TREATMENT OF MEMBRANOUS NEPHROPATHY USING RITUXIMAB

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Summary
The aim is to analyse rituximab as a potential treatment for membranous nephropathy, its efficacy, and adverse effects. Study method- a systematic literature review. A search for scientific publications was performed using the Medline (Pubmed) and Google Scholar search systems. The selected articles are written in English.

Results. In 8 selected studies selected population was 324 patients. Total or partial remission was seen in 35-100% patients, 24h proteinuria decreased significantly to all patients. Rituximab was effective when it came to long term proteinuria decrease and improvement of GFR. Adverse effects were mild or insignificant, and patients tolerated the agent well. The most common side effects were infusion-related reactions, cardiovascular complications, or infections.

Conclusions. Based on these studies, Rituximab is an effective treatment for membranous nephropathy. It is a safe agent with less adverse effects which are mild and do not require hospitalization. Although therapy consisting of alkylating agents and steroids is still recommended for patients with very high-risk kidney disease, rituximab is an alternative option for patients at moderate/high risk of kidney damage.

Introduction
Membranous nephropathy (MN) is one of the main reasons of primary nephrotic syndrome (NS) in adult age and is described as a deposition of immune complexes on the glomerular basal membrane and basal membrane thickening [1]. In severe cases without treatment, MN may lead to end stage kidney failure. Most patients MN course is benign and requires no treatment at all, as spontaneous complete remission of proteinuria occurs in 5 - 30% patients in 5 years, and partial remission occurs to 25 - 40% patients in 5 years [2–4]. Guidelines suggest that MN treatment should include steroids, cyclophosphamide, or cyclosporine in various management protocols, but immunosuppressants should be restricted to patients with NS and persistent proteinuria, due to them deteriorating renal function. Moreover, these classic management protocols have many side effects and have diverse long-term outcomes [5,6]. However, the recommended treatment does not always prevent renal failure and remission does not always occur. Although the pathogenesis of idiopathic MN remains incompletely defined, a huge breakthrough was reached in treatment strategy, when a study of Becket al., showed that approximately 70% of patients with idiopathic MN have circulating autoantibodies against phospholipase A2 receptor 1 (PLA2R) which is located on the surface of normal human podocytes [7,8]. This confirmed that MN is an autoimmune disorder and exploration of agents that selectively depletes B cells and therefore could reduce NS and resolve glomerular injury of MN began [5]. One of the specific agents chosen was anti-CD monoclonal antibody rituximab, which eliminates circulating B cells and could be safer and more specific treatment for patients with idiopathic MN [9]. Now rituximab is considered a possible first-line treatment option for MN [10]. A handful of clinical trials evaluated rituximab in recent years, so we have collected available literature and case series to review rituximab’s use in treating MN, efficacy outcomes and what adverse effects of the therapy were reported.

The aim of the study - to analyse rituximab as a potential treatment for membranous nephropathy, it’s efficacy and adverse effects.

Materials and methods
Literature review was conducted for publications in English indexed in Medline (Pubmed) and Google Scholar
between 2009 and September 2020. The search terms were used: "rituximab", "membranous nephropathy", "idiopathic", "treatment" or "idiopathic membranous glomerulonephritis". Subsequently, a search was conducted using "rituximab" combined with "side effect", or "drug reaction". The references of the articles retrieved by PubMed and Google Scholar search engines were reviewed manually. Abstracts from meetings with no corresponding full-length publication were not considered. Publications that included children under age 18 and single case reports were also excluded.

When available, categories of data were extracted from each study:

1) Clinical diagnosis - target population were patients diagnosed with idiopathic MN
2) Treatment approach (dosage, number of cycles)
3) Follow up time in which patients were tracked and whether nephrotic proteinuria occurred
4) Whether subsequent treatment involved the use of rituximab (alone or with other agents)
5) Complete/partial remission rate in the rituximab group.

Results

Ninety studies were identified by our research strategy. After further inspection, excluding duplicates, off-topic studies, 55 studies did not meet inclusion criteria. A more thorough review and abstract reading led to the further exclusion of 19 studies. 16 studies left in total. After reading the full text and excluding the narratives, conference speeches and single case reviews - 8 available studies [11–18] were left that included 324 patients in total (Figure 1.). The largest group of patients came from two studies: 100 patients involved in Ruggenenti et al. study, and 65 patients in Fervenza et al. research. Other studies included case series of 13 to 38 patients.

Patient inclusion criteria in the studies were severe proteinuria and biopsy proven idiopathic MN diagnosis. Patient selection and data about prior management, treatment protocols varied significantly and did not allow thorough analysis. For example, Ruggenenti et al. included patients that prior received immunosuppressive regimens (n = 32). Additionally, some patients received steroids (n = 21) or cyclosporine (n = 14) before the clinical trial. In Fervenza et al., study patients were also selected with biopsy proven MN, but no data about prior treatment was provided. Yet it was stated that patients received best-practice supportive care for at least 3 - 6 months. 6 out of 8 studies did not provide rituximab treatment protocols or patient background. In the most studies rituximab was first line therapy, however, Fiorentino et. al. study also included rituximab as second-line treatment (Table 1.).

Rituximab treatment course and outcomes. Different applications of rituximab were used in the studies. Ranging from 1 single dose of 375 mg/m², 4 weekly doses of 375 mg/m² to 2 doses of 1 g of rituximab on day 1 & 15. A different approach was used in Bagchi et al. study, where patients received 2 doses of 500 mg of the agent 7-10 days apart. In Fervenza et al. study, if proteinuria was reduced by 25% by 6 months and no remission was observed, a second cycle of rituximab was given to the patient. In Ruggenenti et al., study patients received rituximab for 4 weeks and the second cycle of rituximab was considered if > 5 circulating B- cells per mm² was detected after the first cycle. Waldman et al., Bagchi et al., Fiorentino et al., studies tracked B - cell (> 5 cells / ml) count and did not depend on remission status. If B - cell depletion was observed, rituximab was not administered. Moroni et al. only used one cycle of rituximab and observed the patients afterwards. In most cases, rituximab was first line therapy, used alone or in combination with other agents. Most studies analyzed rituximab only and did not have control groups, but some compared Rituximab group with other treatment options – Fervenza et al. study

![Figure 1. Study assessment](image-url)
compared it with cyclosporine, Dahan et al. study- with non-immunosuppressive antiproteinuric treatment (NIAT). The treatment and follow up period varied from 6 to 41 months.

Rituximab was effective in treating patients with biopsy proven MN. Complete or partial remission was observed in all studies, ranging from 35% to 100%. It is worth noting that a relevant portion of patients who responded to rituximab remained proteinuric but achieved partial remission. Remission rates tend to increase with longer follow-up periods. Few of the studies suggest that rituximab was as effective as cyclosporine when it comes to reaching remission, but rituximab showed that it is superior in long term proteinuria management. Proteinuria decreased in all studies significantly. Additionally, Ruggenenti et al., studies showed that over the course of treatment GFR was slowly increasing in patients with complete and partial remission. Other studies showed various results: Waldman et al. stated that modest renal function decline was observed after rituximab induction, Fiorentino et al. observed that renal function remained stable for the entire follow-up time, Moroni et al., patients also had an increase in GFR. 5 out of 8 studies mentioned nephrotic proteinuria relapse which occurred to 4.7- 40% of all treated patients. Fiorentino et al., Bagchi et al., Moroni et al., demonstrated that some of the patients were non-responders to rituximab and might need additional treatment. 4 of Bagchi et al. patients had deteriorating renal function, Moroni et al. study had 2 non-responders, and Fiorentino et al. study - 9 non-responding patients.

There is evidence that patients with rituximab therapy may develop resistance overtime. Despite that, the studies provide enough evidence supporting the use of rituximab as induction treatment, achieving remission in approximately two-thirds of all patients without the need of concomitant corticosteroid therapy (Table 2.).

Table 1. Overview of prospective rituximab trials in membranous nephropathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Year</th>
<th>Study design</th>
<th>Proteinuria before rituximab, g/ 24 h</th>
<th>Renal function before rituximab*</th>
<th>Agents used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segarra et. al</td>
<td>13</td>
<td>2009</td>
<td>Uncontrolled</td>
<td>1.13 (0.85-1.45)</td>
<td>210.44 (61.89-282.94)</td>
<td>Rituximab + steroids/MMF for 1-month, later rituximab</td>
</tr>
<tr>
<td>Ruggenenti et. al</td>
<td>100</td>
<td>2012</td>
<td>Uncontrolled</td>
<td>9.1 (5.8-12.8)</td>
<td>106.1 (85.8-150.3)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Dahan et. al</td>
<td>37</td>
<td>2016</td>
<td>Randomized controlled trial</td>
<td>&gt;5</td>
<td>93.8 (76.9-122.2)</td>
<td>NIAT**+ rituximab</td>
</tr>
<tr>
<td>Waldman et. al</td>
<td>16</td>
<td>2016</td>
<td>Phase 2 Pilot Study</td>
<td>10.8 ±2.8</td>
<td>120.25 (±12.4)</td>
<td>Rituximab/ cyclosporine induction, later rituximab</td>
</tr>
<tr>
<td>Fiorentino et. al</td>
<td>38</td>
<td>2016</td>
<td>Uncontrolled</td>
<td>5.4 (4-10.6)</td>
<td>97.3 (70.72-130.83)</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Moroni et. al</td>
<td>34</td>
<td>2017</td>
<td>Uncontrolled</td>
<td>11.9±8.2</td>
<td>117.5±53.04</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Bagchi et. al</td>
<td>21</td>
<td>2018</td>
<td>Uncontrolled</td>
<td>6.2±22.0</td>
<td>79.6±26.5</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Fervenza et. al</td>
<td>65</td>
<td>2019</td>
<td>Randomized controlled trial</td>
<td>8.9 (6.7-12.9)</td>
<td>114.9±35.4</td>
<td>Rituximab</td>
</tr>
</tbody>
</table>

*Renal function is represented by creatinine level in serum, μmol/L.
** NIAT- non-immunosuppressive antiproteinuric treatment

Side effects of Rituximab. 7 out of 8 studies mentioned some adverse effects (AE) of the treatment with rituximab with the exception of Segarra et. al study. Ruggenenti et al. study had patients that experienced few serious side effects (SE), most of them where cardiovascular, some of them were fatal. Fervenza et al., the study acknowledges respiratory tract issues and infusion-related reactions as the most common AEs of rituximab. Other studies mentioned that AEs were mild or not related to the agent itself and no hospitalization was required. The population was too small to make conclusions about the SE, however literature does suggest SEs such as fever, gastrointestinal symptoms, and cold symptoms are common among patients using rituximab [19, 20]. According to literature, rituximab may also cause severe arrhythmias and angina, however cardiac failure was reported rarely [21]. According to the reports, infusion-related reactions were 32% after the first infusion and 11% after second one, and no serious reactions occurred [22]. Studies have also observed hema-
logic toxicity [23]. Single-center retrospective cohort study of 738 patients with autoimmune diseases treated with rituximab reported a cumulative incidence of late-onset neutropenia of 6.6% at 1 year. The total rates were higher in patients with lupus nephritis (25%) compared with patients with MN (8.2%) or other diseases (7.6%) [24]. Mild and severe infections which required antibiotic treatment were observed, such as pneumonia, cellulitis, urinary tract infections [25]. In MEN-TOR trial the overall number of severe infectious events per 100 patients was 7.7 for rituximab and 12.3 for cyclosporine A (p = 0.23). There is evidence that rituximab also could cause interstitial lung disease that could be caused by the release of cytotoxic substances [26]. Altogether, SEs were mild and severe ones were rare. The total occurrence of side effects in studies is presented in Table 3. Other studies show that rituximab remains well tolerated over time and after multiple courses. No new safety risks were identified, and there was no increase in the rate of any events with prolonged exposure to rituximab during observations [27].

### Discussion

After pathogenesis in MN was identified, new treatment options were recognized by researchers. This literature review demonstrated the potential use of rituximab in treating patients with biopsy proven MN. Most of the authors concluded that this agent can be used as an effective way to reach partial or complete remission and could prevent terminal kidney failure. Moreover, this management strategy was also beneficial to patients and improved patient life quality due to infrequent administration, in comparison with twice daily oral cyclosporin or corticosteroids. Studies demonstrated that rituximab is well tolerated, has minor adverse effects. Serious events were not frequent in rituximab groups in comparison with steroids and alkylating agents, however rare but fatal conditions such as late onset neutropenia or cardiovascular events should be taken into consideration. As recommended by the currently updated new KDIGO guidelines for glomerular diseases, rituximab is a new first-line treatment option for patients with idiopathic MN. Although therapy consisting of alkylating agents and corticosteroids is still recommended for patients at very high risk for progressive kidney disease, rituximab is an alternative option for most patients at moderate and high risks [28].

Despite the promising results and new recommendations, Rituximab has some issues that have not been resolved. First, there are no treatment protocols or dosing regimens to be used for patients with MN. It is also hard to evaluate if rituximab is cost effective. Initial treatment costs were higher with rituximab than following the classic Ponticelli [29] method or using cyclosporin. However, Fervenza et al. stated that overall costs were lower because of longer remission which was obtained with rituximab. Rituximab appears to have fewer complications and no indication of an increased risk of malignancy, which means fewer hospitalizations from a long-term perspective in contrast to typical treatment with corticosteroids [30]. Furthermore, with a high percentage of spontaneous remissions in MN, it is difficult to evaluate whether achieved remission due to rituximab or spontaneous during follow up. Most patients additionally receive other types of treatment before the therapy, which also may have impact to the treatment outcomes.

### Table 2. Overview of dosing regimens and treatment outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rituximab doses</th>
<th>Mean follow up, months</th>
<th>Complete/ partial remission, %</th>
<th>Relapse of nephrotic proteinuria, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segarra et al. (2009)</td>
<td>4 weekly 375 mg/m² doses</td>
<td>30</td>
<td>100</td>
<td>23.0</td>
</tr>
<tr>
<td>Ruggenenti et al. (2012)</td>
<td>4 weekly 375 mg/m² doses</td>
<td>24</td>
<td>65</td>
<td>27.6</td>
</tr>
<tr>
<td>Dahan et al. (2016)</td>
<td>375 mg/m² on day 1 and 8</td>
<td>17 (median)</td>
<td>35</td>
<td>N/A</td>
</tr>
<tr>
<td>Waldman et al. (2016)</td>
<td>1 g day 1 &amp; 15</td>
<td>41</td>
<td>54</td>
<td>18.8</td>
</tr>
<tr>
<td>Fiorentino et al. (2016)</td>
<td>4 weekly or 2 weekly 375 mg/m² doses</td>
<td>15</td>
<td>76.3</td>
<td>N/A</td>
</tr>
<tr>
<td>Moroni et al. (2017)</td>
<td>Single dose or 2 x 375 mg/ m²</td>
<td>23.9 (±18.6)</td>
<td>44.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Bagchi et al. (2018)</td>
<td>500 mg day 1 &amp; 7</td>
<td>12</td>
<td>61.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Fervenza et al (2019)</td>
<td>1 g day 1 &amp; 15</td>
<td>24</td>
<td>60</td>
<td>40.0</td>
</tr>
</tbody>
</table>
Conclusions

1. Rituximab is an optional agent in treating biopsy proven MN which can be used in some cases in patients with moderate to high risk of renal damage. It was effective when it came to long term proteinuria decrease and improvement of GFR.

2. Rituximab was proven to be a safe drug with few adverse effects. Serious or fatal complications were rarely reported. The most common ones were infusion-related reactions and cardiovascular events, and hospitalization need was rarely reported.

3. More randomized clinical trials should be initiated, and specific Rituximab treatment guidelines should be developed for the clinicians to follow.

References


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MEMBRANINĖS NEFROPATIJOS GYDYMAS RITUKSIMABU

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Raktažodžiai: membraninė nefropatija, rituximabas, nefrozinis sindromas, glomerulonefritis.

Santrauka
