (prograf) at 84% (6). The delta value has been set at -0.1. Clinically this has been chosen as a 10% worse remission rate in tacrolimus (prograf) compared to steroids, is likely to be clinically acceptable in view of the potential benefits of a non steroid based regime.

3.1 STUDY OUTCOME MEASURES

1. Primary Outcomes

Proportion of patients achieving complete remission from nephrotic syndrome (normalisation of serum albumin and urine PCR <50 units) at 8 weeks.

2.Secondary Outcomes

Proportion of patients achieving complete remission from nephrotic syndrome (normalisation of serum albumin and urine PCR <50 units) at 16 and 24 weeks.

Proportion of patients achieving remission who then relapse.

Nature, severity and frequency of adverse events.

Change in baseline glomerular filtration rate

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

1. Patients presenting to the WLRTC with nephrotic syndrome (hypoalbuminaemia and protein creatinine ratio (PCR) >100units), secondary to minimal change disease.
2. Age over 18.

4.2 EXCLUSION CRITERIA

1. Hepatitis B, hepatitis C or HIV infection
2. Untreated infection
3. Females who are pregnant, breast feeding, or at risk of pregnancy and not using a medically acceptable form of contraception.
4. Patients who have been treated with immunosuppression over the last 18 months.
5. Patients who have had more than 3 relapses of nephrotic syndrome within 5 years
6. Any condition judged by the investigator that would cause the study to be detrimental to the patient

4.3 WITHDRAWAL CRITERIA

If patients show no response by 6 months, then treatment will be withdrawn and alternative regimes implemented as clinically indicated.
Patients are free to withdraw from the trial at any point. This will not affect their clinical care in anyway.

5. TREATMENTS

Arm 1: Tacrolimus (prograf) 0.05mg/kg bd aiming for trough tacrolimus levels of 6-8ng/l, however if at 8 weeks the patient is not responding, the target tacrolimus levels will rise to 9-12ng/l. This will be continued for 12 weeks from the time of complete remission, then tapered and stopped over 4-8 weeks.

Arm 2: Prednisolone 1mg/kg/day (maximum 60mgs/day).
Omeprazole 20mgs/day (for gastric protection), calcichew D3 (for bone protection) 2 tablets /day.
One week post complete remission from proteinuria urine PCR <50 units, the steroid dose will be halved for 4-6 weeks, then tailed off over a further 4-6 weeks to ensure a minimum of 16 weeks therapy.

In addition all patients will receive

Angiotensin Receptor Blocker (+ / - ACEI) titrated to keep BP <125/75
Statin to maintain cholesterol < 4
Prophylactic low molecular weight Heparin if Albumin < 20mg/L
Aspirin 75mg OD if Albumin > 20<30mg/L

If South Asian, previous known TB or considered high risk for TB:
Isoniazid 150mg OD
Pyridoxine 50mg weekly

If there has been no response after 6 months, then alternative treatment will be considered on clinical grounds.

6.INTERACTION WITH OTHER DRUGS

The patients will be advised not to take any new drugs without discussing them with us first in case they interact with the study medication.

7. ASSESSMENT AND FOLLOW-UP

At baseline:

Full blood count, glucose, biochemical profile, immunoglobulins and electrophoresis
Viral screen: Hep B & C, HIV
Urine PCR
Weight
BP

Weekly for 4 weeks

Blood count, glucose, biochemical profile
Tacrolimus levels (patients in arm 1)
Urine PCR
Weight
BP

Monthly for 6 months

Blood count, glucose, biochemical profile
Tacrolimus levels (patients in arm 1)
Urine PCR
Weight
BP

A repeat renal biopsy will be offered at 6 months to all patients who have not achieved complete remission if clinically indicated.

Once complete remission has been obtained and treatment withdrawn patients will be monitored in clinic every 1-3 months as clinically indicated for the next 2 years. Standard blood/urine tests will be carried out as per standard clinical care.

8. LOSS TO FOLLOW-UP

Attempts will be made to contact the patient and if they have moved their treatment to another centre at that point they shall be excluded from the trial as data collection may not be reliable.

9.TRIAL CLOSURE

Recruitment to the trial will be terminated once there are 26 patients in each arm.

10.STATISTICS AND DATA ANALYSIS

Primary Outcome:

Proportion of patients achieving complete remission from nephrotic syndrome (normalisation of serum albumin and urine PCR <50 units) at 8 weeks.

Primary Analysis:

Non inferiority of tacrolimus (prograf) to prednisolone will be assessed by testing whether the difference in proportion of subjects achieving complete remission in the tacrolimus and prednisolone groups is greater than the non inferiority margin. Alternatively, and equivalent in testing procedure, the lower limit of the 95% confidence interval for the difference in proportion may be compared to the non inferiority margin (12).

Secondary Outcomes:

Proportion of patients achieving complete remission from nephrotic syndrome (normalisation of serum albumin and urine PCR <50 units) at 16 and 24 weeks.
Proportion of patients achieving remission who then relapse.

Nature, severity and frequency of adverse events.
Change in baseline glomerular filtration rate

Secondary analysis

Non inferiority of tacrolimus (prograf) to prednisolone will be assessed at 16 and 24 weeks using a test of proportion (Chi-square or Fishers exact).
The proportion of patients relapsing with nephrotic syndrome over 2 years will be assessed using a test of proportions (chi-squared or Fishers exact).
The severity and frequency of adverse events will be compared between groups using contingency table approaches such as the Cochran-Armitage trend test for ordinal severity data and Fisher exact test for counts. The analysis may be stratified by type or nature adverse events.
The change in glomerular filtration rate will be assessed using an unpaired t-test if data found to be normal or a Mann-Whitney test otherwise.

11 DATA MONITORING AND ADVERSE EVENTS

Data will be anonymised post randomisation. Data will be recorded on the case report forms and entered into a database which will be password protected.
It is anticipated that the treatment will be well tolerated as tacrolimus (prograf) 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, Dr Megan Griffith, Chief investigator, and to the sponsor, Dr Robina Coker, 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.

12.REGULATORY ISSUES

12.1 CLINICAL TRIALS

Clinical Trials Approval will be obtained from the MHRA prior to commencement of the trial.

12.2 ETHICS APPROVAL

Ethics approval will be obtained from the local ethics committee prior to commencement of the trial.

12.3 CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. The time allowed for consideration will be determined by the clinical urgency of the need to commence treatment and will vary from a few hours to few days. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so will be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

12.4 CONFIDENTIALITY

Participants' identification data will be required for the registration process. Subsequent data will be anonymised.

12.5 INDEMNITY

Imperial College NHS Trust holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

12.6 SPONSOR

Dr Robina Coker of Imperial College NHS Trust will act as the main sponsor for this study.

13. DURATION

5 years, with 24 months recruitment and 36 months follow up.

APPENDICES

- Bibliography
- Membership of West London Renal and Transplant Centre Glomerulonephritis Research Group

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Appendix 2: Membership of the Glomerulonephritis Research Group West London Renal and Transplant Unit July 2009

Dr Liz Lightstone	Consultant Nephrologist (Chairman)
Professor Terry Cook	Consultant Pathologist
Dr Candice Roufosse	Consultant Pathologist
Dr Tom D Cairns	Consultant Nephrologist
Rania Betmouni	Renal Pharmacist
Prof Charles Pusey	Consultant Nephrologist
Dr Marie Conlon	Renal Registrar
Dr Alan Salama	Consultant Nephrologist
Dr Megan Griffith	Consultant Nephrologist
Dr Neill Duncan	Consultant Nephrologist
Dr Marina Loucaidou	Consultant Nephrologist
Dr Ruth Tarzi	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 Nick Mansfield	Renal Registrar
Dr Anisha Tanner	Renal Registrar

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