

New Treatments for Idiopathic Membranous Nephropathy

By Claudio Ponticelli

The treatment of idiopathic membranous nephropathy (IMN) has been a matter of discussion for many years. Given the variable clinical course and potential toxicity of current regimens, the main issue nephrologists face at the moment are who to treat and with what regimen. Conservative management is justified for patients with subnephrotic proteinuria, inasmuch as spontaneous remission occurs more frequently in these patients, and their long-term prognosis is usually excellent.

By contrast, patients with nephrotic syndrome (NS) may show a progression to ESRD and are more frequently affected by any of several extrarenal complications. Thus, initiation of specific therapy is indicated for patients with declining renal function or full-blown NS (1). The guidelines of Kidney Disease: Improving Global Outcome (KDIGO) recommend a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids, and oral alkylating agents. The continuous use of alkylating agents may also be effective but is associated with a greater risk of severe adverse events. Cyclosporine or tacrolimus have been suggested as alternative options in nonresponders or in patients who do not tolerate treatment with steroids and cytotoxic drugs (2).

In the past few years, the discovery that most patients with IMN have circulating antibodies directed against the M-type phospholipase A2 receptor provided important insights into the mechanistic interpretation of IMN (3). Further studies confirmed that this receptor represents the main antigen involved, although other podocyte antigens may also play a role in the pathogenesis of this disease.

In the same period of time, new drugs have been used for IMN, three of which show a potential beneficial effect: mycophenolate mofetil (MMF), adrenocorticotropic hormone (ACTH), and rituximab.

Mycophenolate mofetil

Retrospective studies and three small randomized controlled trials (RCTs) evaluated the effects of MMF in IMN. Only a small rate of remission was reported by observational studies when MMF was used as monotherapy, and negative results were reported by a French trial. That trial randomized 36 patients to either MMF alone (2 g per day for 12 months) or symptomatic therapy, and the rates of remission were similar (4). Still, a response in about two-thirds of patients (predominantly partial remission) was reported by a retrospective study in which MMF was combined with oral prednisone and methylprednisolone pulses. However, patients with NS frequently experienced relapse after treatment was interrupted (5). Two small RCTs with short-term follow-up reported remissions in about 70 percent of patients treated with MMF and steroids—a rate similar to that observed in patients assigned to a steroid/cytotoxic drug regimen (6, 7).

These data are insufficient to enable any firm conclusion to be drawn. Trials with adequate sample size and follow-up are needed to better clarify the efficacy and safety of MMF with corticosteroids in IMN. At present, this therapy may be considered for patients who do not respond to other treatments. To prevent relapses, this therapy should be given for at least 1 year if well tolerated.

Adrenocorticotropic hormone

Berg et al. (8) first showed that prolonged administration of synthetic ACTH (Synacthen) could obtain remission in patients with IMN and NS. A small RCT compared a 12-month course of Synacthen, 1 mg twice a week for 1 year, with a 6-month regimen based on steroids alternated with a cytotoxic drug every month. After a mean follow-up time of 23 months, no difference in the rate of remission or in the mean decline in proteinuria was seen between the groups (9). In an observational study, natural ACTH (Acthar gel), given at a dose of 80 units subcutaneously twice a week for 6 months, was used in 11 patients with IMN and NS. Three complete remissions and six partial remissions were observed (10). No relevant side effects have been reported in patients treated with synthetic or natural ACTH, but it should be taken into account that prolonged treatment may be complicated by diabetes, osteoporosis, or hypertension.

The available small studies suggest a potential role for ACTH in IMN. Yet, synthetic ACTH is no longer commercially available, whereas natural ACTH is burdened by an excessively high cost. Given that the mechanism of action of ACTH is related to the stimulation of melanocortin receptors (11), it is possible that less expensive and more specific synthetic melanocortin receptor agonists will be developed in the near future.

Rituximab

Recently, Ruggenti et al. (12) reported their cumulative experience with rituximab in 100 patients with MN. After a mean follow-up time of 29 months, 27 patients showed complete remission and 38 partial remission, the median time to response being around 7 months. The response to treatment did not change whether rituximab was used in treatment-naïve patients or in patients previously treated with ineffective regimens. No severe side effects were reported. However, 4 patients died, cancer developed in 3, and progression to ESRD occurred in 4. The authors attributed these events to previous treatment, but a direct or indirect role of rituximab cannot be excluded. Good results have also been reported in other observational studies. In a multicenter study of 20 patients treated with four weekly courses of rituximab repeated after 6 months, 2 patients did not respond, 4 entered complete remission, 12 underwent partial remission, 1 patient had limited response, and 1 experienced relapse. No severe adverse events were reported (13).

From the available reports it can be extrapolated that 65 percent to 80 percent of patients may have a complete or partial (more frequent) response to rituximab. However, apart from the high cost, the optimal dose, timing, and duration of re-treatment and the long-term benefit-to-harm ratio of rituximab remain incompletely explored. It is also unclear whether patients with renal dysfunction, tubulointerstitial lesions, or both will be sensitive or resistant to such treatment.

Summary and conclusions

At present, there are at least five different options for treating nephrotic patients with IMN. Therapies based on cycling cytotoxic agents/steroid administration or

calcineurin inhibitors have been tested by RCTs, meta-analyses, and retrospective clinical studies to assess their effectiveness and safety profile. It is more difficult to determine the role of new treatments in IMN in the absence of rigorous studies and long-term follow-up times.

MMF associated with corticosteroids might be an alternative therapy in patients with contraindications or poor response to cytotoxic therapy. However, solid studies are required to confirm the efficacy of this association and to indicate the optimal dosage and duration of therapy.

The mechanism of action of ACTH is completely different from that of immunosuppressive agents. Only a few small studies have been conducted with ACTH. The results are interesting, but Synacthen has been retired, and the exceedingly high cost of gel ACTH may impede further development of this treatment in IMN.

The results with rituximab are impressive. However, as discussed above, more answers are needed. Trials comparing the efficacy and toxicity of rituximab with regimens based on cytotoxic/steroid administration will be welcome. The decision on whom, when, and how to treat is completely up to each clinician. However, it should be kept in mind that whatever the treatment, an early response is seldom observed. In many cases, remission can develop months or even years after the therapy has been completed. ●

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Pregnancy in Women with Glomerular and other Chronic Kidney Disease and the Need for International Collaboration

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Patients with kidney disease are at increased maternal and fetal risk during pregnancy. In particular, glomerular-based kidney disease is overrepresented among younger patient populations and is therefore a common form of kidney disease that requires management during pregnancy. Potential untoward outcomes include progression of underlying renal dysfunction, worsening of urine protein excretion and hypertension, and untoward fetal outcomes including intrauterine growth restriction and preterm delivery. However, prognostication of an individual woman's pregnancy-associated risk in the setting of chronic kidney disease (CKD) remains profoundly challenging, especially in the context of glomerular-based kidney disease, wherein there is often a combination of different degrees of renal insufficiency, proteinuria, and hypertension. Most studies to date are too small to account for the potential differential impact of these important factors on pregnancy outcome, leaving the clinician to approximate risk for one of a young woman's most important life decisions, wherein a bad outcome can have a profound impact on both her long-term health and that of her child. Because the literature provides limited guidance, divergent opinions arise with respect to the impact of kidney disease on future CKD progression and on pregnancy outcomes.

Early studies generally used serum creatinine level to stratify pregnancy risk based on the following thresholds: mild (≤ 123 $\mu\text{mol/L}$ [1.4 mg/dL]), moderate (124–220 $\mu\text{mol/L}$ [1.4 to <2.5 mg/dL]) and severe (≥ 220 $\mu\text{mol/L}$ [2.5 mg/dL]) renal insufficiency. It has been well in excess of a decade since Jones and Hayslett published their classic report in the *New England Journal of Medicine* noting that women with advanced stages of CKD are at risk for loss of kidney function and compromised pregnancy outcomes (1). In this report of 67 women and 82 pregnancies, pregnancy-related loss of kidney function was noted in 43 percent of pregnancies, with 10 percent of women rapidly experiencing progression toward ESRD. Of interest, not all the accelerated loss occurred in patients with the most severe renal compromise, inasmuch as progression to ESRD was also noted in 3 of 9 patients with moderate renal insufficiency—a proportion similar to that in the severe renal insufficiency group. A significant limitation of this study was its reliance on serum creatinine as a marker of renal function, which is too imprecise to stratify women before pregnancy because it does not take into account patient size and muscle mass. Furthermore, in young women, serum creatinine is often inadequately reflective of the actual degree of histologic renal damage. Finally, no adjustments were made for either the degree of urine protein or the presence of hypertension.

Subsequent studies have therefore used the Modification of Diet in Renal Disease formula to classify preconception renal insufficiency. In a more recent study, which excluded women with diabetes or lupus, 49 women with stage 3–5 CKD were divided into four groups based on preconception estimated GFR (eGFR) (≥ 40 or <40 mL/

min/1.73 m²) and proteinuria (≥ 1 or <1 g/24 h) (2). In women with eGFR 40 mL/min/1.73 m² or higher, there was no difference in the rate of eGFR decline up to 1 year after pregnancy, irrespective of preconception proteinuria. By contrast, among women with eGFR below 40 mL/min/1.73 m², the rate of eGFR decline was increased in those with proteinuria 1 g/24 h or higher (2). Although the findings that relate proteinuria and severe renal disease to reductions in eGFR confirm the earlier literature, the absence of any eGFR reduction in the ≥ 40 mL/min/1.73 m² group warrants further scrutiny because only 6 women were included in this group with more moderate disease. Furthermore, a recent study that stratified women using the Chronic Kidney Disease Epidemiology Collaboration equation demonstrated that more than 10 percent of patients with stage 2 CKD experienced at least a 25 percent increase in serum creatinine during pregnancy or shortly after delivery (3). Whether this change in renal function was transient was not clear from this study because follow-up data beyond 6 weeks postpartum were not provided.

With respect to fetal and maternal well-being, underlying kidney disease also predisposes to poor outcomes. In a large study of 640 women with stage 1 CKD with hypertension, the odds ratio for pre-eclampsia, small-for-gestational age, or preterm births was significantly elevated and increased with the degree of renal insufficiency (odds ratio = 10.09, 95 percent confidence interval 2.38–42.87, and odds ratio = 2.58, 95 percent confidence interval 1.40–4.75 in women with an eGFR of 60–74 and 75–89 mL/min, respectively) (4). Although microalbuminuria was not noted to increase the odds of the aforementioned maternal or fetal outcomes, none of the patients within this study had macroalbuminuria. As such, the effect of higher levels of urinary protein on pregnancy outcomes could not be examined. Finally, a recent meta-analysis of CKD and pregnancy demonstrated an overall risk of adverse maternal and fetal events that was at least fivefold and twofold higher, respectively, than in the general population (5). However, the poor methodologic quality of the studies included in the review was cited as a major limitation regarding this estimate (5).

Among the few definitive conclusions that can be made about CKD and pregnancy is that risk increases with the degree of renal dysfunction and is further heightened by comorbid conditions like hypertension. Typically, mild kidney disease (CKD stage 1) does not result in a progression of renal dysfunction, but it may still contribute to poor placental implantation and adverse maternal and fetal outcomes. Severe renal insufficiency (CKD stage 4–5), by contrast, frequently compromises maternal and fetal well-being. Pregnancy outcomes in the intermediate CKD stages require further clarification and disease-specific variations, accounting for different diseases, degrees of proteinuria, and even degrees of renal damage. Prior reports of lupus-associated and diabetic nephropathy having worse outcomes than other glomerular diseases should be tested. Because of the heterogeneity and poor meth-

odologic quality of the existing literature, an overall risk estimate is currently difficult to generate. Well-designed studies with adequate numbers of participants are needed to clarify the pregnancy-associated risk faced by women with underlying CKD, and this is likely to require several centers working together to generate the information desperately required to assist the vast majority of young women with kidney disease in making adequately informed pregnancy decisions. ●

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