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TECHNOLOGY REVIEW: FOCUSED CRITICAL APPRAISAL

Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy: A Critical Appraisal of the MENTOR Study

Service Line:	Technology Review
Issue:	29
Publication Date:	February 2020
Report Length:	13 Pages

CADTH

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Cite As: *Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy: A Critical Appraisal of the MENTOR Study*. Ottawa: CADTH; 2020 Feb. (CADTH Technology Review: Focused Critical Appraisal; no. 29).

Acknowledgments: Sheri Pohar, Danielle MacDougall. An earlier version of this report was reviewed by a clinical expert.

ISSN: 2369-7385 (online)

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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The objective of a CADTH Focused Critical Appraisal is to examine the methodology, scientific rigour, and clinical findings of a published study.

Background

Primary membranous nephropathy is an autoimmune disease and one of the most common causes of nephrotic syndrome in Caucasian adults.[1,2] Nephrotic syndrome is characterized by proteinuria (> 3.5 g per 24 hours), hypoalbuminemia (< 30 g/dL), hyperlipidemia, and peripheral edema. Patients are also at risk of thromboembolism.[3] Nephrotic syndrome may lead to end-stage renal disease (ESRD).[4]

The treatment goal of patients with primary membranous nephropathy is to achieve proteinuria remission to prevent renal damage.[2] Treatments include supportive therapies for hypertension, hyperlipidemia, edema, and for preventing thromboembolism.[1,2] There is evidence to show that immunosuppressive therapy reduces proteinuria, all-cause mortality, and progression to ESRD.

The current guideline *KDIGO Clinical Practice Guideline for Glomerulonephritis* June 2012 recommend cyclophosphamide combined with corticosteroids for six months. Alternatively, calcineurin inhibitors (cyclosporine or tacrolimus) may be administered for six months.[5] The KDIGO 2012 guidelines did not consider rituximab as a possible treatment for primary membranous nephropathy.[6]

In July 2019, the MENTOR study — MEmbranous Nephropathy Trial Of Rituximab — on the remission of proteinuria in 130 patients with primary membranous nephropathy was published.

Trial Under Review

This report includes a summary and appraisal of the MENTOR study — Fervena FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med*. 2019;381(1):36-46.[6]

Description of Trial Under Review

Objectives

The objective of the MENTOR study was to investigate if rituximab was noninferior to cyclosporine in inducing and maintaining remission of proteinuria in patients with primary membranous nephropathy.

Trial Characteristics and Statistical Analysis

Study Design

The MENTOR study was an open-label, randomized, multi-centre, non-inferiority study conducted in the US (18 sites) and Canada (three sites).[6]

Eligible patients with primary membranous nephropathy (N = 130) were randomized 1:1 to receive rituximab or cyclosporine treatment for six or 12 months. A computer-generated randomization list was prepared by the central study centre using permuted blocks of two or

four, stratified by site. Patients were allocated to treatments using a Web-based randomization system. Study drugs were administered open-label to patients for six or 12 months, followed by an additional 12-month observation period.

Funding for the study was provided by Genentech and the Fulk Family Foundation.

Inclusion and Exclusion Criteria

Patients with primary membranous nephropathy were eligible for enrolment in the MENTOR study[6] if they met the following criteria:

- 18 to 80 years of age, with membranous nephropathy diagnosed by renal biopsy. Biopsy reports were adjudicated by the study's principal investigators and renal pathologists, based on pre-set diagnostic criteria (an original biopsy that includes light, immunofluorescence, and electron microscopy showing subepithelial projections ["spikes"] along the capillary walls on methenamine silver stain by light microscopy, granular deposition of IgG and C3 along the capillary walls on immunofluorescence microscopy, and subepithelial deposits on electron microscopy)
- proteinuria > 5 g per 24 hours based on the average of two 24-hour urine samples collected within 14 days despite three or more months of angiotensin II blockade
- stable 24-hour creatinine clearance of at least 40 mL/min/1.73m^2 of body surface area
- prior to randomization, patients had to undergo at least three months of best-practice supportive care that consisted of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockade (ARB) therapy with adequate blood pressure control (target < 130/80; accepted < 140/80 mm Hg in at least 75% of readings). Those who had not received best-practice supportive care prior to randomization entered a three-month run-in period. Patients were eligible if they had a < 50% decrease in proteinuria after the three-month ACEI or ARB treatment period
- patients were required to stop prednisone or mycophenolate mofetil for at least one month, and alkylating agents for at least six months prior.

Patients were excluded if they had type 1 or type 2 diabetes, an active infection, or a secondary cause of membranous nephropathy. Those with a history of resistance to cyclosporine, other calcineurin inhibitors, rituximab, or alkylating agents were also excluded, although patients who had responded to one of these drugs but relapsed after three or six months were eligible.

Interventions

Rituximab 1,000 mg was administered by intravenous (IV) infusion on day 1 and day 15, and patients were assessed for treatment response at six months. Those who achieved complete remission (urine protein ≤ 0.3 g per 24 hours and serum albumin ≥ 3.5 g/dL) received no further rituximab doses. Patients who showed a partial response at six months (defined as at least a 25% reduction in proteinuria, but who did not meet the criteria for complete remission) received an additional two-dose course of rituximab 100 mg IV (day 181 and day 195). All patients received acetaminophen 1,000 mg and diphenhydramine 50 mg orally, 30 minutes to 60 minutes prior to the infusion of rituximab. Prior to the dose on day 1 and day 181, patients also received IV methylprednisolone 100 mg.

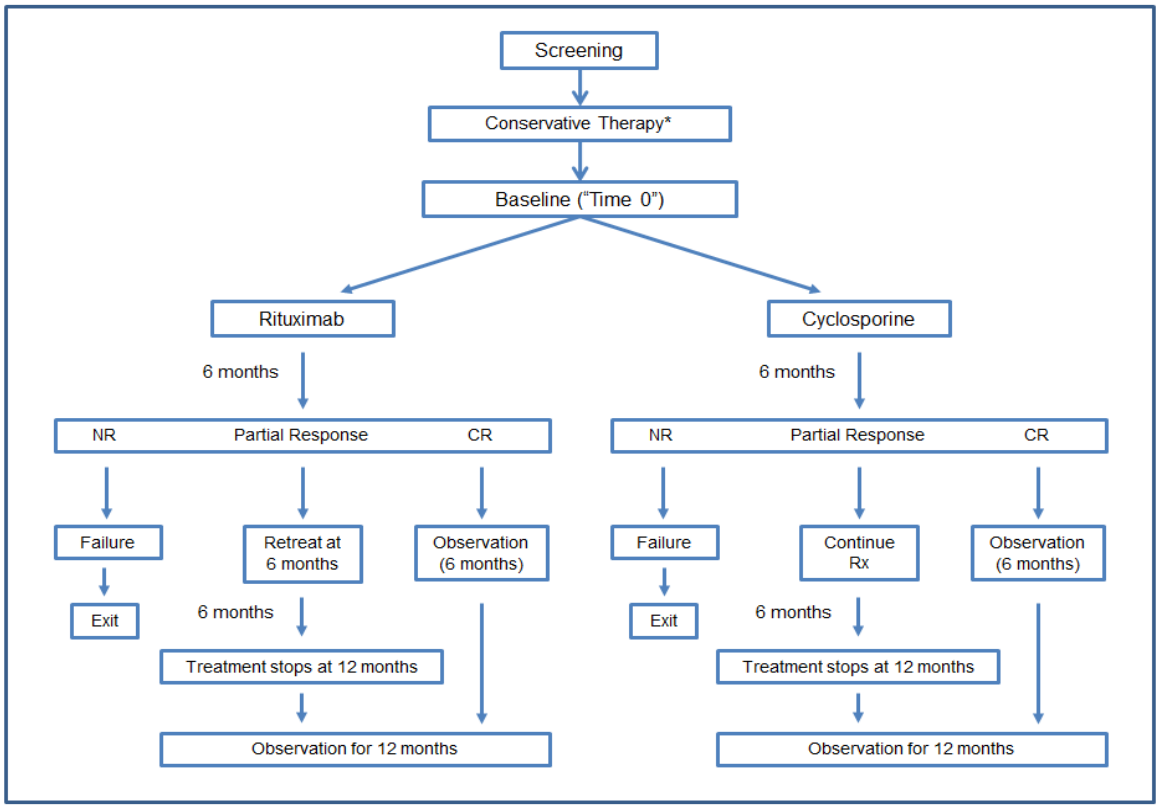
Patients randomized to oral cyclosporine received starting doses of 3.5 mg/kg per day in two divided doses administered 12 hours apart. Neoral brand cyclosporine was the preferred product for the study. Doses were adjusted to achieve trough blood levels of 125 ng per mL

to 175 ng per mL. Trough levels were tested every two weeks until target levels were reached and levels were monitored throughout the study. At six months, patients who achieved complete remission had cyclosporine therapy tapered off over the course of two months. For those patients who showed a partial response, cyclosporine was continued until 12 months, after which cyclosporine was tapered off. For the tapering regimen, the dose of cyclosporine was reduced by one-third each month for two months and then discontinued. During the trial, the dose of cyclosporine was reduced in patients who had an unexpected > 30% increase in serum creatinine levels and was discontinued if renal function did not return to baseline following dose modification.

Patients in both groups who had a < 25% decrease in urine protein at six months were withdrawn from the study and considered to have treatment failure. Rituximab and cyclosporine were administered open label.

All patients received dietary counselling as per the standard of care. Patients with significant hyperlipidemia were to receive atorvastatin 10 mg to 40 mg daily (or equivalent), and those randomized to rituximab also received trimethoprim plus sulfamethoxazole daily for prophylaxis for pneumocystis pneumonia.

Figure 1: MENTOR Study Design



CR = complete response (defined as proteinuria ≤ 0.3 g/24 hours and serum albumin ≥ 3.5 g/dL; MENTOR = MEmbranous Nephropathy Trial Of Rituximab; NR = non-response (defined as < 25% reduction from baseline proteinuria).

Note: Partial response at 6 months is defined as ≥ 25% reduction from baseline proteinuria but not a complete remission.

Source: Fervenza et al. 2019[6] from N Engl J Med, Fervenza FC, Appel GB, Barbour SJ, et al., Rituximab or cyclosporine in the treatment of membranous nephropathy, 381(1):36-46. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Outcome Assessment

The primary outcome was the proportion of patients who achieved complete remission or partial remission of proteinuria 24 months after randomization. Secondary outcomes included relapse at 24 months; serum levels of antibodies to the M-type phospholipase A2 receptor (anti-PLA2R); health-related quality of life; adverse events; ESRD; complete or partial remission at six, 12, or 18 months; complete remission at six, 12, 18, or 24 months; time to complete or partial remission; and slope of creatinine clearance values over the course of the 24 months.

Complete remission was defined as urine protein ≤ 0.3 g per 24 hours and serum albumin ≥ 3.5 g/dL; partial remission was defined as a reduction of urine protein ≥ 50% plus a final urine protein of ≤ 3.5 g per 24 hours but > 0.3 g per 24 hours.

Relapse was defined as the development of proteinuria > 3.5 g per 24 hours in patients who had achieved complete or partial remission.

Treatment failure was defined as the following:

- < 25% reduction of proteinuria from baseline to six months
- relapse
- stopped treatment because of disease activity or adverse event
- used an immunosuppressive drug other than the study drug before 12 months
- used any immunosuppressant drug between 12 and 24 months
- patients who did not meet the criteria for complete or partial remission at 24 months
- patients lost to follow-up.

Patients who had missing data at 24 months would be considered treatment failures unless they had achieved complete or partial remission at 18 months. ESRD was defined as creatine clearance ≤ 15 mL per minute, the initiation or dialysis, or renal transplantation.

Health-related quality of life was measured using the Kidney Disease Quality of Life Short Form (KDQOL-SF) version 1.3 at month six, 12, and 24 for patients who had achieved a partial or complete remission. The KDQOL-SF includes the 36-item Short Form Health Survey (SF-36) plus subscales related to kidney disease. The study protocol stated that the physical health and mental health composite scores of the SF-36, the burden of kidney disease, symptom or problems, and effects of kidney disease on daily life subscales would be given precedence.

Statistical Analysis

The primary analysis of the proportion of patients who achieved complete remission or partial remission of proteinuria at 24 months was based on the intention-to-treat (ITT) population, with an additional non-inferiority analysis based on the per-protocol population. The ITT population included all randomized patients, with any patient who withdrew or had missing data considered a nonresponder. The per-protocol population included all patients who received a full course of study drug and had data at the 24-month visit.

Family-wise type I error was controlled using a stepwise statistical analysis, with the primary outcome for the ITT population tested first for non-inferiority and then superiority. Non-inferiority was also tested based on the per-protocol population. Rituximab was deemed noninferior to cyclosporine if the lower limit of the 95% confidence interval (CI) for the

difference in percentage of patients with complete or partial remission at 24 weeks was larger than –15%. The non-inferiority margin was based on data from Cattran et al.[7] corresponding to half the risk difference between cyclosporine and placebo in the proportion of responders. The investigators stated that this level of difference was acceptable given that rituximab would have other advantages over cyclosporine in dosing frequency, need for monitoring, and tolerability. Tests for non-inferiority and superiority of the primary outcome were based on z-tests using a generalized linear model with a binomial distribution and identity link function. Tests for non-inferiority were one-sided (alpha 0.025) and tests for superiority were two-sided (alpha 0.05).

A Bonferroni correction was used to control type I error for a secondary non-inferiority analyses of the proportion of patients with complete or partial remission at 12 months in the ITT population; thus significance was met if the one-sided *P* value was < 0.0125. There was no control of the type I error rate for all other secondary outcomes, and the authors stated these outcomes were considered exploratory. Risk differences and 95% CI for binary outcomes were tested using a two-sided Chi-squared test and time-to-event data were analyzed using Kaplan–Meier curves and Cox regression models (based on the ITT population). Continuous outcomes were analyzed using analysis of covariance models adjusted for baseline outcome values and with no imputation for missing data. The authors stated that because data for continuous outcomes were not collected after patients met the criteria for treatment failure, the analysis of outcomes such as health-related quality of life and renal function included only those patients who had achieved partial or complete remission at each time point.

Planned subgroup analyses included age (≤ 50 years, > 50 years), sex, baseline proteinuria (< 8 g/24hours, ≥ 8 g/24 hours), baseline anti-C status (≤ 40 u/mL, > 40 u/mL), and previous immunosuppressive therapy (yes, no).

The study had 80% power to detect non-inferiority for the primary outcome based on a one-sided alpha of 0.025, with 63 patients enrolled per group. The power calculations were estimated based on a 15% non-inferiority margin for the difference in per cent of patients who achieved a partial or complete remission at 24 months, assuming 55% and 45% of those in the rituximab and cyclosporine groups, respectively, would meet the criteria.

Results

Baseline Characteristics of Trial Participants

In the MENTOR study, a total of 130 patients were randomized (65 per treatment group).[6] The mean age per group was 51.9 years (standard deviation [SD] 12.6) and 52.2 years (SD 12.4), and most patients were male (72% and 82% for rituximab and cyclosporine, respectively). The mean body mass index was 31.8 kg/m^2 (SD 6.3) for the rituximab group and 29.3 kg/m^2 (SD 5.6) for the cyclosporine group.

At baseline, the median urinary protein was 8.9 g/24 hours in both groups, with an interquartile range (IQR) of 6.8 to 12.3 and 6.7 to 12.9 in the rituximab and cyclosporine groups, respectively. In both groups, the median serum albumin level was 2.5 (IQR 2.1 to 2.9), and 77% of rituximab patients and 71% of cyclosporine patients were anti-PLA2R antibody positive. The median anti-PLA2R antibody levels were as follows: rituximab 409 U/mL (IQR 163 to 834); cyclosporine 413 U/mL (IQR 206 to 961). In the rituximab group, 29% of patients had a history of immunosuppressive therapy compared with 31% in the

cyclosporine group. The baseline mean creatinine clearance was 84.9 mL/min/1.73m^2 (SD 29.8) in the rituximab group and 87.4 mL/min/1.73m^2 (SD 34.4) in the cyclosporine group.

In the rituximab group, one patient (1.5%) did not receive any study drug, and two others (3%) had incomplete follow-up data. A total of four patients in the cyclosporin group had incomplete follow-up (6%). More patients in the cyclosporine group discontinued treatment (n = 11, 17%) than in the rituximab group (n = 2, 3%). Two patients per group stopped therapy due to worsening kidney function. Seven patients in the cyclosporine group and none in the rituximab group stopped due to adverse events. Two patients in the cyclosporine group switched to a non-study intervention.

The ITT analysis population included 65 patients per group and the per-protocol population included 63 patients per group. Treatment exposure, adherence to therapy, and mean cyclosporine dose were not reported.

Efficacy

The percentage of patients who met the criteria for partial or complete remission at 24 months was higher in the rituximab group (39/65, 60%) than the cyclosporine group (13/65, 20%), with a risk difference of 40.0% (95% CI, 24.6% to 55.4%; ITT). Rituximab was noninferior and superior to cyclosporine at 24 months based on the ITT population ($P < 0.001$ for both analyses) and was also noninferior based on the per-protocol population (risk difference 41.3 %, 95% CI, 25.7% to 56.9%; $P < 0.001$). The risk difference in the percentage of patients with complete or partial remission at 12 months was 7.7% (95% CI, –9.3% to 24.7%), which also met the criteria for non-inferiority based on the 15% non-inferiority margin ($P < 0.004$).

The percentage of patients with complete or partial remission at six, 12, 18, or 24 months was 35%, 60%, 62%, and 60% in the rituximab group compared with 49%, 52%, 23%, and 20% in the cyclosporine group (ITT population). The results were consistent across subgroups based on age, level of proteinuria, anti-PLA2R status, and previous immunosuppressive therapy. Results were similar for subgroups based on sex after adjustment for baseline anti-PLA2R levels.

Complete remission was achieved by 0%, 14%, 28%, and 35% of patients in the rituximab group and 2%, 5%, 2%, and 0% of patients in the cyclosporine group at six, 12, 18, and 24 months. The risk difference of complete remission at 24 months was 35.4% (95% CI, 23.8% to 47.0%, ITT population) for rituximab versus cyclosporine.

Treatment failure at 12 months and 24 months was reported in 26% and 40% of patients in the rituximab group compared with 32% an 80% of those in the cyclosporine group (ITT population). The hazard ratio for time-to-treatment failure was 0.34 (95% CI, 0.21 to 0.54) for rituximab versus cyclosporine. Among patients who achieved complete or partial remission at 12 months, 5% (2 of 39) of patients in the rituximab group and 53% (18 of 34) in the cyclosporine group met the criteria for relapse. Three additional patients (9%) in the cyclosporine group and none in the rituximab group met other criteria for treatment failure.

Health-related quality of life data from select KDQOL-SF subscales were reported at 6, 12, and 24 months for the subset of patients who had complete or partial remission at each time point. The number of patients with data varied from 11 to 38 patients per group, which represented 17% to 58% of the randomized population. Most analyses showed no statistically significant differences between groups.

Other continuous outcomes — such as creatinine clearance, urinary protein, and anti-PLA2R levels — were only reported for those patients who had a complete or partial remission, not the ITT population. Thus, they share similar limitations as the health-related quality of life outcomes data; i.e., selection and attrition bias. As these limitations preclude drawing conclusions from the results, these data have not been summarized in this report.

Safety

The percentage of patients who experienced an adverse event was 71% and 78% in the rituximab and cyclosporine groups, respectively. The most common adverse events in the rituximab group were infusion-related reactions (25%), other respiratory tract infections (14%), cough (11%), and pruritus (11%). In the cyclosporine group, the most common adverse events were increased creatinine levels (23%), other respiratory tract infections (14%), gastrointestinal pain (14%), nausea or vomiting (14%), fatigue (12%), and headache (11%).

Serious adverse events were reported in 17% of those in the rituximab group and 31% in the cyclosporine group. Of the serious adverse events, infections and cardiovascular events were reported by more patients in the cyclosporine group (12% and 11%, respectively) than in the rituximab group (6% and 2%). No deaths occurred during the trial and one patient in the cyclosporine group developed ESRD. Seven patients in the cyclosporine group (11%) and no patients in the rituximab group stopped treatment due to adverse events.

Critical Appraisal of Trial Under Review

Internal Validity

The MENTOR study used accepted methods to randomize patients and conceal allocation. In general, the baseline characteristics of patients appear to be balanced between groups, and any difference noted, such as the proportion of the males and mean body mass index, were not thought to be clinically important. The number of patients with incomplete follow-up data for the primary outcome was higher in the cyclosporine group than rituximab (6% versus 3%); however, all randomized patients were included in the ITT analysis and those with missing data were considered non-responders.

The study was open-label; thus, patients and investigators were aware of treatments received. As the primary outcome was based on objective laboratory values, knowledge of the treatment received was not expected to affect the results of the primary outcome. Subjective outcomes, such as health-related quality of life or reporting of harms may have been influenced by expectations of treatment. No information was provided on co-interventions patients received during the trial, which may have been influenced by knowledge of study drug administered.

Overall, the dosing regimen of cyclosporine appears to be acceptable. The starting dose of cyclosporine was consistent with those described in the KDIGO guideline,[5] other randomized controlled trials in patients with primary membranous nephropathy,[7,8] and in clinical practice,[9] but the tapering regimens and target trough levels varied. In the MENTOR study, cyclosporine was tapered off over the course of two months, which was acceptable based on input from the clinical expert consulted for this review. Longer tapering regimens of six months to 18 months have been reported in the literature; however, it is unclear if longer tapering durations reduce the risk of relapse.[9] In the trial, no data were provided on the median duration of therapy. Data on cyclosporine trough levels suggest that some patients may have received subtherapeutic levels, although the expert consulted for the review

stated that this would not threaten the validity of the study. In clinical practice, some patients will have low cyclosporine trough levels, which is often related to treatment adherence.

The non-inferiority margin of 15% was based on half the difference between cyclosporine and placebo observed in an RCT of 51 patients with steroid-resistant membranous nephropathy (Cattran et al.).[7] As per FDA guidance, the non-inferiority margin should reflect the largest loss of effect that would be clinically acceptable and depends on the availability of good-quality historical trials for the active control drug.[10] There is some uncertainty in the margin selected in the MENTOR study given that cyclosporine has not consistently shown significant differences in maintaining remission compared with no treatment or conservative management,[11] and there were a number of differences between the study by Cattran et al.[7] and the MENTOR study, which suggests that consistency of the active control effect may not be assumed. However, the limitations with the non-inferiority margin are less of an issue given that rituximab showed superiority over cyclosporine for the primary outcome, with 95% CI that excluded the null for both the ITT and per-protocol population.

The study was powered to detect a difference in the remission, defined as either complete or partial reduction in proteinuria. The urinary protein levels used to define complete and partial remission were consistent with those reported in the literature, although some sources also include criteria for stable renal function in their definitions of remission.[9,12,13] Whereas remission of proteinuria is frequently used as a key outcome for trials in membranous nephropathy, it is a surrogate outcome. The duration and severity of proteinuria has been associated with long-term prognosis in patients with primary membranous nephropathy.[12] Patients who achieve a complete or partial remission (either spontaneously or with treatment) have shown better kidney survival than those who do not achieve remission of proteinuria.[12] Moreover, patients who stay in remission have better renal outcomes than those who relapse.[14] Thus, it appears that there is evidence to support remission as a surrogate for longer-term outcomes.

Numerous secondary outcomes were reported in the MENTOR study, with no control of the type I error rate, and therefore any statistically significant findings should be interpreted considering the inflated risk of type I error. The report's authors stated these secondary outcomes should be considered exploratory. In addition, some of these outcomes had limitations regarding how they were defined or analyzed. The definition of treatment failure included patients who stopped treatment early. Considering that treatments were not intended to be administered long-term, and spontaneous remissions are possible, patients who stopped treatments prematurely may go on to have remission. Given that there were more patients who stopped cyclosporine early due to adverse events, the analysis of treatment failure may be biased in favour of rituximab. Although health-related quality of life was measured in the trial, these data were only reported for patients who met the criteria for partial or complete remission. A similar approach was used for other continuous outcomes, such as creatinine clearance and anti-PLA2R levels. Due to the extent of missing data and the selection bias, the reported data do not represent the randomized patient population and cannot be used to draw inferences about the effect of rituximab.

The sample size and duration of the trial was likely insufficient to detect infrequent adverse events or those that had a longer lag time. Since laboratory data were not systematically collected in patients who met treatment failure criteria, it is possible that some adverse events, such as cyclosporine-related nephrotoxicity, may not have been detected.

External Validity

The MENTOR study included patients with biopsy-confirmed, primary membranous nephropathy not controlled with diet and ACEI or ARB therapy. Based on the baseline urinary protein levels of 8.9 g/24 hours (IQR 6.7 to 12.3), the patients enrolled were consistent with a moderate- to high-risk group.[9] The study included patients from three Canadian sites, although most study sites were from the US. Overall, 71% of patients screened entered the study, with limited information available on the characteristics of patients who were excluded. The trial excluded patients greater than 80 years of age,
whose renal function was deteriorating or who had type 1 or type 2 diabetes. Thus, the generalizability of the findings to these patient populations is unclear. According to the clinical expert consulted for this report, the patients enrolled appear to be reflective of Canadian patients with primary membranous nephropathy, although there is some uncertainty regarding the ethnic diversity of participants given that data on race was not reported.

A potential limitation of the trial was the selection of cyclosporine as a comparator. According to the clinical expert consulted for this review, many nephrologists would consider cyclophosphamide or another alkylating agent as a first-line agent for high-risk patients, with cyclosporine reserved for moderate-risk patients. The expert stated that, although cyclosporine is frequently used, tacrolimus may be considered the preferred calcineurin inhibitor by some clinicians. Further studies comparing rituximab to cyclophosphamide are needed to determine rituximab's place in therapy.

Summary and Conclusion

The MENTOR study enrolled 130 patients with primary membranous nephropathy not adequately controlled by supportive therapy. Patients were randomized to receive open-label rituximab 1,000 mg intravenously on day 1 and day 15, or six months of oral cyclosporine at a starting dose of 3.5 mg/kg/day (adjusted to achieve trough blood levels of 125 ng per mL to 175 ng per mL). Patients with a partial remission at six months received another course of rituximab or an additional six months of cyclosporine; the study drug was stopped for all other patients. Patients were followed for a total of 24 months. The primary outcome was the proportion of patients who achieved complete remission (urine protein ≤ 0.3 g per 24 hours and serum albumin ≥ 3.5 g/dL) or partial remission (reduction of urine protein ≥ 50% plus a final urine protein of ≤ 3.5 g per 24 hours but > 0.3 g per 24 hours) at 24 months.

Rituximab was superior to cyclosporine in maintaining the complete or partial remission of proteinuria at 24 months. Rituximab was also noninferior to cyclosporine in complete or partial remission at 12 months.

The frequency of adverse events was similar in both groups, with more patients who received cyclosporine reporting serious adverse events than those who received rituximab. No deaths occurred during the trial and one patient in the cyclosporine group developed ESRD. The sample size and duration of the trial, however, may be insufficient to detect infrequent adverse events or those that had a longer lag time.

Key limitations included the sample size (65 patients per group) and open-label design. Due to the extent of missing data and selection bias, no conclusions can be drawn regarding the relative treatment effects of rituximab versus cyclosporine on health-related quality of life, creatinine clearance, and anti-PLA2R levels.

References

1. Angioi A, Lepori N, Lopez AC, Sethi S, Fervenza FC, Pani A. Treatment of primary membranous nephropathy: where are we now? *J Nephrol.* 2018;31(4):489-502.
2. Bomback AS, Fervenza FC. Membranous nephropathy: approaches to treatment. *Am J Nephrol.* 2018;47 Suppl 1:30-42.
3. Wang CS, Greenbaum LA. Nephrotic syndrome. *Pediatr Clin North Am.* 2019;66(1):73-85.
4. Rojas-Rivera JE, Carriazo S, Ortiz A. Treatment of idiopathic membranous nephropathy in adults: KDIGO 2012, cyclophosphamide and cyclosporine A are out, rituximab is the new normal. *Clin Kidney J.* 2019;12(5):629-638.
5. Willis K, Cheung M, Slifer S. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl (2011).* 2012;2(Supplement 2):1-143. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2012-GN-Guideline-English.pdf. Accessed 2020 Jan 28.
6. Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med.* 2019;381(1):36-46.
7. Cattran DC, Appel GB, Hebert LA, et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int.* 2001;59(4):1484-1490.
8. Cattran DC, Greenwood C, Ritchie S, et al. A controlled trial of cyclosporine in patients with progressive membranous nephropathy. Canadian Glomerulonephritis Study Group. *Kidney Int.* 1995;47(4):1130-1135.
9. Alfaadhel T, Cattran D. Management of membranous nephropathy in Western countries. *Kidney Dis (Basel).* 2015;1(2):126-137.
10. Non-inferiority clinical trials to establish effectiveness. Guidance for industry. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2016: https://www.fda.gov/media/78504/download.
11. Chen Y, Schieppati A, Cai G, et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. *Clin J Am Soc Nephrol.* 2013;8(5):787-796.
12. Thompson A, Cattran DC, Blank M, Nachman PH. Complete and partial remission as surrogate end points in membranous nephropathy. *J Am Soc Nephrol.* 2015;26(12):2930-2937.
13. Couser WG. Primary membranous nephropathy. *Clin J Am Soc Nephrol.* 2017;12(6):983.
14. Cattran DC, Kim ED, Reich H, Hladunewich M, Kim SJ. Membranous nephropathy: quantifying remission duration on outcome. *J Am Soc Nephrol.* 2017;28(3):995-1003.