Rituximab is preferable to cyclophosphamide for treatment of membranous nephropathy: CON

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There is strong evidence to support the efficacy of alkylating agents in the treatment of patients with membranous nephropathy. Randomized controlled trials, that included patients with membranous nephropathy and nephrotic syndrome, reported remission rates of 77-93% (1), which translated in improved kidney survival in studies with long follow-up (2, 3). In one study kidney survival at 10 years amounted 92% in the treated patients and 60% in controls (2). Of note, the 60% kidney survival in the control group suggested that the treatment strategy (i.e. treating all patients with membranous nephropathy and nephrotic syndrome) exposed many patients unnecessarily to the risk of immunosuppressive therapy. Indeed, in this control group the cumulative rate of complete and partial remission was 47%, and one third of patients were in remission at last follow-up. Subsequent studies showed that treatment can be restricted to patients at high risk of disease progression (reviewed in van de Logt 2016 (1)). The largest study included 254 patients with membranous nephropathy and nephrotic syndrome. After median follow-up of 57 (32-90) months, only 124 patients (49 %) had received immunosuppressive therapy. Renal survival was 86 % after 10 years and remission of proteinuria developed in 83 % of patients (4). Obviously, treatment that prevents development of kidney failure and obviates the need for renal replacement therapy is of great benefit, both for the individual patient and for society. Based on the evidence (and the calculated cost-efficacy) national and international guidelines recommended treatment with cyclophosphamide and steroids for patients with membranous nephropathy, nephrotic syndrome and high risk for disease progression (5).

Many physicians and patients are reluctant to use cyclophosphamide and steroids, because of the associated toxicity. Indeed, the use of cyclophosphamide is associated with many short-term side effects such as infections, anemia, leukocytopenia, thrombocytopenia, and liver dysfunction. Still, most can be easily managed with dose reduction, temporary withdrawal, and/or administration of antibiotics. The most feared side effects are infertility (maximal cumulative dose 10 g/day) and malignancy (maximal cumulative dose 36 g).
Therefore, the recent introduction of less toxic immunosuppressive therapies has created great interest. Calcineurin inhibitors were proposed as alternative, based on high remission rates reported in the initial studies (1). Meanwhile, enthusiasm for these agents has waned. More recently, rituximab was proposed as first line therapy, again primarily based on short-term studies suggesting high proteinuria remission rates, and the notion that the toxicity of rituximab is low. However, rituximab has not been compared to cyclophosphamide in a randomized control trial; there is as yet no evidence that treatment with rituximab improves kidney survival in patients with membranous nephropathy; there is no data to proof that rituximab can be used in a restrictive treatment strategy. In the current era of evidence-based medicine, these limitations should be discussed with our patients.

A detailed analysis of the studies that are used to claim success of rituximab points to many caveats:

1. There are no data on long-term follow-up, nor on hard renal end-points. Rituximab is advocated based on the remission rates. However, remission of proteinuria may not be the best predictor of kidney outcome. In this respect, it is important to bear in mind the initial “apparent” success of calcineurin inhibitors. Many studies reported high remission rates, ranging from 75 – 88% (6-8). However, during follow-up most patients relapsed. In a study that reported 5 year follow-up data, 10% of patients had died, and 30% of patients had reached a kidney failure end-point (defined as doubling of serum creatinine) (9). In multivariable analysis renal function deterioration was associated with multiple relapses.

2. Efficacy of rituximab is lower than suggested. For more than a decade, the efficacy of rituximab was largely supported by data derived from a large Italian cohort including 132 patients with MN and nephrotic proteinuria. A detailed analysis, after a follow-up of 30.8 (6.0-145.4) months, showed that non-responder rate was 36%. Moreover, relapse rate was approximately 30 % (10). Since these were observational data, and we do not know spontaneous remission rate, we cannot estimate the real benefit of rituximab. The
'GEMRITUX' study, a randomized controlled trial from France, provided better evidence (11). This study proved that rituximab was more effective than no treatment in inducing remissions. At the end of follow-up (median 23 months) remission rate was 66% with rituximab and 45% with conservative therapy. Thus this study confirmed the 35% failure rate. Moreover, since 45% of patients developed spontaneous remission the attributable efficacy rate is only 38% \((66-45)/(100-45)\). There has been a debate that the relatively low efficacy of rituximab might be related to the use of a low dose of rituximab (in the Italian cohort study most patients received only one dose of rituximab 375mg/m², in the Gemritux trial patients received two doses of rituximab 375 mg/m²). Indeed, a French study suggested that two doses of rituximab of 1 gram were more effective (12). The recent randomized controlled MENTOR study used a high dose of rituximab (cumulative dose 4 grams) (13). Unfortunately, the MENTOR study had short follow-up (last observation only 18 months after the rituximab administration), and does not provide proof for efficacy on hard renal end-points. Moreover, also in this study efficacy was limited: 22% of patients did not respond initially and were excluded from the study. Thirty-nine of 65 patients (60%) were in partial or complete remission at the last follow-up (24 months). Otherwise stated: at 24 months 60% of rituximab treated patients were in partial or complete remission as compared to 20% in the control group, an attributable efficacy rate of 50% \((60-20)/(100-20)\).

3. Efficacy of rituximab in patients with kidney insufficiency is unproven. Thus, there are no data to support its use in patients with reduced eGFR. A small retrospective study evaluated the association between baseline characteristics and proteinuria response at 3 months after rituximab (14). The study included only 14 patients, 6 non-responders and 8 responders (defined as proteinuria reduction > 40%). Biopsy-based interstitial fibrosis and tubular atrophy was a determinant of response: the TI score was <1.7 in responders and >1.7 in non-responders. Of note, not-unexpectedly, renal function was also different, with a serum creatinine of 2.1 (SD 1.0) mg/dl in non-responders and 1.3 (0.4) in responders. Thus, this
small study suggests that rituximab is of limited benefit in patients with severe kidney
dysfunction.

4. Although there are no randomized controlled trials that compare rituximab with
cyclophosphamide and steroids, there are data to suggest that rituximab is inferior to
cyclophosphamide and steroids. Van den Brand et al compared two European cohorts,
treated with either rituximab or cyclophosphamide and steroids (15). Partial remission rate
was lower in the rituximab treated cohort (adjusted HR 0.63). This observation was
supported by the finding that rituximab was also less effective in inducing an immunological
remission than cyclophosphamide especially in patients with high anti-PLA2R1 antibody
(aPLA2R1ab) levels (16). Figure 1 illustrates the observations in patients in the highest tertile
of aPLA2R1ab levels (150-776 RU/ml). aPLA2R1ab levels decreased to levels < 14 RU/ml (the
cut-off to define positive and negative) in 86 % (12/14) of cyclophosphamide treated patients
and in 23 % (3/13) of rituximab treated patients. Interestingly, in a recent study aPLA2R1ab
levels using a cut-off of 150 RU/ml identified high risk patients with a specificity of 80 % (17).

Conclusion:

There is sufficient evidence to support the notion that rituximab is not preferable to cyclophosphamide
for treatment of patients with membranous nephropathy and high risk of progressive disease. Based on
the available data we suggest that there is a window of opportunity for rituximab in patients with
membranous nephropathy, normal eGFR, nephrotic syndrome, and aPLA2R1ab levels below 150 RU/ml.
When discussing therapy with the individual patient it is important to provide a balanced view that
includes a discussion of benefits and risks. The risks associated with cyclophosphamide-based therapy
must include the risks associated with the concomitant use of corticosteroids. Patient characteristics such
as age, obesity, and glucose-intolerance as well as predicted rate of eGFR loss (and thus risk of ESRD) will
shift the balance.
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Figure 1. Observations in patients in the highest tertile of aPLA2R1ab levels (150-776 RU/ml).
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