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Original Article

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Long-Term Efficacy of Treatment with Cyclosporine in Idiopathic Membranous Nephropathy: Remission Is Not Enough

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ABSTRACT

Background: Membranous nephropathy (MN) is an autoimmune disease in which circulating autoantibodies bind to a podocyte antigen, causing nephrotic syndrome. Despite several treatment options, their long-term benefits are still not established. The aim of this study is to investigate the long-term efficacy of cyclosporine and methylprednisolone in MN treatment.

Methods: In this retrospective study, we included adults with biopsy-proven idiopathic MN. At diagnosis, all patients received conservative treatment, and those who did not show remission after 6 months received immunosuppression with cyclosporine and methylprednisolone. Those that despite no remission chose not to receive immunosuppression served as controls.

Results: Sixty patients were included in the study with a follow-up of 94.8 ± 55.5 months. Forty-nine patients had nephrotic syndrome, and 47 received immunosuppression, while 13 received no treatment. Out of those who received immunosuppression, 63.8% showed complete, 14.9% partial, and 19.1% no remission of nephrotic syndrome. End-stage kidney disease (ESKD) or doubling of serum creatinine was reached by 12. Out of those who received no immunosuppression, 23.1% showed complete, 30.8% partial, and 23.1% had no remission. Doubling of serum creatinine or ESKD was reached by 1. Kidney survival was not altered by immunosuppression and was not different among those who received immunosuppression and had no or up to 3 relapses. Either complete or partial remission was accompanied by better kidney survival.

Conclusion: Treatment of idiopathic MN with cyclosporine and methylprednisolone offers a reliable option for proteinuria remission. Nevertheless, this option does not alter long-term disease progression.

Keywords: Membranous nephropathy, cyclosporine, immunosuppression, conservative treatment, kidney survival

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INTRODUCTION

Membranous nephropathy (MN) can cause severe proteinuria and nephrotic syndrome in adults. It presents at a median age of 50 years with a male predominance (2 : 1) and an incidence of 1.2 cases/100.000 persons/year.[1] It is now recognized that MN is an autoimmune disease that specifically targets kidneys, where autoantibodies present in the circulation aim and bind to an antigen on glomerular podocytes. This pathophysiological pathway leads to the formation of immune complex deposits in the glomerular capillary walls.[2] In countries with advanced health systems, about 75% of MN cases are primary (i.e., with no identifying cause), and the remainder are secondary to chronic infections (hepatitis B), autoimmune diseases (commonly lupus), specific medications, and neoplasias.[2] After several decades of basic research in 2009, the target autoantigen in idiopathic MN was first recognized as the M-type phospholipase A2 receptor.[3,4] Thereafter, more autoantigens were described, which overall are responsible for

adult idiopathic MN in almost 80% of cases (reflecting almost 55% of all MN cases). The main podocyte antigens identified till now are phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A, neural epidermal growth factor-like 1 protein, and semaphorin 3B, with even more probably coming up in the next few years.[5]

Nephrotic syndrome is common at presentation, but subnephrotic range proteinuria in most patients with MN develops gradually over months. This feature is attributed to the progressive accumulation of autoantigens on podocytes and the subsequent development of podocyte injury.[5] The natural history of MN can vary amongst individuals, with about one-third of them experiencing spontaneous remission (more often in patients with proteinuria <8 g/day) after 15-20 months for partial and 25-40 months for complete remission, while relapses occur in 25%-30% of patients.[6] Autoantibody levels should be reduced and eliminated before any significant clinical remission occurs. High titers of anti-PLA2R are linked with an increased risk of adverse kidney effects and a reduced chance of remission.[1]

Treatment options depend on disease severity as determined by proteinuria degree, baseline kidney function, and the titer of anti-PLA2R.[5] Thus, one end of this perspective includes patients with low risk for disease progression [normal estimated glomerular filtration rate (eGFR) at diagnosis and proteinuria <3.5 g/day] that can be conservatively treated. The mainstay of conservative treatment consists of loop diuretics (± amiloride and thiazide diuretics) for edema control and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) for proteinuria reduction.[1] Prescription of statin-based therapy and prophylactic anticoagulation (when serum albumin is <2.2 g/dL) is also recommended.[1] Those with increased risk for kidney function deterioration are the ones with proteinuria of more than 8 g/day and rapid decline of kidney function who are treated with immunosuppression-based protocols. Immunosuppressive treatment options in adult patients with MN exclude corticosteroid monotherapy, as it has been shown to be ineffective. Pediatric patients, though, could be an exception to that standard.[5] Alkylating agents (cyclophosphamide or chlorambucil) plus corticosteroids, as with Ponticelli regimen,[7] have a proven efficacy in achieving nephrotic syndrome remission, but with an increase in adverse effects profile and a long-term risk for development of malignancy.[8]

MAIN POINTS

- Treatment of idiopathic membranous nephropathy (MN) with cyclosporine is highly effective concerning nephrotic syndrome remission.
- Long-term kidney survival is not altered by cyclosporine in idiopathic MN.
- Kidney survival is similar for those with no or up to 3 relapses.
- Either complete or partial remission was accompanied by a better kidney survival in idiopathic MN.

Several other treatment approaches have been employed, with an emphasis on immunosuppression. Calcineurin inhibitors (CNIs) are often prescribed in patients with MN and moderate risk for disease progression.[5] These include cyclosporine (CsA) with[9] or without corticosteroids[10] and tacrolimus,[11] with an increased probability of nephrotic syndrome remission (around 70%) but also with a high rate of proteinuria relapse after treatment cessation. More recent data suggest, though, that treatment with these agents has no long-term benefit for patients with MN.[12] Other agents that are currently used include the B-cell-depleting agent rituximab, which has shown a favorable outcome in inducing proteinuria remission, although this may be reached even after 24-36 months from the first administration.[1,13,14] Moreover, rituximab has shown a favorable safety profile and could replace cytotoxic-based regimens as first-line immunosuppression in those with MN and a certain risk profile for disease progression.[15]

Thus, despite several treatment options for MN, depending on disease severity and progression risk assessment, the long-term benefit of these therapeutic regimens is still far from well established. The aim of this retrospective study is to investigate the long -term efficacy of the combination of CsA and methylprednisolone in the treatment of patients with MN.

MATERIAL AND METHODS

Study Design and Participants

This was a retrospective study in which patients who were followed from January 2005 and onwards at our outpatient clinic were included. Inclusion criteria comprised: age >18 years, kidney biopsy-proven idiopathic MN, and serum creatinine levels of less than 2 mg/dL at diagnosis. For most of the patients, there was no available measurement of serum anti-PLA2R titers. Kidney function (eGFR) was assessed with the Modification of Diet in Renal Disease (MDRD) formula at diagnosis and at each visit throughout follow-up.[16] We excluded patients with secondary MN as a result of known chronic infection with hepatitis B or C virus or HIV, active tumors, positive antibodies to double-stranded DNA, current treatment with gold or penicillamine, and nonsteroidal anti-inflammatory drugs. Furthermore, we excluded patients who received immunosuppressive treatment other than CsA and methylprednisolone.

At diagnosis, all patients received conservative treatment consisting of ACEi or ARB at the maximal tolerated dose. Patients who did not go into spontaneous remission 6 months after the initiation of conservative treatment and continued to show nephrotic syndrome or nephrotic range proteinuria received immunosuppression consisting of a combination of CsA and prednisolone. Patients who despite these clinical features, chose not to receive immunosuppression, continued conservative treatment, and served as the control group. This latter group did not receive any immunosuppressive treatment at any point

during follow-up. Cyclosporine was administered twice daily at a starting total dose of 2 mg/kg of body weight (bw) with target trough blood levels of 100 ng/mL for 18 months. Then, CsA was gradually tapered by 0.5 mg/kg bw/day per month until discontinuation of treatment at 24 months. Prednisolone was initiated at a dose of 0.5 mg/kg bw/day, which was tapered to 5 mg on alternate days at 12 months and discontinued at 18 months.[17] Patients who experienced nephrotic syndrome relapse received a second course of the same regimen.

Follow-Up and Definitions

Parameters such as body weight, blood pressure, serum biochemical profile, and 24-hour urinary protein of each patient were recorded at each visit. Complete remission of nephrotic syndrome was considered when proteinuria was reduced to <0.3 g/24 h and partial remission when proteinuria was between 0.3 and 3.5 g/24 h or decreased by at least 50% from the initial value and was <3.5 g/24 h. When proteinuria remained over 3.5 g/24 h, patients were considered to have no remission. As a clinical outcome, we used the end point of doubling of baseline serum creatinine and/or development of end-stage kidney disease (ESKD) during follow-up. The ratios of remission of nephrotic syndrome according to treatment were also examined.

All patients included in the study provided a written informed consent for using their historical clinical data in an anonymous manner. The study was approved as a noninterventional retrospective study by the University Hospital of Patras ethics committee as it included patients retrospectively that were treated with an established and approved regimen against nephrotic syndrome (approval number: 0211/March 21, 2022) and is in accordance with the Helsinki Declaration as revised in 2013.

Statistical analysis

Continuous data are presented as means ± standard deviation. The normality of the data distribution was examined with the Kolmogorov–Smirnov test. Normally distributed data were compared with Student's *t*-test and skewed continuous data with Mann– Whitney *U*-test for investigating the differences of means. Categorical variables are expressed as numbers and percentages and were compared with the χ^2 or Fisher's exact test. Survival analysis was performed using Kaplan–Meier and the log-rank (Mantel–Cox) test to determine significant differences between the clinical outcome end-point of those patients that received immunosuppression and those that received only supportive treatment. The same analysis was performed to test differences in clinical outcome end-point between those patients that received immunosuppression and had different degrees of proteinuria at baseline or at the time of initiation of immunosuppressive treatment, as described in the most recent risk stratification algorithm for MN, i.e., <3500, 3500-8000 and >8000 mg/24 h.[5] Finally, we examined clinical outcome end-point depending on remission of nephrotic syndrome (complete, partial, or no remission) and between those that showed at least 1 relapse of nephrotic syndrome or no relapses.

All tests were 2-tailed with a $P < .05$ set for statistical significance. All analyses were performed using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego, Calif, USA) and Statistical Package for the Social Sciences Statistics (SPSS) software for Windows v.26 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

In this study, we included 60 patients (42 males) with idiopathic MN and a mean age of 56.2 ± 14 years at biopsy. Forty-seven patients received immunosuppressive treatment with a combination of CsA and methylprednisolone, while 13 patients received no treatment. The mean follow-up was 94.8 ± 55.5 months, and the total immunosuppressive treatment duration (all cycles combined) was 31 ± 24.7 months. Clinical characteristics of patients after conservative treatment for 6 months are presented in Table 1.

Clinical Course

Overall, 33 patients showed complete remission, 11 had partial remission, and 12 patients had no remission of nephrotic syndrome at 24 months after the initiation of conservative or immunosuppressive treatment. The end point of ESKD or doubling of serum creatinine was reached by 13 patients, while 41 continued to show stable kidney function at the end of follow-up. Six patients were lost to follow-up. Of those with complete or partial remission, 22 showed no relapses of nephrotic syndrome and 20 patients 1-3 relapses. Patients clinical and laboratory data at the end of follow-up are presented in Table 2.

Out of those who received immunosuppression (47) all clinically showed nephrotic syndrome at the time of treatment initiation, and all but 1 had 24-hour proteinuria of more than 3.5 g. Thirty (63.8%) patients showed complete remission of nephrotic syndrome, 7 (14.9%) had partial remission, and 9 (19.1%) patients had no remission at 24 months after the initiation of treatment. The end point of ESKD or doubling of serum creatinine was reached by 12 patients, while 32 continued to show stable kidney function during the end of follow-up. Three patients were lost to follow-up. Of those with complete or partial remission, 16 showed no relapses of nephrotic syndrome and 20 patients 1-3 relapses.

Out of those who received no immunosuppressive treatment (13), 3 (23.1%) patients showed complete remission of nephrotic syndrome, 4 (30.8%) had partial remission, and 3 (23.1%) patients had no remission at 24 months after diagnosis. The end point of ESKD or doubling of serum creatinine was reached by 1 patient. Three patients were lost to follow-up. Of those with complete or partial remission, 6 showed no relapses of nephrotic syndrome.

Table 1. Patients Basic Clinical Characteristics and Lab Values 6 Months After Diagnosis (Parameters Presented as Median and Interquartile Range Were Appropriate)

Characteristic	Patients Treated with CsA (N = 47)	Controls (N = 13)	*P*
Age (years)	58 (IQR: 46-68)	57 (IQR: 48.5-64.5)	ns
Sex (males/females)	33/14	9/4	ns
eGFR (MDRD mL/min/1.73 m^2)	68 (IQR: 55-88.25)	73.5 (IQR: 36-85.75)	ns
Serum creatinine (mg/dL)	1 (IQR: 0.9-1.3)	1 (IQR: 0.825-1.95)	ns
Urine protein (24-hour urine collection in mg)	6570 (IQR: 4290-10800)	6100 (IQR: 3825-7250)	ns
Follow-up (months)	92 (IQR: 57-129)	87 (IQR: 5.5-120.5)	ns
Proteinuria degree			
< 3500 mg/24 hours	1	1	ns
3500-8000 mg/24 hours	31	11	
> 8000 mg/24 hours	15	1	
Comorbidities			
Hypertension	26/21	8/5	ns
Microhematuria (yes/no)	3/44	5/8	.003
Macrohematuria (yes/no)	0/47	0/13	-

CsA, cyclosporine; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; ns, nonsignificant.

Table 2. Patients Clinical and Laboratory Data at the End of Follow-Up (Parameters Presented as Median and Interquartile Range Were Appropriate)

Characteristic	Patients Treated with CsA (N = 44)	Controls (N = 10)	*P*
eGFR (MDRD mL/min/1.73 m^2)	67.5 (IQR: 22.75-85)	80 (IQR: 66-96)	ns
Serum creatinine (mg/dL)	1.2 (IQR: 0.9-2.1)	0.9 (IQR: 0.8-1.1)	ns
Urine protein (24-hour urine collection in mg)	1790 (IQR: 239-5712)	640 (IQR: 307.3-3266)	ns
Remission (complete/partial/no)	12/13/19	2/6/2	ns
End-stage kidney disease or doubling of serum creatinine	12	1	ns

CsA, cyclosporine; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; ns, nonsignificant.

Kidney Function Progresses in Relation to the Degree of Proteinuria, Remission, and Relapses of Proteinuria.

The clinical outcome as expressed with the end point of ESKD or doubling of serum creatinine was not significantly altered in patients that received immunosuppressive treatment with CsA and methylprednisolone in comparison to patients that received no treatment. In fact, controls showed an estimate for clinical outcome development of 165.3 months (95% CI, 128.4-202.3), while those that received CsA had an estimate of 163.5 months (95% CI, 135.6-191.3, *P* = ns) (Figure 1).

In patients that received immunosuppressive treatment with CsA and methylprednisolone, clinical outcome was not significantly different among those with different degrees of proteinuria according to the most recent risk stratification of disease progression[5] (Figure 2). Accordingly, there was no difference in clinical outcome between those patients that presented at diagnosis with proteinuria less than 3500 mg in 24-hour urine collection and those with proteinuria between 3500 and 8000 mg/24 h or those with more than 8000 mg/24 h (log rank test, *P* = .252). Moreover, there was also no difference in clinical outcome according to the degree of proteinuria at the time of initiation of immunosuppressive treatment (log rank test, *P* = .252) (Figure 3).

Nevertheless, patients who showed either a complete or partial remission of nephrotic syndrome after treatment presented a better overall clinical outcome in comparison to those that had no remission. Those with complete remission showed an estimate median for the development of the clinical outcome of 204.6 months (95% CI, 173.4-235.9), while those with partial remission 193.5 months (95% CI, 190.6-196.4) and those with no remission only 73.6 months (95% CI, 36.2-110.9) (*P* < .001) (Figure 4).

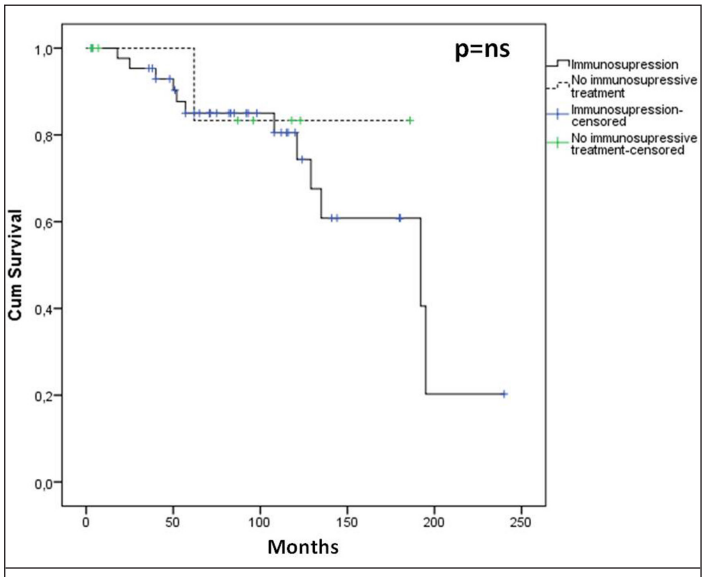

Figure 1. End-stage kidney disease or doubling of serum creatinine between patients that received immunosuppressive treatment with CsA and methylprednisolone in comparison to patients that received only conservative treatment.

Analysis for the development of the clinical outcome in patients who were treated with CsA and methylprednisolone showed no significant difference between those that had no relapses of nephrotic syndrome after treatment (median 177.6 months, 95% CI, 134.5-220.7) and those that experienced up to 3 relapses (median 188.3 months, 95% CI, 150.2-226.4). Nevertheless, kidney function preservation was significantly diminished in patients that showed no remission of nephrotic syndrome after treatment (log-rank Mantel–Cox test, $P < .001$) (Figure 5).

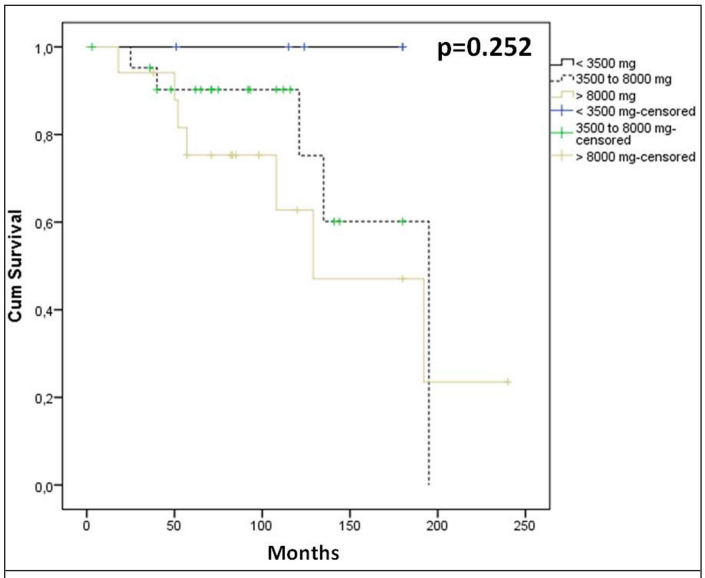

Figure 2. End-stage kidney disease or doubling of serum creatinine among those patients that received immunosuppressive treatment with CsA and methylprednisolone and different degrees of proteinuria at diagnosis.

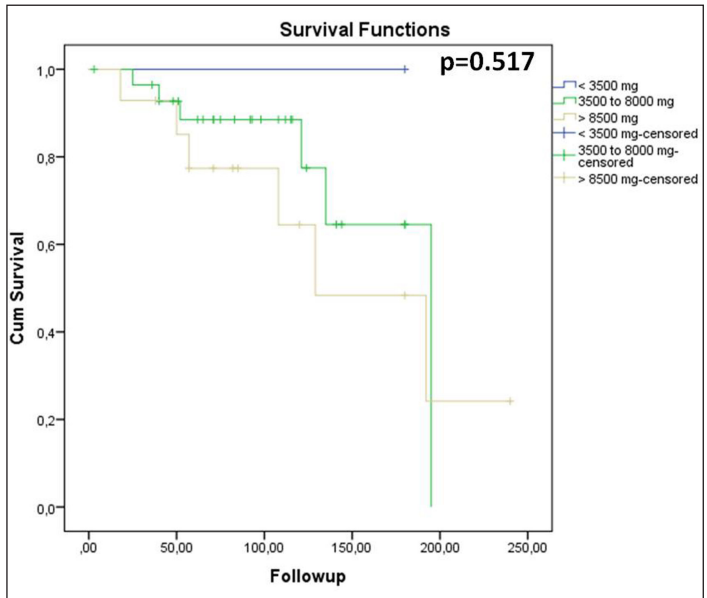

Figure 3. End-stage kidney disease or doubling of serum creatinine among those patients that received immunosuppressive treatment with CsA and methylprednisolone and different degrees of proteinuria at the point of initiation of treatment.

DISCUSSION

In this study, concerning the clinical course and treatment of patients with MN and long-term follow-up, we have shown that the combination of CsA and methylprednisolone is effective in achieving remission of nephrotic syndrome (complete and partial) in more than 70% of cases; nevertheless, this is not accompanied by a significant benefit in kidney function preservation in comparison to those that received no treatment. Furthermore, achieving a full or even partial remission of nephrotic syndrome,

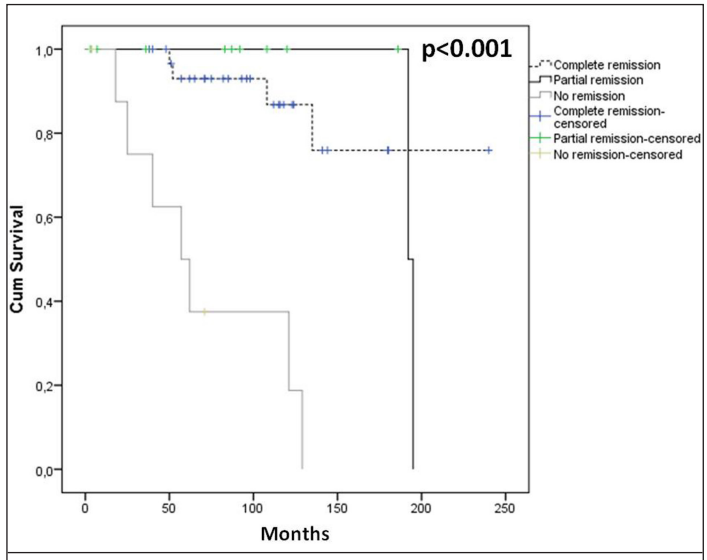

Figure 4. End-stage kidney disease or doubling of serum creatinine in patients that showed either a complete or partial remission of nephrotic syndrome after treatment in comparison to those that had no remission.

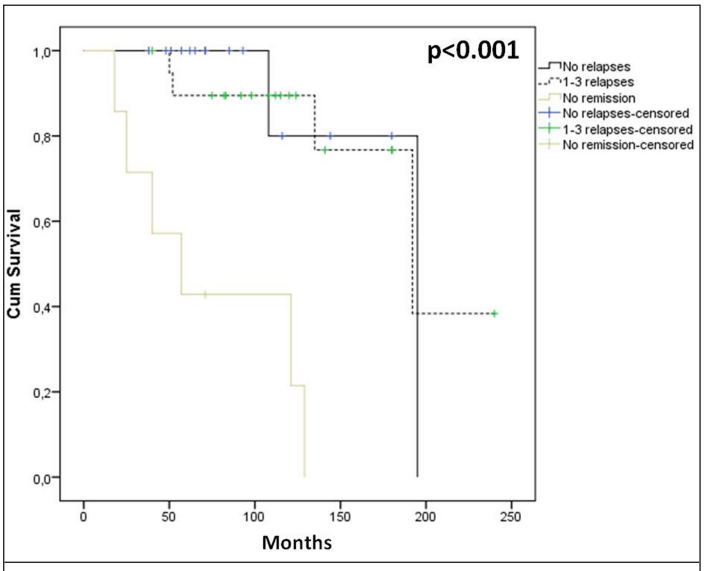

Figure 5. End-stage kidney disease or doubling of serum creatinine in patients who were treated with CsA and methylprednisolone and showed no relapses versus up to three relapses of nephrotic syndrome or no remission.

either with supportive or immunosuppressive treatment, is accompanied by significantly better overall kidney function preservation in comparison to no remission. Finally, relapses of nephrotic syndrome after treatment with CsA and methylprednisolone do not seem to alter the favorable effect of remission in terms of overall kidney function preservation.

Our results are in accordance with the findings of a large meta-analysis consisting of 6 studies and 202 patients. In this meta-analysis, there was no superiority concerning kidney survival for CsA, with or without corticosteroids, over no treatment or ACEi.[18] Moreover, in a UK randomized controlled trial with 108 patients who were assigned in 1 : 1 : 1 ratio to either prednisolone and chlorambucil, CsA, or supportive treatment alone, the primary outcome of 20% decline in kidney function from baseline was not different between those that received CsA or conservative treatment.[12] In our study, patients that received CsA showed no better kidney survival in comparison to those who received conservative treatment. These clinical findings are also in accordance with previous studies with repeat biopsies in patients with MN after treatment with CsA and methylprednisolone, which showed that this regimen does not attenuate disease progression or kidney scaring.[17,19] Interpreting our findings, one should take into account, that despite mean baseline 24-hour proteinuria at diagnosis, was not significantly higher in those who received CsA in comparison to those that received no treatment, the number of patients that had 24-hour proteinuria over 8000 mg at the time point of initiation of CsA was greater than the controls (15 vs. 1 patient). Nevertheless, when we examined the effect of CsA on different degrees of proteinuria and thus different groups of disease progression, we found no significant differences in kidney survival among those patients with baseline proteinuria or proteinuria at the time of immunosuppression initiation of less than 3500 mg/24 h, and those with proteinuria between 3500 and 8000 mg/24 h or those with more than 8000 mg/24 h. Based on this finding, we can assume that CsA effect on proteinuria is only mechanistic, with low or even no immunomodulating effect. Other agents that target B cells, such as rituximab, achieve durable suppression of circulating PLA2R-Abs, which in the case of calcineurin inhibitor use, tend to rebound after cessation.[20]

Concerning the remission of proteinuria (nephrotic or non-nephrotic syndrome), historical data show that one-third of patients with MN enter spontaneous remission.[21,22] Younger age, female sex, and medium- or lower-range proteinuria (< 8 g/24 h) are factors more commonly associated with this course. Nevertheless, these data are drawn from a prestandardized conservative treatment implementation era with renin–angiotensin–aldosterone system inhibitors (RAASi). More recent studies have clearly shown that RAAS inhibition with ACEi or ARBs is an independent predictor of spontaneous remission, especially in patients with proteinuria <8 g/24 h (but >3.5 g/24 h), which can reach 36% at 3 years after diagnosis.[6] Furthermore, MN resolves in a slow time frame, which features a partial remission at first, before complete remission which could cover even a 5-year time span.[5] In a study of 166 patients with idiopathic MN, an impressive 86.7% of those that were treated conservatively achieved remission. Nevertheless, this group of patients had lower disease severity than those treated with immunosuppression.[23] However, although RAASi is a cornerstone of conservative treatment, it is not expected to alter immune pathophysiological mechanisms in active disease with high anti-PLA2R titers. Therefore, patients who will probably benefit the most are either at an early non-nephrotic stage, or have progressed to advanced disease.[1] In our cohort, complete (3) or partial (4) remission of proteinuria was achieved in more than 50% of patients that received only conservative treatment with RAASi, but of those, only 1 had severe proteinuria (>8 g/24 h) and 1 had nonnephrotic range proteinuria at 6 months after diagnosis.

Remission of proteinuria, either partial or complete, immensely improves kidney function preservation. This was clearly shown in our study, where patients with proteinuria remission (complete and partial) after treatment with CsA had an estimated period of kidney function preservation of 173.4-235.9 months, while those with no remission had only 73.6 months. In a study of 128 patients with MN, achieving even partial remission was strongly associated with improved kidney survival.[24] Furthermore, Troyanov et al[25] reported that only 30% of those with no remission preserve kidney function, in comparison to 100% and >70% for patients with complete or partial remission, respectively. Finally, the favorable effects of remission in terms of kidney function preservation are seen independently, whether this is spontaneous or induced by immunosuppressive therapy.[5] In contrast, those with unresponsive-to-treatment nephrotic syndrome typically show overt kidney function deterioration.

Treatment with CsA and corticosteroids is highly effective for proteinuria remission in patients with idiopathic MN.[5] In early uncontrolled studies of this regimen, even at a low dose of CsA, a high rate of partial or complete remission (>84%) was achieved at 12 months.[26,27] In a retrospective study of 381 patients with MN who received CNIs (CsA or tacrolimus) as first-line treatment, 81% showed at 24 months complete or partial remission.[28] In the MENTOR trial, 52% of patients that were assigned to receive CsA had a complete or partial remission 12 months after the initiation of treatment.[13] The STARMEN trial, which used a more elaborate treatment scheme, randomly comparing patients that received either cyclical corticosteroid and cyclophosphamide for 6 months or sequential treatment with another CNI inhibitor (tacrolimus in a full dose for 6 months and tapering for another 3 months) and rituximab (1 gram at month 6), showed that patients who received tacrolimus had a complete or partial remission that reached only 44% at 6 months (attributed thus only to tacrolimus administration).[14] In our study, 78.7% of patients achieved complete or partial remission 24 months after the initiation of treatment with CsA, confirming previous results of the high response rate of this treatment option.

Relapse rate with the use of CNIs is high, either early on after treatment discontinuation or during dose tapering.[5] In our study, relapse rate was 52.6% at the end of follow-up. Nevertheless, the development of relapses did not significantly affect the clinical course of the disease. In fact, those patients that showed no proteinuria relapse after a 2-year course on CsA and methylprednisolone had no better kidney function preservation in comparison to those that showed frequent relapses. This is in accordance with previous studies. In a retrospective study of 95 patients with MN, where 38% received immunosuppression (either CsA or cyclophosphamide), relapse rate reached 48.2% in those treated with CsA, though relapses were not associated with an increased risk of ESKD or death.[29] In another retrospective study, of those patients treated with immunosuppression (mostly cyclophosphamide), the 10-year relapse rate was only 31%, and relapses did not seem to affect kidney function.[8] However, in a retrospective study of 128 patients with MN, relapse rate was associated with lower eGFR during follow-up and an increased risk of ESKD.[24] In that study, though, most patients received immunosuppressive treatment with cyclophosphamide. Accordingly, a study by Troyanov et al[25] reported that relapses worsened the slope of kidney function decline.

Limitations of our study include its retrospective design and lack of randomization in treatment administration. Although the number of patients that received treatment is adequate, the number of patients that served as controls is low. Nevertheless, the overall baseline clinical features of patients between those who received and those that did not receive immunosuppressive treatment were not significantly different. Thus, comparisons made could provide important information on the effectiveness and long-term value of immunosuppression with CsA in MN. Nevertheless, interpretation of these comparisons in relation to the control group should be made with caution. Finally, one of the strengths of our study is the long follow-up, which potentiates a reliable depiction of the course of MN either with or without treatment with CsA.

In conclusion, treatment of idiopathic MN with CsA and methylprednisolone combination offers a reliable option for proteinuria remission. Nevertheless, this option does not seem to alter the long-term disease progression, such as with alkylating agents and maybe B-cell-depleting agents.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of the University Hospital of Patras (Date: March 21, 2022, Number:0211).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.S.G.; Design – P.K., D.S.G.; Supervision – D.S.G.; Data Collection and/or Processing – M.P., A.M., P.P.; Analysis and/or interpretation – M.P., E.P.; Literature search – M.P., A.M.; Writing Manuscript – M.P.; Critical review – E.P., D.S.G.

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