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Rituximab Is Preferable to Cyclophosphamide for Treatment of Membranous Nephropathy: COMMENTARY

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The best approach when treating patients with membranous nephropathy (MN) has been an ongoing debate. Most experts agree that in patients who are at increased risk of progression to ESKD, immunosuppression is required. Who are these patients at increased risk, and which immunosuppression should we use? The answer to the first question is not straightforward. We currently use a combination of starting eGFR, stability of eGFR, degree of proteinuria, complications from nephrotic syndrome, Phospholipase A2 receptor (PLA2R) antibodies levels, and their trajectory as ways of estimating risk of progression (1). This approach is neither systematic nor universal. Indeed, this lack of a systematic approach has resulted in including patients with lower risk of progression in clinical trials, especially when assessing efficacy of an immunosuppressive drug versus conservative measures.

The answer to the second question is that it depends! Who is the patient we are talking about? Is the patient a woman in reproductive age with somewhat preserved eGFR and nephrotic syndrome? Or is the patient an older man with recent rapid decline of eGFR and PLA2R Ab titer of 1200 RU/ml? These nuances will and should affect our management. We cannot have a one-size-fits-all approach to patients with MN. Perhaps we as the moderators of this debate have the easier job of addressing these nuances rather than "picking a side."

Oliva-Damaso *et al.* (2) and van de Logt *et al.* (3) both lay out convincing evidence on the effectiveness of their chosen therapy (4–7). What is not clear from what has been outlined by van de Logt *et al.* (3) is the presence of solid evidence to suggest effectiveness of cyclophosphamide long term but lack of such evidence in patients treated with rituximab. The data on long-term outcomes of cyclophosphamide are on the basis of a limited number of patients. In the study by Jha *et al.* (8) that evaluated the long-term outcome in a prospective manner in patients treated with cyclophosphamide, there were only 53 patients in the study, and of those, only 46 had follow-up at by 10 years. Most importantly, in the study by van den Brand *et al.* (9) that compared outcomes of patients treated with cyclophosphamide with those of patients who were treated with rituximab in the same cohort (median follow-up of over 3 years), the rate of renal failure between the two groups was similar. In addition, it has been argued that the attributable efficacy rate of rituximab at 2 years on the basis of the MENTOR study was low (50%). It may appear that the attributable efficacy rate of cyclophosphamide on the basis of the study by Jha *et al.* (8) was higher at 64%. However, we should remember that the comparison group in the MENTOR trial was cyclosporin (which is effective in treatment of MN) and that the comparison group in the study by Jha *et al.* (8) was conservative management (10). Therefore, it would be misleading to compare attributable efficacy rate between studies when control groups are different. Moreover, the conservative group did not receive RAAS blockade for the first 24 months, which can result in overestimating the effectiveness of cyclophosphamide.

There are only two studies that have directly compared the effectiveness of rituximab with cyclophosphamide in the same trial—a prospective trial by Scolari *et al.* (11) (the RI-CYCLO trial) and a retrospective study by van den Brand *et al.* (9). The STARMEN trial has been interpreted by some as a trial to directly compare cyclophosphamide with rituximab. This interpretation in our opinion is incorrect. One arm in the study used the Ponticelli regimen. The other arm used 6 months of a calcineurin inhibitor (which is known to be inferior to rituximab) and only a one-time dose of rituximab at 6 months, and then, data were interpreted at 24 months. The combination of a drug inferior to rituximab with an inadequate dose of rituximab would be bound to have a lower response rate. In addition, as pointed out by Oliva-Damaso *et al.* (2), the patients in the tacrolimus/rituximab group had higher PLA2R antibody titers, which can make the tacrolimus/rituximab arm appear less effective. Thus far, the only prospective study to directly compare rituximab with cyclophosphamide has been the RI-CYCLO trial. This was an open-label, randomized, controlled trial that included 74 patients (37 in each groups). Patients received either rituximab (1 g two times) or the Ponticelli regimen (11). Unlike the MENTOR trial, rituximab was not repeated at 6 months regardless of the change in proteinuria. At 12

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months, 16% in rituximab group versus 32% in cyclophosphamide group achieved complete remission (CR; odds ratio [OR], 0.4; 95% confidence interval [95% CI], 0.13 to 1.23). The rates of CR or partial remission (PR) at 12 months were also similar in rituximab and cyclophosphamide groups (62% versus 73%; OR, 0.61; 95% CI, 0.23 to 1.23) and at 24 months (85% versus 81%; OR, 1.32; 95% CI, 0.33 to 5.29). Even though there was no statistically significant difference in the remission rate at 12 months (likely due to lack of power), the cyclophosphamide group had twice as many remissions compared with the rituximab group. This difference between the two groups, however, completely disappeared by 24 months, and the number of patients in remission increased significantly. This highlights several important points: (*1*) assessing proteinuria early to gauge the effectiveness of a given drug in trials of MN is inappropriate, (*2*) cyclophosphamide can likely induce remission faster than rituximab, and (*3*) two doses of rituximab alone may not be enough to treat a patient with PLA2R-positive MN. Since recognition of PLA2R antibodies (and other antibodies alike) (12), the goal should be to achieve immunologic remission (a point highlighted by Oliva-Damaso *et al.* [2]). Therefore, if by 6 months, patients still have positive PLA2R antibodies, they need to receive additional doses of rituximab. Indeed, if the same approach as the MENTOR trial was applied to the RI-CYLCO trial, at minimum 16 patients (43% of the rituximab group) would have received additional doses of rituximab (11,13). This approach unfortunately cannot be easily implemented in a clinical trial setting. However, lack of adequate dosing should not be interpreted as lack of effectiveness.

As noted above, van den Brand *et al.* (9) compared the effectiveness of rituximab and cyclophosphamide in a retrospective cohort with a median follow-up of 40 months. The combined end point of doubling of serum creatinine, ESKD, and death from any cause was no different between the two group. The rates of CR were also similar. However, there were higher rates of PR in cyclophosphamide group. However, 70% of the patients in the rituximab group received only a one-time dose of 375 mg/m^2 (perhaps lower than any studies ever done in MN). However, when evaluating the 30% of patients in the rituximab group who received four doses (375 mg/m^2), the PR rate was similar to the cyclophosphamide group, which again highlights the importance of adequate dosing.

Ultimately, as nephrologists we do not doubt the effectiveness of cyclophosphamide, but what we fear are the side effects. We cannot rely on clinical trial data from three decades ago to provide us solace that the true toxicity of cyclophosphamide is low. Ponticelli *et al.* reported only a handful of side effects with use of cyclophosphamide and prednisone. This low rate of side effects is unheard of and perhaps is more a reflection of less stringent reporting in the past than true low rate of toxicity. The short-term toxicity, which includes serious infections and pancytopenia, can certainly be managed with close monitoring of the patient, dose reduction, and/or temporary withdrawal as noted by van de Logt *et al.* (3). However, the key words here are "close monitoring," which at minimum requires once every other week CBC checks. This type of follow-up can be achieved easier when the patient is in a clinical trial, but in real practice, it requires commitment from both the patient and most importantly, the physician. This point was illustrated by van den Brand *et al.* (14) who showed that in their retrospective cohort (outside of a clinical trial), the rates of serious adverse events, including fatal events, were significantly higher in the cyclophosphamide group. There were a total of nine deaths in the cyclophosphamide group, and five were directly attributed to cyclophosphamide (infections and malignancies); there were four deaths in the rituximab group, and none were attributed to rituximab. Similarly, the nonserious adverse events were significantly higher in the cyclophosphamide group (127 events) versus in the rituximab group (52 events). The side effects included myelotoxicity, infections, steroid-induced hyperglycemia, and malignancies (9). The side effect related to steroid use is one that is less commonly talked about but can be serious. The side effect of malignancy is one that may not be captured during a clinical trial due to short-term follow-up. In another study by van den Brand *et al.* (14) in which the outcomes of 127 patients with MN treated with cyclophosphamide were evaluated, the adjusted incidence of malignancy was three times increased in the cyclophosphamide group compared with the noncyclophosphamide group at a median follow-up of 6 years (14).

Another side effect of concern is infertility in women of childbearing age. The infertility is dependent on the cumulative dose of cyclophosphamide and can occur when exposure is up to 10 g as noted by van de Logt *et al.* (3). Therefore, in a 70-kg woman who receives cyclophosphamide at a dose of 2.5 mg/kg per day for total of 100 days, the exposure will be achieved in <60 days. This side effect can be devastating for the patient. Indeed, in the STARMEN trial, the mean average cyclophosphamide dose was 10.3 g (15). One also needs to consider that MN can and does relapse in up to 50% of patients (16). In PLA2R-positive MN, the early signs of relapse can be detected by re-emergence of the antibody in the circulation. What should these patients be treated with next? Another course of cyclophosphamide? Some patients may have more than one relapse. How many courses of cyclophosphamide are acceptable? The modified Ponticelli regimen is fixed and hard to redose due to risk of toxicity, which makes it difficult to tailor it to the patients on the basis of their response and changes in their PLA2R antibody titer, whereas rituximab allows for a more individualized approach. Another commonly noted concern with rituximab is its cost and coverage by insurance. However, an economic analysis from the United Kingdom suggests that rituximab is a potentially more cost-effective treatment than cyclophosphamide (17).

When might we consider use of cyclophosphamide? As noted above, cyclophosphamide likely does act quicker than rituximab , and therefore, in a patient who is losing kidney function fast, a drug that can treat the disease faster would be more advantageous. In addition, there are data to suggest that in patients with high PLA2R antibody titers, rituximab may be less effective in lowering the antibody titers (18). In these patients, cyclophosphamide may be preferred. We should point out, however, that when these patients with high PLA2R titers were retreated with rituximab, they did respond (19). In addition, there are now

Table 1. Pros and cons of cyclophosphamide and rituximab in treating membranous nephropathy

Agents	Pros	Cons
Cyclophosphamide	In use for several decades and familiar to most nephrologists	Significant toxicity: myelotoxicity, infertility, and malignancy (cumulative dose dependent)
	More readily available, particularly in developing countries	Steroid side effects: Cushing syndrome, uncontrolled diabetes, infections, poor wound healing, mood problems
	Established efficacy in several randomized, controlled trials	Need for frequent laboratory monitoring
	May be more effective in patients with high PLA2R antibodies titer	Fixed regimen that cannot be tailored to the patient's need
	May achieve remission faster	
Rituximab	Established efficacy in several randomized, controlled trials	May achieve remission slower than cyclophosphamide
	Intravenous dosing, which may improve adherence	Requires redosing
	Favorable side effect profile and good tolerability	Infusion-related reactions
	Avoid exposure to high-dose steroid	Insurance coverage
	Can be tailored on the basis of antibody titers and allows for an individualized approach	
	Better option for patients of childbearing ages due to absence of reproductive toxicity	

PLA2R, phospholipase A2 receptor.

more potent anti-CD20 drugs (such as obinutuzumab) available that have been shown to be effective in patients with rituximab-resistant PLA2R-positive MN (20). The use of the newer anti-CD20 agents should be explored in the future in patients with high PLA2R antibody titers. The pros and cons of rituximab versus cyclophosphamide are shown in Table 1.

In summary, if "primum non nocere" or "first, do no harm" is what we always uphold while doing our due diligence to deliver the best care possible for our patients, rituximab would be our preferred choice in treatment of patients with MN.

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Author Contributions

N. Klomjit and L. Zand conceptualized the study, were responsible for data curation, wrote the original draft, and reviewed and edited the manuscript; N. Klomjit was responsible for software and visualization; and L. Zand provided supervision.

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