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 end stage kidney disease (ESKD), immunosuppression is required. But who are the patients that are at increased risk and which immunosuppression should we use? The answer to the first question is not straight forward. We currently use a combination of starting eGFR, stability of eGFR, degree of proteinuria, complications from nephrotic syndrome, PLA2R antibodies levels and their trajectory as ways of estimating risk of progression. This approach is neither systematic nor universal. Indeed, this lack of 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: it depends! Who is the patient that we are talking about? Is the patient a female in their reproductive age with somewhat preserved eGFR and nephrotic syndrome? Or is the patient an older male 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”.

Bomback et. al and Wetzel et. al both lay out convincing evidence on the effectiveness of their chosen therapy. What is less clear from what has been outlined by Wetzel et. al, 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 outcome of cyclophosphamide are based on limited number of patients. In the study by Jha et. al 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. that compared outcomes of patients treated with cyclophosphamide to those 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 were similar. In addition, it has been argued that the attributable efficacy rate of rituximab at 2 years based on the MENTOR study was low (50%). It may appear that the attributable efficacy rate of cyclophosphamide based on the study by Jha et al. 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 the comparison group in the study by Jha et. al. was conservative management. 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 over-estimating the effectiveness of cyclophosphamide.

There are only two studies that have directly compared the effectiveness of rituximab to cyclophosphamide in the same trial. A prospective trial by Scolari et.al (the RI-CYCLO trial) and a retrospective study by van der Brand et. al. 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 while the other 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 was 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 by
Bomback et al. the patients in the tacrolimus/rituximab group had higher PLA2R antibody titer 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 either received rituximab (1 gram x2) or the Ponticelli regimen. Unlike the MENTOR trial, rituximab was not repeated at 6 months regardless of the change in proteinuria. At 12 months, 16% in rituximab group versus 32% in cyclophosphamide group achieved complete remission (CR) (OR 0.4, 95% CI 0.13-1.23). The rate of complete or partial remission (PR) at 12 months were also similar in rituximab and cyclophosphamide group (62% vs 73%, OR 0.61 (95% CI 0.23-1.23)) and at 24 months (85% vs 81%, OR 1.32 (0.33-5.29)). 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 to 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, 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) the goal should be to achieve immunological remission (a point highlighted by Bomback et al.). Therefore, if by 6 months a patient still has positive PLA2R antibodies, they need to receive additional doses of rituximab. Indeed, if the same approach as MENTOR trial was applied to RI-CYCLO trial, at minimum 16 patients (43% of the rituximab group) would have received additional doses of rituximab. This approach unfortunately cannot be easily implemented in a clinical trial setting. But lack of adequate dosing should not be interpreted as lack of effectiveness.

As noted above, van den Brand et al. compared the effectiveness of rituximab and cyclophosphamide in a retrospective cohort with a median follow up of 40 months. The combined endpoint 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. But 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/m² (perhaps lower than any studies ever done in MN). But when evaluating the 30% of patients in the rituximab group that received 4 doses (375mg/m²) 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 effect is unheard of and perhaps is more a reflection of less stringent reporting in the past rather 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 Wetzel et al. But the key word here is “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. who showed that in their retrospective cohort (outside of a clinical trial), the rate of serious adverse events including fatal events were significantly higher in the cyclophosphamide group. There were total of 9 deaths in the cyclophosphamide group, and 5 were directly attributed to cyclophosphamide (infections and malignancies) vs. 4 deaths in the rituximab group and none were attributed to rituximab. Similarly, the non-serious adverse events were significantly higher in the cyclophosphamide group (127 events) vs in the rituximab group (52 events). The side effects included myelotoxicity, infections, steroid-induced hyperglycemia, and malignancies. 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 de Logt et al. in which the outcome of 127 patients with MN treated with cyclophosphamide was evaluated, the adjusted incidence of malignancy was 3 times increased in the cyclophosphamide group compared to the non-cyclophosphamide group at a median follow-up of 6 years.

Another side effect of concern is infertility in women of childbearing ages. The infertility is dependent on the cumulative dose of cyclophosphamide and can occur when exposure is up to 10 grams as noted by Wetzel et al. Therefore, in a 70 kg female who receives cyclophosphamide at a dose of 2.5 mg/kg/d for total of 100 days, the exposure will be achieved in less than 60 days. This side effect can be devastating for the patient. Indeed, in the STARMEN trial the mean average cyclophosphamide dose was 10.3 grams. One also needs to consider that MN can and does relapse in up to 50% of the patients. 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 re-dose due to risk of toxicity which makes it difficult to tailor it to the patients based on 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 UK suggests rituximab as a potentially more cost-effective treatment than cyclophosphamide.

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 is data to suggest that in patients with high PLA2R antibody titers, rituximab may be less effective in lowering the antibody titers. In these patients, cyclophosphamide may be preferred. We should point out, however, that when these patients with high PLA2R titer were re-treated with rituximab they did respond. In addition, there are now more potent anti-CD20 drugs (such as Obinutuzumab) available and have been shown to be effective in patients with rituximab resistant PLA2R positive MN. 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 is 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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| Agents       | Pros                                                                                     | Cons                                                                                     |
|--------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Cyclophosphamide | - In use for several decades and familiar to most nephrologist  
|              |   - More readily available particularly in developing countries  
|              |   - Established efficacy in several randomized control trials  
|              |   - May be more effective in patients with high PLA2R antibodies titer  
|              |   - May achieve remission faster                                                     | - Significant toxicity: myelotoxicity, infertility, and malignancy (cumulative dose dependent)  
|              |                                                                                        | - Steroid side effects: Cushing syndrome, uncontrolled diabetes, infections, poor wound healing, mood problems  
|              |                                                                                        | - Need for frequent laboratory monitoring  
|              |                                                                                        | - Fixed regimen that cannot be tailored to the patient’s need  
| Rituximab   | - Established efficacy in several randomized control trials  
|             | - Intravenous dosing which may improve adherence  
|             | - Favorable side effect profile and good tolerability  
|             | - Avoid exposure to high dose steroid  
|             | - Can be tailored based on antibody titers and allows for an individualized approach  
|             | - Better option for patients of childbearing ages due to absence of reproductive toxicity | - May achieve remission slower than cyclophosphamide  
|             |                                                                                        | - Requires redosing  
|             |                                                                                        | - Infusion-related reactions  
|             |                                                                                        | - Insurance coverage  

Table 1: Pros and Cons of cyclophosphamide and rituximab in treating membranous nephropathy