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A Randomized, Controlled Trial of Tacrolimus plus MMF versus Tacrolimus Alone in Resistant Membranous Nephropathy

A. Study Purpose and Rationale

Membranous nephropathy (MN) is one of the most common causes of the nephrotic syndrome in non-diabetic adults. It is idiopathic in 75 percent of cases, but can also develop secondary to a variety of diseases and drugs, including systemic lupus erythematosus (SLE), hepatitis B, hepatitis C, malignancy, penicillamine, NSAIDs, and gold. The natural course of MN is quite variable: up to 30% of patients have spontaneous complete remission (CR) of proteinuria at 5 years, between 25 and 40% of patients have spontaneous partial remission (PR) of proteinuria at 5 years, and the rest progress; the rate of ESRD in patients who are untreated is 14% at 5 years (and 41% at 15 years).[i] In order to decide which patients would be the best candidates for treatment, patients have been stratified into subsets of risk of progression to CKD, and the risks and benefits of treatment can be discussed within this framework.

In all patients, therapy for the nephrotic syndrome includes angiotensin inhibition with an ACEI or ARB, lipid lowering therapy, a low-salt and low-protein diet, and loop direutics for edema. In patients with moderate or high risk of progression, immunosuppressive therapy should be considered. Regimens that have been shown to have efficacy in achieving remission of proteinuria and preventing progression to ESRD include a combination of the cytotoxic drug cyclophosphamide and glucocorticoids.[ii]

Calcineurin inhibitors, including cyclosporine (CyA) and tacrolimus have also been shown to have efficacy in MN, in inducing remission of proteinuria and preventing progression to ESRD, although they have also been associated with higher rates of relapse. In a randomized trial of 51 patients who were resistant to steroids were treated with prednisone plus CyA or placebo for 6 months; 75% had CR or PR compared with 22% with placebo, but the relapse rate was high so that one year later, only 39% were still in remission (compared to 13% with placebo).[iii] Tacrolimus has been studied in a randomized trial of 48 patients with MN; this showed 56% remission at 6 months and 72% by 12 months, though within 7 months after tacrolimus withdrawal, 9 out of 19 patients (47%) with CR or PR had relapsed, resulting in a relapse-free remission rate of 40% at 24 months.[iv]

Mycophenolate mofetil (MMF) is an immunosuppressive agent that is used to prevent rejection in solid-organ transplantation. It is a prodrug of mycophenolic

acid (MPA) and its method of action is to inhibit the enzyme inosine monophosphate dehydrogenase (IMPDH) and thereby block purine biosynthesis in activated lymphocytes. It induces apoptosis of activated T-lymphocytes and inhibits B- and T-cell proliferation. In addition to solid-organ transplantation, MMF has been studied in other autoimmune diseases, including systemic lupus erythematosus, dermatomyositis, and psoriasis, and is being studied with increasing frequency as an alternative treatment in primary glomerulopathies, including minimal change disease, focal segmental glomerulosclerosis, IgA nephropathy, and idiopathic membranous nephropathy.

The data on the efficacy and safety of MMF therapy in primary glomerulopathies, namely in MN, has been conflicting. In a series of 8 patients who had failed prior therapy with steroids, cyclophosphamide, and/or cyclosporine A in which MMF was given as the sole treatment for 9 months, all patients showed complete or partial remission with a significant decrease in proteinuria (average proteinuria 1.9 g/d after 9 months).[v] In a group of 46 patients that included 17 with MN, two patients (13.3%) achieved a complete remission and 8 patients (60%) achieved a partial remission after treatment with MMF for an average of 12 months.[vi] Two patients relapsed after MMF was stopped but both responded to retreatment. There was no change in median SCr and there were significant improvements in both serum albumin and cholesterol. Studies with less positive outcomes include a series of 16 nephrotic patients with MN (15 resistant to steroids, 6 to cytotoxic therapy, and 5 to cyclosporine) were treated with MMF for a mean of 6 months; six patients had a 50% reduction in proteinuria but only 2 achieved a partial remission.[vii] Lastly, a 1-year randomized, controlled, open label trial of MMF therapy did not increase the probability of partial or complete remission (37% experienced CR or PR in the MMF group and 41% in the control group).[viii] However, this study was limited by its small size (19 patients in the MMF group and 17 in the control group).

The combination of tacrolimus and MMF in idiopathic membranous nephropathy has been looked at small studies, including a pilot study of 21 patients where MMF was variably added to tacrolimus plus steroids after 3 months in cases where remission had not been achieved. There was a high rate of remission (71.4% with either double or triple therapy) but also a high rate of relapse (52%).[ix] However, the combination of MMF and tacrolimus has not been examined in a randomized, controlled fashion.

The purpose of this study is to examine the efficacy of treatment with the dual immunosuppressive regimen of tacrolimus and MMF in patients with idiopathic membranous nephropathy who have been resistant to or intolerant of steroids and/or cytotoxic therapy.

B. Study Design and Statistical Analysis

This will be a prospective, randomized, controlled clinical trial to evaluate the efficacy of a regimen of tacrolimus and MMF compared with tacrolimus alone in the

treatment of biopsy-proven idiopathic membranous nephropathy that has been resistant to steroids and/or cytotoxic therapy. The participant pool will consist of patients who present to NewYork-Presbyterian Hospital / Columbia University Medical Center either for primary evaluation or as referrals from other physicians. Written consent will be obtained from all participants prior to study enrollment.

Patients will be randomized either to a control group (tacrolimus alone) or to the treatment group (tacrolimus plus MMF). Randomization will be stratified according to clinical prognostic factors, namely baseline urinary protein excretion and serum creatinine. Baseline proteinuria <8 g/d and normal serum creatinine at baseline have both been associated with an increased probability of remission from proteinuria and lower risk of developing ESRD.[x]

All patients will be instructed to maintain the same doses of ACEI or ARB that they were taking prior to study initiation to avoid confounding given the known anti-proteinuric properties of these agents. Other anti-hypertensive drugs will be prescribed as needed to achieve target BP of < 135/85. Patients will also be treated to achieve a goal LDL <160 mg/dL with dietary interventions and/or statin therapy. Statin therapy may be initiated during the study, and statin doses may be adjusted as needed. Other treatments common to both groups may include loop diuretics as indicated for edema, as well as a low-salt, low-protein diet.

The primary outcome will be a composite of the probability of achieving complete or partial remission and the probability of relapse after remission, or in other words, the probability of relapse-free remission. Both complete and partial remission will be used because both are predictive of renal survival, that is, decreased likelihood of progression to ESRD.[xi] Complete remission is defined as <0.3 g/d proteinuria plus stable renal function (eGFR within 15% of baseline). Partial remission is defined as >0.3 but <3 g/d proteinuria with a >50% reduction in proteinuria from baseline plus stable renal function. Relapse is defined as an increase in 24-h proteinuria to >3.5 g/d in patients who had partial or complete remission. The secondary outcomes will include doubling of baseline SCr levels and progression to ESRD.

At the conclusion of the 6-month study protocol, patients who experienced remission (complete or partial) will be followed for an additional 12 months to determine whether remission is sustained and to monitor for any treatment-related long-term toxicities. Patients with persistence or relapse of nephrotic range proteinuria will be offered alternative therapies at their physician's discretion.

Categorical data will be analyzed using the chi-square test for proportions. Using multivariate analysis, we will look for variables that significantly correlate with partial or complete remission, including age, sex, race/ethnicity, baseline level of proteinuria, baseline level of albumin, baseline SCr, baseline eGFR (at study entry), and previous treatment with CYC (yes/no).

Sample Size Calculation: The determination of sample size is based on previous studies of a 6-month course of calcineurin inhibitors in steroid-resistant idiopathic MN, showing a 45% probability of relapse-free remission after one year. Assuming an effect size of 30%, and in order to achieve 80% power with a 5% Type I error rate, a sample size of 50 patients in each group was calculated using the Chi square test.

C. Study Procedure

Both groups of patients will be treated with tacrolimus starting at 0.05 mg/kg/day in 2 divided doses. Blood will be drawn weekly to determine tacrolimus trough levels and the dose will then be adjusted in order to achieve target whole-blood trough levels of 5-10 ng/mL. Tacrolimus treatment will be continued for 6 months and will then be tapered off gradually over the next 6 months.

Patients randomly assigned to the treatment group will be started on MMF therapy at a dose of 250 mg/day which will be progressively increased by 250 mg/day every other day to a target dose of 2 g/day in 2 divided doses. Treatment with MMF will be continued for 6 months and then will be tapered off over a period of 2 weeks. WBC will be checked every week during the first month, every other week during the second and third months, and then every month for the remainder of the study.

Patients will undergo detailed clinical assessments at study entry, every month for the first 2 months, and then every other month for the duration of the study. The assessments will include a 24-hour urine collection for protein and creatinine excretion, and creatinine clearance. eGFR will be calculated according to the 4-variable Modification of Diet in Renal Disease Study equation. Patients will be seen more frequently as indicated by their clinical course.

Patients in both treatment groups will be monitored closely for signs of tacrolimus toxicity. If SCr increases by 33% or more on two or more determinations, tacrolimus doses will be reduced by 25 to 50%. The tacrolimus dosage will also be reduced 25 to 50% for other adverse effects. When manifestations of tacrolimus toxicity fail to improve within 2 weeks, the tacrolimus dosage will be reduced further. If the serum creatinine remains increased 50% over baseline or if adverse effects persist despite repeated tacrolimus dosage reductions, the patient will have to be withdrawn from the study.

D. Study Drugs

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase, which is involved in de novo purine synthesis in activated lymphocytes.

Side effects of MMF include:

Hematologic (leukocytopenia, anemia, thrombocytopenia)

Cardiovascular (hypertension, edema)

Infections (respiratory tract infection, UTI)

Gastrointestinal disturbances (diarrhea, nausea, abdominal pain)

Malignancy (risk of development of lymphoma and skin malignancy has been reported)

Dermatologic (rash)

Tacrolimus is a calcineurin inhibitor that suppresses cellular immunity by inhibiting T-lymphocyte activation.

Side effects of tacrolimus include:

Cardiovascular (hypertension, edema)

Endocrine (glucose intolerance)

Neuromuscular (tremor)

Gastrointestinal (diarrhea, nausea, abdominal pain)

Hematologic (anemia, leukopenia, thrombocytopenia)

E. Medical Devices

N/A

F. Study Questionnaires

N/A

G. Study Subjects

Inclusion citeria:

Age > 18 years

Patients with biopsy-proven idiopathic membranous nephropathy and nephrotic syndrome (24-hour protein excretion of >3 g/day and hypoalbuminemia with albumin <3 g/dL)

Renal biopsy within three years of study entry

GFR >60 mL/min per 1.73 m2 body surface area at study entry

ACEI or ARB therapy for at least 6 months before study entry

Baseline BP <135/85

Prior demonstrated steroid resistance (defined as failure to achieve CR or PR after a course of at least 3 months of daily prednisone at 1 mg/kg/day) OR relapse and resistance to retreatment OR intolerance of, contraindications to, or patient preference against steroid therapy

Prior demonstrated cyclophosphamide resistance (defined as failure to achieve CR or PR after treatment with pulse IV CYC with a total dose of at least 6 g) OR relapse and resistance to retreatment OR intolerance of, contraindications to, or patient preference against cytotoxic therapy

Exclusion criteria:

Secondary MN or any systemic disease known to be associated with secondary MN

Tacrolimus or MMF use during the 30-day period before study entry

Previous treatment with CyA for >6 month period

Active or chronic infection (including Hep B, Hep C, or HIV infection)

Preexisting malignancy

Diabetes mellitus

Pregnancy in female patients

Peptic ulcer disease or chronic diarrhea

White blood cell count below 2.5×10^9/L, a platelet count below 100×10^9/L, hemoglobin concentration less than 7 g/dL

H. Recruitment of Subjects

Patients will be recruited from NewYork-Presbyterian Hospital / Columbia University Medical Center. Nephrologists at NYPH/CUMC will be informed of the study protocol and encouraged to consider whether their patients would be appropriate for the study.

I. Confidentiality of Study Data

All data will be de-identified and stored securely.

J. Potential Conflict of Interest

There are no potential conflicts of interest to disclose.

K. Location of Study

This study will be conducted in the outpatient nephrology clinics (both the fellow clinic and faculty clinics) at NewYork-Presbyterian Hospital / Columbia University Medical Center.

L. Potential Risks

The risks associated with the study are related to the potential side effects of the two drugs involved in the study. The list of potential adverse effects can be found in section D, “Study Drugs”.

M. Potential Benefits

The potential benefits of this study include attaining a complete or partial remission from nephrotic-range proteinuria and potentially decreasing the risk of progressing to end-stage renal disease.

N. Alternative Therapies

Alternative therapies include steroids and cyclophosphamide (which the patients have either shown resistance to, have relapsed on, have contraindications to, have been intolerant of, or have declined based on patient preference). Another alternative treatment is CyA, another calcineurin inhibitor that has been studied in MGN. Tacrolimus was chosen as the calcineurin inhibitor in this study for the reasons discussed in section A, “Study Purpose and Rationale”. An additional alternative therapy is rituximab, which is also currently being studied in MGN.

O. Compensation to Subjects

Participants will not be compensated for participation in this study.

P. Costs to Subjects

Participants will not incur costs associated with participation in this study.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A

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