Mycophenolate Mofetil Monotherapy in Membranous Nephropathy: A 1-Year Randomized Controlled Trial

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Background: Treatment of patients with membranous glomerulonephritis (MGN) is controversial because of the lack of clear benefit of the immunosuppressive regimens on patient or renal survival. The objective of this study is to evaluate the efficacy and safety of mycophenolate mofetil (MMF) for patients with MGN.

Study Design: 1-year prospective, randomized, and controlled clinical trial.

Setting & Participants: 36 patients with biopsy-proven idiopathic MGN and nephrotic syndrome.

Intervention: 19 patients received MMF (2 g/d) for 12 months and 17 patients were in the control group. All patients had the same conservative treatment based on renin-angiotensin blockers, statins, low-salt and low-protein diet, and diuretics in case of edema.

Outcomes & Measurements: End points were the mean proteinuria over creatinuria ratio in mg/g throughout the study and numbers of complete and partial remissions at 1 year (month 12). Data were analyzed on an intention-to-treat analysis.

Results: Mean proteinuria over creatinuria ratio was stable in both groups throughout the study ($P = 0.1$). Mean proteinuria over creatinuria ratio was 4,690 ± 2,212 mg/g in the MMF group and 6,548 ± 4,601 mg/g in the control group (95% confidence interval of the difference, −619 to +4,247; $P = 0.1$). Remission was complete in 3 patients (1 in the MMF group, 2 in the control group; $P = 0.5$) and partial in 11 patients (6 in the MMF group, 5 in the control group; $P = 0.9$). The probability of complete or partial remission did not differ between the 2 groups after 12 months (relative risk, 0.92; 95% confidence interval, 0.48 to 1.75; $P = 0.7$). Kidney function was stable in the 2 groups according to estimated glomerular filtration rate and serum creatinine level.

Limitations: The small number of patients and short follow-up prevent generalizations.

Conclusions: A 12-month regimen of MMF did not decrease mean proteinuria over creatinuria ratio or increase partial and complete remissions. Serious adverse effects were observed in 4 patients (20%) receiving MMF.

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INDEX WORDS: Membranous nephropathy; nephrotic syndrome; mycophenolate mofetil; randomized trial.

Membranous glomerulonephritis (MGN) is the most frequent cause of nephrotic syndrome in adults.[1] Treatment of patients with MGN is a much debated issue because of the natural history of MGN and inconsistencies of therapeutic trials.[2-4]

The natural history of MGN under a conservative approach is known. A minority of patients (~20%) experience end-stage renal failure, whereas 20% to 40% achieve spontaneous remission. The most frequent course is persistence of nephrotic syndrome with slow progression to decreased kidney function.[5,6]

Some risk factors for progression toward end-stage renal failure have been identified, mainly in retrospective studies. The most predictive factors are proteinuria greater than 10 g/d, high serum creatinine level at diagnosis, and deterioration in

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kidney function in the 6 months after the diagnosis.[7] However, it is still difficult for nephrologists to predict which patients will progress to renal failure and thus warrant immunosuppressive treatment.

Randomized controlled trials evaluating immunosuppressive treatments are scarce and results are controversial.[8,9] The most recent systematic review failed to show a long-term effect of steroids, alkylating agents, calcineurin inhibitors, and antiproliferative agents on patient and/or renal survival.[10] There was weak evidence that alkylating agents increased the remission rate.[10] However, 2 recent studies, 1 with tacrolimus and the other with the Ponticelli protocol, have revived the debate because they reported a greater rate of remission in the treated group.[11,12]

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase, which is involved in de novo purine synthesis in activated lymphocytes. MMF has been shown to prevent glomerular lesions in different experimental models of glomerulonephritis.[13,14] MMF monotherapy has been used only in case series of patients with MGN.[15-19] We therefore conducted a randomized controlled study to evaluate the efficacy and safety of MMF monotherapy in patients with MGN.

METHODS

This study was a 1-year, prospective, multicenter, randomized, parallel, open-label, and controlled trial conducted in 6 university hospitals in the South of France between January 2004 and January 2007. The study protocol was reviewed and approved by the Comité Consultatif de Protection des Personnes se Prétant à la Recherche Biomédicale, and written informed consent was provided by all participants.

Entry criteria were idiopathic biopsy-proven MGN, age older than 18 years, nephrotic syndrome (proteinuria $>$ 3 g/day with hypoalbuminemia with albumin level $<$ 3 g/dL [$<$30 g/L] and serum creatinine level $<$ 2.26 mg/dL [$<$200 μmol/L]). Exclusion criteria were secondary MGN regardless of the cause, diagnosis of MGN for more than 6 months, and patients previously treated with an immunosuppressive agent.

Patients were randomly assigned to either a control group (conservative treatment) or a group treated with MMF (conservative treatment plus MMF) for 1 year. Randomization was performed by each center through a centralized Internet on-line application provided by the sponsor (minimization method). Randomization was stratified according to sex and center.

All patients received the same conservative treatment based on angiotensin-converting enzyme (ACE) inhibitors, statins, low-salt and low-protein diet, and loop diuretic in case of edema. Nephrologists were instructed to give the highest dose possible of ACE inhibitors with a target systolic blood pressure less than 130 and greater than 100 mm Hg and a target diastolic blood pressure less than 80 and greater than 60 mm Hg. In case of ACE-inhibitor intolerance (cough or angioedema), patients were prescribed angiotensin receptor blockers (ARBs). For hypertensive patients, other antihypertensive drugs were prescribed in addition to ACE inhibitors/ARBs at each nephrologist's discretion. Target low-density lipoprotein cholesterol level was 1.6 g/L. Statins were prescribed for patients who did not reach this level despite dietary advice. A low-salt ($\leq$4 g/d of sodium chloride) and low-protein (0.8 g/kg/d) diet was initiated in all patients. Loop diuretics were prescribed in case of edema. All patients except 3 (1 in the MMF group, 2 in the control group) had ACE inhibitors before randomization and thus it was not possible to evaluate the effect of the conservative treatment on the mean proteinuria over creatinuria ratio.

Patients randomly assigned to the treatment group started MMF therapy at a dose of 250 mg/d, progressively increased by 250 mg every other day to 2 g/d. White blood cell count was checked every week during the first month, every other week during the second and third months, and once a month until month (M)12. After completion of the trial, MMF therapy was progressively stopped in 15 days.

Follow-up visits were scheduled monthly during the first 2 months (M1, M2) and thereafter every other month until M12 (M4, M6, M8, M10, M12). At each visit, a complete physical examination was performed, including blood pressure). Blood pressure was measured after 5 minutes of rest in a lying position. The average of 2 blood pressure measurements was recorded. Secondary effects of treatments were collected. At each visit, blood was sampled for a standard hemogram, creatinine, urea, ionogram, glucose, total protein, albumin, total cholesterol, low-density and high-density lipoprotein fractions, triglycerides, and calcium. A 24-hour urine sample was collected at each visit, and 24-hour creatinine, urea, ionogram, and protein were measured. Mean proteinuria over creatinuria ratio and estimated glomerular filtration rate (eGFR) according to the 4-variable Modification of Diet in Renal Disease Study equation were calculated at each visit.

End Points

The primary end point was mean proteinuria over creatinuria ratio (milligrams per gram) throughout the study in both groups. The secondary end point was number of patients reaching complete or partial remission. Complete remission was defined as proteinuria with protein less than 0.3 g/24 h plus normal kidney function (eGFR $>$ 60 mL/min/1.73 m^2 [$>$1 mL/s/1.73 m^2]). Partial remission was defined as proteinuria with protein greater than 0.3 and less than 3 g/d with normal kidney function (eGFR $>$ 60 mL/min/1.73 m^2 [$>$1 mL/s/1.73 m^2]). Other secondary end points were number of patients with a 20% decrease in eGFR at the end of the study and a 20% increase in serum creatinine level.

Sample Size

Sample size calculation was based on the largest case series of MGN treatment with MMF using mean proteinuria