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Calcineurin Inhibitors in Membranous Nephropathy

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See Clinical Research on Page 2653

Primary membranous nephropathy (MN) is a frequent cause of nephrotic syndrome in adults. The natural outcome of the disease is variable. Some subjects may enter spontaneous remission of proteinuria, while other patients show persistent proteinuria and slow progression to end-stage kidney disease. Patients with severe and unremitting nephrotic syndrome may also suffer from disabling and even life-threatening extrarenal complications, including thromboembolic events and cardiovascular disease. Proteinuria and kidney function can assess the risk of progression. Patients entering complete remission (<0.2 or <0.3 g per day with normal kidney function) can maintain stable kidney function in the long-term. Also, partial remission may predict a fair outcome, but relapses of nephrotic syndrome are frequent. The long-term outcome depends on the duration of remission and on the treatment used to obtain remission.

Management of primary MN has been a matter of debate. There is a general agreement on the use of symptomatic therapy (diuretics, blood pressure control, reduction of proteinuria with renin-angiotensin system inhibition, treatment of dyslipidemia, and, in select patients, anticoagulation); however, it is still discussed whether it is better to start "specific" therapy early, or to delay therapy until some "marker" predictive of a likely poor outcome develops. The choice of the type of therapy has also been a matter of discussion. Several drugs are now available for and have been evaluated in the treatment of MN. Glucocorticoids, alkylating agents, calcineurin inhibitors, and rituximab, have received the greatest attention.

In 2012, the Kidney Disease: Improving Global Outcomes guidelines recommended that initial therapy of MN consist of a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids, and oral alkylating agents (also called Ponticelli regimen). Calcineurin inhibitors (CNIs) were recommended as alternative regimens. The role of rituximab in patients resistant to both alkylating agent-based and CNI-based regimens remains undefined.[1] Several observational, nonrandomized, studies reported a high rate of remission (mainly partial) with the use of rituximab. Recently, substantial progress has been achieved owing to 3 head-to head randomized controlled trials that compared the effects of rituximab against CNI or Ponticelli regimen (Figure 1). The MENTOR trial assigned 130 patients with MN to receive cyclosporine for 12 months or rituximab, 2 infusions administered 14 days apart, to be repeated in case of partial response. There were no significant differences in the proportion of patients entering complete or partial remission with rituximab (35%) or cyclosporine (49%) at 6 months or at 12 months (60% and 52%, respectively), but at 24 months, 39 patients (60%) in the rituximab group and 13 (20%) in the cyclosporine group had a complete or partial remission ($P < 0.001$), owing to the high number of relapses after cyclosporin discontinuation. Serious adverse events occurred in 11 patients (17%) in the rituximab group and in 20 (31%) in the cyclosporine group. Among patients in remission who tested positive for anti–phospholipase A2 receptor antibodies, the decline in autoantibodies was faster and of greater magnitude and duration in the rituximab group than in the cyclosporine group.[2] In 86 adults with MN and nephrotic proteinuria, the STARMEN trial compared the regimen with corticosteroids alternating monthly with cyclophosphamide for 6 months to low-dose tacrolimus (0.05 mg/kg per day for 6 months and tapering for another 3 months) plus 1 g of rituximab at month 6. At 2 years, complete or partial remission occurred in 84% of

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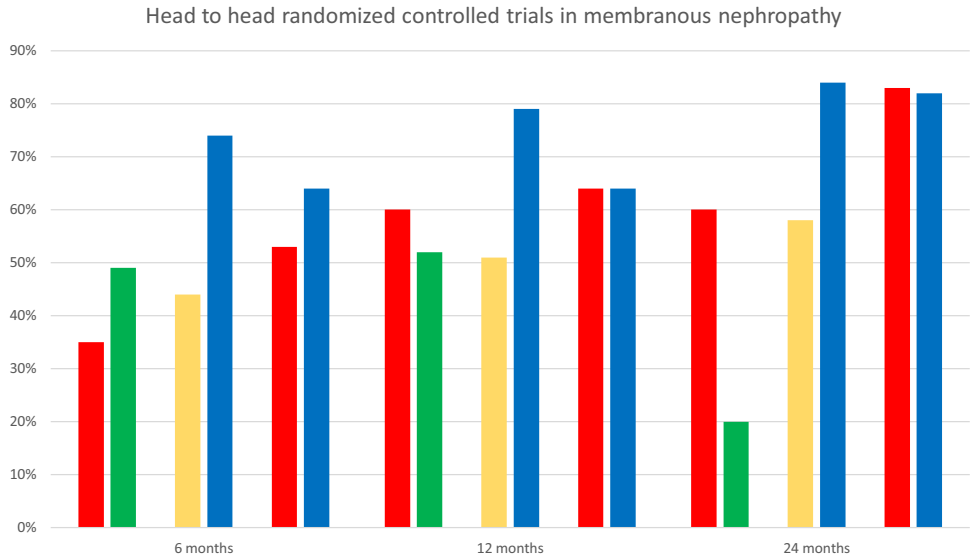

Figure 1. Complete and partial remissions in 3 different head-to-head randomized controlled trials. Results at 6, 12, and 24 months. The first 2 columns indicate the MENTOR trial (in red rituximab, in green cyclosporine). The second 2 columns indicate the STARMEN trial (in yellow tacrolimus plus rituximab, in blue cyclic regimen). The last 2 columns indicate the RYCYCLO trial (in red rituximab, in blue the cyclic therapy).

patients in the corticosteroid-cyclophosphamide group (complete remission in 60%) and in 58% in the tacrolimus-rituximab group (complete remission in 26%). In contrast with MENTOR, relapses of nephrotic proteinuria occurred in only 3 patients (12%) in the tacrolimus-rituximab group, versus 1 patient (2.7%) in the corticosteroid-cyclophosphamide group. Serious adverse events were similar in the 2 groups.[3] The RI-CYCLO trial assigned 74 adults with MN and proteinuria >3.5 g per day to receive the Ponticelli cyclic regimen for 6 months or 1 g rituximab on days 1 and 15. Complete remission at 12 months was higher in the cyclic regimen arm than in rituximab (32% and 16%, respectively). At 2 years, the probabilities of complete or partial remission were 43% and 82%, respectively, with the cyclic regimen, versus 42% and 83%, respectively, with rituximab. Serious adverse events occurred in 19% of patients receiving rituximab and in 14% receiving the cyclic regimen.[4]

According to these randomized controlled trials, CNIs would achieve fewer complete clinical remissions and would be less likely to maintain remission in comparison with rituximab or the cyclic therapy. In addition, the MENTOR data reported that a decline in kidney function during follow-up is more likely with cyclosporine; however, these trials cannot be considered conclusive.

An important issue is represented by the short-term follow-up. In no case did the follow-up exceed 2 years, too short a period to evaluate the safety and efficacy of a treatment in a disease characterized by slow progression. Moreover, in the MENTOR and STARMEN trials, the period of administration of CNIs was too short to assess their efficacy on the outcome of MN.

The first issue has been faced by Ramachandran et al.[5] In that not protocolized trial, the authors updated at 6 years the results of a randomized trial in which 70 patients with MN and nephrotic proteinuria resistant to antiproteinuric therapy were assigned to cyclic therapy with corticosteroids and cyclophosphamide for 6 months (modified Ponticelli regimen) or tacrolimus for 1 year, plus prednisone, 0.5 mg/kg per day, for 6 months. At the end of 6 years, 21 (62%) participants in the modified Ponticelli regimen and 9 (28%) in the tacrolimus group maintained relapse-free remission (relative risk 2.19), and 30 (88%) patients in Ponticelli regimen versus 17 (53%) patients in tacrolimus were in remission (relative risk 1.66). Both groups often had relapses (9 patients in cyclic terapy vs. 16 in tacrolimus). None of patients treated with the modified Ponticelli regimen reported a solid organ or hematologic malignancy. This study confirmed the long-term superiority of a 6-month cyclical therapy over 1 year of tacrolimus.

The other issue is represented by the short period of CNI administration. In the MENTOR trial, cyclosporine was given for only 1 year and in the STARMEN trial, tacrolimus was administered for approximately 9 months. The current experience with the use of CNIs in glomerular diseases shows that early relapses of proteinuria are frequent after withdrawal of CNI. A possible option to reduce relapses may consist of the administration of rituximab. This dug was evaluated in the STARMEN trial, in which a single dose of rituximab was administered just

at the start of tacrolimus tapering, and the number of relapses was relatively low (12%). Encouraging results with the combination cyclosporin-rituximab also have been reported.[6] Alternatively, patients with MN who achieved remission should continue treatment with smaller doses of tacrolimus or cyclosporine to prevent the deleterious consequences of persistent nephrotic syndrome. Some nephrologists are reluctant to use CNI for prolonged periods, being afraid of kidney toxicity. The risk of CNI-related nephrotoxicity is usually dose-dependent, and can be prevented by using low doses and monitoring kidney function. A single center reported that the use of cyclosporine for 20 years does not cause progressive increase in serum creatinine if kidney transplant recipients are carefully monitored during the follow-up.[7] A retrospective analysis of the clinical courses of more than 4000 cyclosporine-treated kidney allograft recipients followed from 1 to 10 years did not demonstrate any differences in the long-term rate of attrition of graft function between cyclosporine- and non–cyclosporine-treated patients.[8] Theoretically, patients can remain on CNI as long as the drug is providing some benefit and there are no adverse side effects.

To remain on the safe side, we recommend selecting patients before administering CNI. Patients with severe hypertension and kidney insufficiency are not good candidates for CNI. Serum creatinine and blood pressure should be monitored every 7 to 10 days in the early period and at least every month after 4 weeks. If serum creatinine increases >30% over the baseline, the doses of CNI should be reduced; if no improvement is obtained, a kidney biopsy may be considered to check for histological evidence of nephrotoxicity. CNI should be given at the smallest effective dose for at least 6 months. If proteinuria is not reduced by 50% by the end of this time frame, an alternate therapy should be considered, although in some cases the response may occur later. Treatment targets should include complete or partial remission of proteinuria, maintenance of stable estimated glomerular filtration rate (not more than 30% of pretreatment level), avoiding hypertension. Measuring CNI blood levels, although recommended by the manufacturing companies, is not strictly necessary. The relevance of therapeutic blood monitoring is limited by the large intra- and interpatient variability, which severely limits the accuracy of pharmacokinetic models and bioavailability estimates. On the other hand, CNI blood levels do not reflect their intracellular (i.e., pharmacologically active) concentrations. At any rate, some random check may be useful to verify that the patient is really assuming the prescribed CNI.

In summary, the available data suggest that the initial treatment in MN should rest on cyclic therapy or rituximab. The cyclic regimen might be preferred, being associated with earlier complete remissions. However, although not substantiated by a long-term trial,[9] concern remains that cyclophosphamide may be associated with disquieting adverse events, including gonadal toxicity, infection, and neoplasia. Thus, some nephrologists feel that a cyclophosphamide-based approach should be limited to patients with disabling or life-threatening nephrotic syndrome or progressive loss of kidney function. Prolonged use of low-dose CNI is still important in managing nephrotic patients with contraindications or resistance to cyclical regimen or rituximab. In patients who respond, CNI should be tapered off very gradually to prevent relapse. On the other hand, the combination of rituximab and CNI could be effective both to speed proteinuria decrease and to avoid relapses after CNI discontinuation. The role in MN of new CNI, such as voclosporin, require adequately powered placebo-controlled trials.

DISCLOSURES

All the authors declared no competing interests.

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