Rituximab or cyclosporine A for the treatment of membranous nephropathy: economic evaluation of the MENTOR trial

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ABSTRACT

Background and hypothesis. The MENTOR trial (MEmbranous Nephropathy Trial Of Rituximab) showed that rituximab was noninferior to cyclosporine in inducing complete or partial remission of proteinuria and was superior in maintaining proteinuria remission. However, the cost of rituximab may prohibit first-line use for some patients and health-care payers.
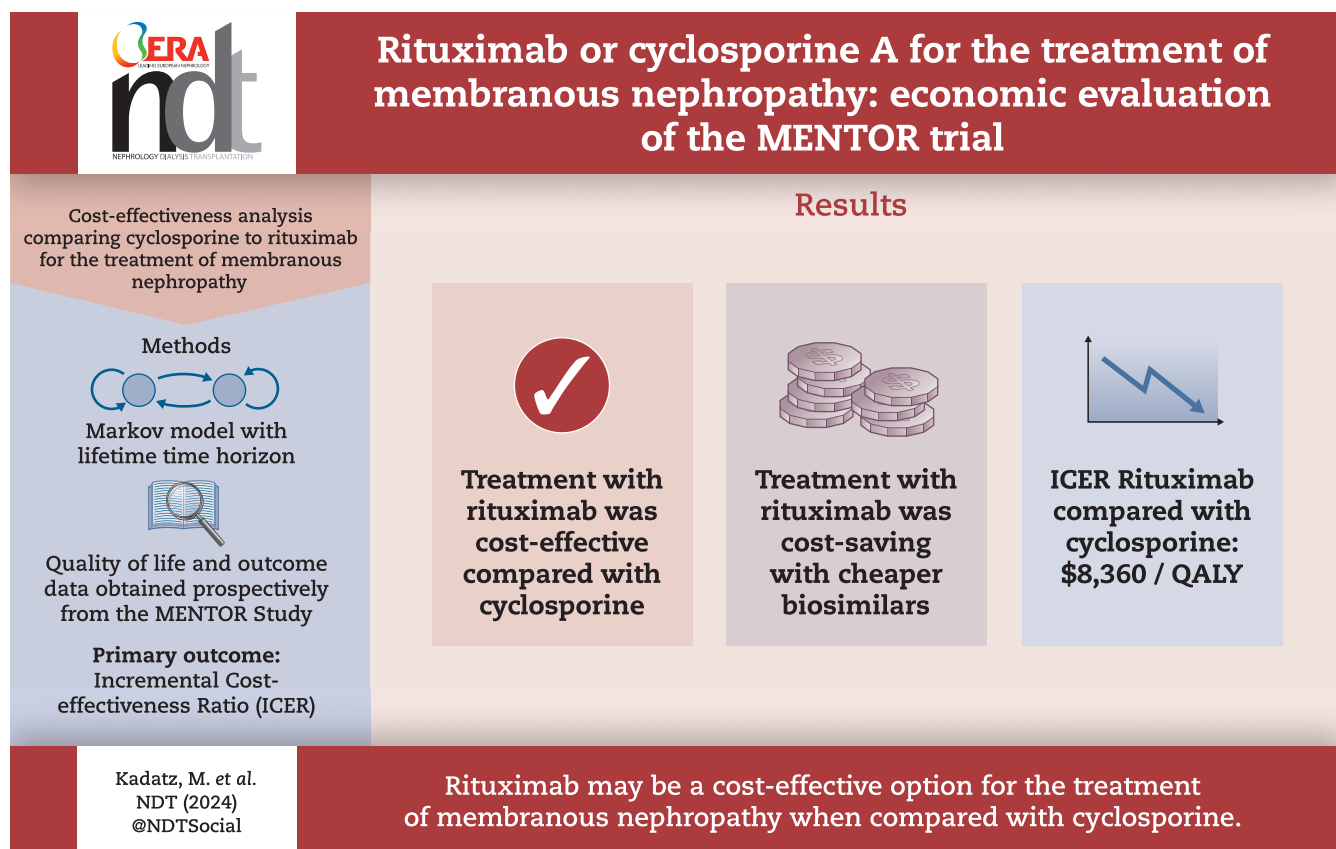
Methods. A Markov model was used to determine the incremental cost-effectiveness ratio (ICER) of rituximab compared with cyclosporine for the treatment membranous nephropathy from the perspective of a health-care payer with a lifetime time horizon. The model was informed by data from the MENTOR trial where possible; additional parameters including cost and utility inputs were obtained from the literature. Sensitivity analyses were performed to evaluate the impact of reduced-cost biosimilar rituximab.

Results. Rituximab for the treatment of membranous nephropathy was cost effective (assuming a willingness-to-pay threshold of $50 000 per quality-adjusted life year (QALY) gained; in $US 2021) compared with cyclosporine, with an ICER of $8373/QALY over a lifetime time horizon. The incremental cost of rituximab therapy was $28 007 with an additional 3.34 QALYs compared with cyclosporine. Lower cost of rituximab biosimilars resulted in a more favorable ICER, and in some cases resulted in rituximab being dominant (lower cost and great benefit) compared to cyclosporine.

Conclusions. Despite the greater cost of rituximab, it may be a cost-effective option for the treatment of membranous nephropathy when compared with cyclosporine. The cost-effectiveness of rituximab is further improved with the use of less expensive biosimilars.

Keywords: cost-effectiveness, cyclosporine, economic evaluation, membranous nephropathy, rituximab

GRAPHICAL ABSTRACT

Rituximab or cyclosporine A for the treatment of membranous nephropathy: economic evaluation of the MENTOR trial

Cost-effectiveness analysis comparing cyclosporine to rituximab for the treatment of membranous nephropathy

Methods

Markov model with lifetime time horizon

Quality of life and outcome data obtained prospectively from the MENTOR Study

Primary outcome: Incremental Cost-effectiveness Ratio (ICER)

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Results

Treatment with rituximab was cost-effective compared with cyclosporine

Treatment with rituximab was cost-saving with cheaper biosimilars

ICER Rituximab compared with cyclosporine: $8,360 / QALY

Rituximab may be a cost-effective option for the treatment of membranous nephropathy when compared with cyclosporine.

KEY LEARNING POINTS

What was known:

- Treatment of membranous nephropathy with rituximab has been shown to result in favorable outcomes compared with cyclosporine and is recommended as a first-line treatment; however, rituximab is more expensive than cyclosporine. This study aimed to determine whether using rituximab compared with cyclosporine to treat patients with membranous nephropathy would be cost effective in the long term given its potential benefits.

This study adds:

- This study found that using rituximab instead of cyclosporine is cost effective compared to cyclosporine for the treatment of membranous nephropathy. In jurisdictions where the cost of rituximab is lower (such as Canada, UK, Europe), the use of rituximab may be cost-saving to the health-care system.

Potential impact:

- This is important information for health-care decision-makers when determining whether rituximab would be funded for patients with membranous nephropathy.

INTRODUCTION

Membranous nephropathy is a leading cause of nephrotic syndrome in adults. [1] While 30% of affected patients will experience spontaneous remission, those who do not achieve remission are at high risk of progression to kidney failure. [2] Furthermore, these patients are at risk for other adverse health outcomes related to the nephrotic syndrome or to immunosuppression therapies used to treat the disease, and accrue significant costs to health-care payers. [3, 4] First-line therapies to induce remission in primary membranous nephropathy have historically included alkylating agents or calcineurin inhibitors. However, alkylating agents are limited by significant drug toxicities and calcineurin inhibitors have a high risk of relapse after completion of therapy.

In 2019 the MEmbranous Nephropathy Trial Of Rituximab (MENTOR) trial demonstrated that rituximab was noninferior to cyclosporine in inducing complete or partial remission of proteinuria after 12 months and was superior in maintaining proteinuria remission after 24 months. [5] Furthermore, patients who received rituximab were observed to have a higher creatinine clearance at the end of 2 years of therapy compared to those treated with cyclosporine, even among the subset of patients who experienced complete or partial remission. With a more favorable side effect profile compared to other alternatives and a higher probability of inducing remission, rituximab is now considered a first-line option therapy in the 2021 KDIGO guidelines for patients with moderate- or high-risk primary membranous nephropathy.

Table 1: Summary of characteristics of patients included in the MENTOR study.[a]

	Rituximab	Cyclosporine
Age, years (SD)	51.9 (12.6)	52.2 (12.4)
Sex, male: % (no.)	72% (47)	82% (53)
Creatinine clearance, ml/min/1.73 m^2 (SD)	84.9 (29.8)	87.4 (34.4)
Median serum albumin, mg/dl (interquartile range)	2.5 (2.1–2.9)	2.5 (2.1–2.9)
Median urinary protein, g/24 h (interquartile range)	8.9 (6.8–12.3)	8.9 (6.7–12.9)
Prior treatment with immunosuppressive therapy, % (no.)	29% (19)	31% (20)
Anti-phospholipase A$_2$ antibody positive, % (no.)	77% (50)	71% (46)

[a]Data adapted from Fervenza *et al. NEJM* (2019) [5].

[6] However, the greater cost of rituximab may be prohibitive to health-care payers or to patients who must pay out-of-pocket [7].

In this economic evaluation we use prospectively obtained data from the MENTOR trial cohort to determine the cost-effectiveness of rituximab to cyclosporine for the treatment of adults with membranous nephropathy using a Markov model [5]. We hypothesized that despite the higher cost of the drug, that rituximab would be a cost-effective treatment option compared with cyclosporine. The primary objective was to inform policy and healthcare decision-makers for treatment guidelines of primary membranous nephropathy.

MATERIALS AND METHODS
Study design

We used Markov models to simulate a fixed cohort of adult patients with primary membranous nephropathy requiring immunosuppressive therapy based on the MENTOR study participants and outcomes. The mean age of this cohort was 52 years; a summary of the characteristics of these patients is presented in Table 1. The model compared the treatment options of rituximab with cyclosporine, as outlined in the MENTOR study. [5] A deterministic method using fixed model inputs was used for the base model. The primary study outcome is the incremental cost-effectiveness ratio (ICER) in US dollars (2021) per quality-adjusted life year (QALY). The base-case model used a healthcare payer perspective with a lifetime time horizon and 6-month cycle length. A secondary model with a 24-month time horizon was also performed to align with the duration of follow-up in the MENTOR study. An annual discounting rate of 1.5% was applied to both cost and utility as per current guidelines. [8] A breakdown of the contribution of each health state to cost and utility in the model was calculated. The models were created using TreeAge Pro© 2021 (TreeAge Software, Williamstown, MA, USA). [9] This study was exempt from the requirement of research ethics board review as no patient level data were collected as part of this analysis.

Health states and outcomes

A graphical representation of model structure is shown in Fig. 1. All patients started in a treatment health state (Rituximab or Cyclosporine), and could transition to partial remission (PR), complete remission (CR), or no response (NR) after 6 months of treatment. Patients in the CR and NR state discontinued treatment, while patients in the PR state continued treatment for another 6-month cycle for a total of 12 months of treatment, which aligns with the treatment approach used in the MENTOR trial. Patients in CR or PR state who experienced a relapse would have retreatment for 6 months if they initially had CR or another 12 months if they initially had PR. The duration of retreatment was dependent on remission status after 6 months of retreatment. Patients in any remission state could progress to kidney failure over their lifetime, at which point they could be treated with kidney transplantation or dialysis. Patients could transition to death from any other health state.
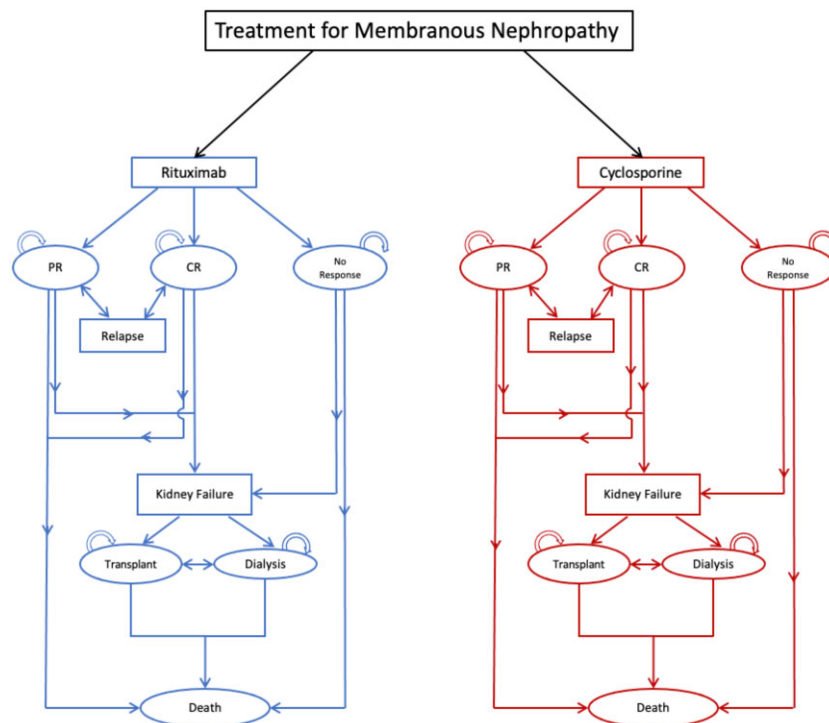
Cost, utility, and probability estimates

The model inputs are summarized in Table 2. The cost of rituximab was based on the price of 1 g of Rituxan® therapy in the USA, [10] while the cost of cyclosporine was calculated based on the mean dose of cyclosporine of patients included in the MENTOR study, multiplied by the cost of cyclosporine per milligram. Costs including kidney biopsies, blood work monitoring, and physician assessments were not included in the model given these would be similar in both treatment groups. Outcomes in the first 24 months of the model were informed by data from the MENTOR study and outcomes beyond 24 months were derived using evidence from a focused literature search (see Supplementary material for further discussion). Utility estimates for the health states of treatment phase, PR, CR, and NR were calculated from results of SF-12 data acquired prospectively during the MENTOR study that were mapped to the EQ-5D index to inform quality of life. [11]

Limited mortality data are available for patients with membranous nephropathy who have not progressed to kidney failure. There were no deaths in the 24-month follow-up of the MENTOR study, and so there was no risk of death in the first 24 months in the model. Beyond 24 months, patients with CR and PR who do not develop kidney failure were assigned a risk of death based on the general population risk from 2020 US life table data. Patients with NR have a known increased risk of death and therefore, a hazard ratio for death of 1.69 was applied. [12] No patients in the 24-month follow-up of the MENTOR study experienced progression to kidney failure; beyond 24 months, the probability of progression of kidney disease to kidney failure varied depending on remission status. [2] Utility values of transplant and dialysis and cost data were derived from the literature. [13] All costs were adjusted to 2021 US dollars using the consumer price index.

Assumptions and limitations

Follow-up in the MENTOR study continued for up to 2 years; therefore, outcome data beyond 2 years was derived from existing literature. Furthermore, there were minimal adverse events reported in the MENTOR study and therefore adverse events were not modeled in this evaluation. Since treatment with alkylating agents was not evaluated in the MENTOR study, treatment with alkylating agents was not included in the model. For patients who achieved CR and PR but subsequently relapsed, it was assumed that patients would have a similar probability of achieving CR and PR after repeat treatment.

In the base-case model, patients who did not achieve CR or PR were assumed to undergo no further therapy. Risk of relapse of membranous nephropathy after kidney transplantation was not included in this model. Utility data from the MENTOR study were only available after mapping EQ-5D data from SF-36 surveys, which may have limitations [14].

Figure 1: Diagram of base-case Markov model.

Table 2: Estimates used in the Markov model with their primary assigned values and probability distributions.

Variable description	Base estimate	Probability distribution	Reference
Cost			
Rituximab (per 1 g)	$9395	Normal	[10]
Cyclosporine (per 1 mg)	$0.058	Normal	[10]
1 year of dialysis treatment	$83 797	Normal	[21]
Organ acquisition for transplant	$70 747	Normal	[22]
First year of transplant	$77 883	Normal	[23]
Subsequent years of transplant	$23 555	Normal	[23]
Utility			
Treatment	0.702	Normal	MENTOR study data
CR (varied by time since treatment initiation)	0.875–0.930	Normal	
PR (varied by time since treatment initiation)	0.735–0.767	Normal	
No remission	0.702	Normal	
Kidney failure on dialysis	0.71	Normal	[13]
Kidney failure with a functioning transplant	0.82	Normal	[13]
Probability estimates beyond 24 months in model[a]			
Probability of reaching kidney failure	varied by time after treatment initiation	N/A	[2]
Probability of death on dialysis	varied by age	NA	[21]
Probability of transplantation after progression to kidney failure	varied by age	NA	[21]
Probability of transplant failure	varied by age	NA	[21]
Relative risk of death in patients with NR to treatment	1.69	Normal	[12]
Risk of death from natural causes	varied by age	NA	[24]

[a] Transition probabilities for the first 24 months obtained directly from MENTOR study data are detailed in Supplementary Table S2.

Sensitivity analyses

To ensure the model findings were robust, we performed a variety of sensitivity analyses. A one-way sensitivity analysis was performed on the model inputs. When available, 95% confidence intervals reported in the literature were used as plausible ranges for these inputs. Otherwise, a range of ±10% was used to generate plausible ranges, except for cyclosporine where a range ±20% was used given potential variation in drug costs across jurisdictions. An independent sensitivity analysis was conducted to examine the impact of the cost of rituximab, which can vary by jurisdiction, as described next.

A probabilistic sensitivity analysis was also performed where uncertainty of parameters was represented by probability distributions for each input parameter (Table 2). The model was

Table 3: Results of deterministic base-case Markov model of rituximab compared to cyclosporine for the treatment of primary membranous nephropathy with a lifetime and 24-month time horizon.

Intervention	Cumulative costs ($)	Cumulative QALYs	Incremental cost ($) (rituximab vs. cyclosporine)	Incremental QALYs (rituximab vs. cyclosporine)	ICER (rituximab vs. cyclosporine)
Lifetime time horizon					
Rituximab	76 525	13.94	28 007	3.35	8360
Cyclosporine	48 518	10.59			
24-month time horizon					
Rituximab	17 258	1.52	14 636	0.062	238 589
Cyclosporine	2622	1.45			

then analyzed repeatedly with various combinations of estimates drawn randomly from each distribution. In this case, we repeated the analysis 10 000 times. The distribution of results from the probabilistic analysis are presented in cost-effectiveness acceptability curves with varying thresholds of willingness-to-pay per additional QALY.

It was observed in the MENTOR study that patients treated with cyclosporine had a creatinine clearance that was 18 mL/min/1.73 m^2 (95% CI: 5–31 ml/min/1.73 m^2) lower than the those treated with rituximab after 24 months, regardless of remission status. We therefore modeled scenarios in which patients treated with cyclosporine had an increased risk of kidney failure based on an expected creatinine clearance of 18 ml/min/1.73 m^2 lower than patients treated with rituximab, with a lower limit of 5 ml/min/1.73 m^2 and upper limit of 31 ml/min based on the observed confidence intervals in the MENTOR study. In this sensitivity analysis we ascribed a relative hazard for the risk of progression to kidney failure of 1.03 for each additional decrease of creatinine clearance by 1 ml/min/1.73 m^2 [2].

Additionally, the base model assumed there would be no subsequent treatment with alternative agents as this was not part of the protocol in the MENTOR study. To evaluate the real-world scenario in which patients might be treated with an alternative agent, we modeled a scenario in which patients who had NR to the initial therapy would be treated with the alternative (i.e. those who had NR to cyclosporine would subsequently be treated with rituximab and vice versa). Treatment with alkylating agents was not evaluated in this scenario.

Finally, there are multiple biosimilars of rituximab currently available, each with varying costs based on jurisdiction or country. We acquired cost estimates for rituximab biosimilars in various countries (Supplementary Table S1) and evaluated the impact of the lower costs on the overall cost-effectiveness of rituximab therapy. It was assumed in this sensitivity analysis that the efficacy of these biosimilars would be equivalent to Rituxan®.

RESULTS
Primary model results

In the base-case deterministic model, treatment with rituximab was associated with an additional 3.35 QALYs, and an increased cost of $28 007 compared with cyclosporine, resulting in a calculated ICER of $8360/QALY (Table 3, Supplementary Fig. 1). In the secondary model with a 24-month time horizon, rituximab treatment was associated with slightly greater QALYs (0.062) with an

Table 4: Summary of categories contributing to the cumulative cost and utility from deterministic analysis of the base model comparing rituximab to cyclosporine for the treatment of primary membranous nephropathy.

| Category	Value Rituximab	Value Cyclosporine
Cost categories ($)		
Drug cost (%)	46 543 (60.8)	8257 (17.0)
Dialysis cost (%)	29 046 (38.0)	39 049 (80.5)
Transplant cost (%)	936 (0.2)	1212 (2.5)
Total	76 525	48 518
Utility categories (QALYs)		
On treatment (%)	0.90 (6.5)	2.59 (12.2)
CR (%)	6.29 (45.2)	0.091 (0.4)
PR (%)	3.55 (25.5)	7.73 (36.5)
NR (%)	2.94 (21.1)	10.09 (47.6)
Dialysis (%)	0.25 (1.8)	0.66 (3.1)
Transplant (%)	0.007 (<0.1)	0.018 (<0.1)
Total	13.94	21.18

increased cost of $14 636 compared with cyclosporine, resulting in a calculated ICER of $238 589/QALY (Table 3).

We found that most of the costs in patients treated with rituximab in the model were derived from drug costs (60.8%), whereas most of the costs in patients treated with cyclosporine were due to progression to kidney failure (80.5%) (Table 4). Furthermore, more patients treated with rituximab achieved complete or PR and had a lower risk of kidney failure compared to cyclosporine, resulting in higher cumulative QALYs over a lifetime time horizon (Table 4).

Sensitivity analyses

The Markov model results were robust in all one-way sensitivity analyses presented in a tornado diagram (Fig. 2). If the discount rate was increased to 5%, the calculated ICER increased to $12 012/QALY, while is the discount rate was 0%, the ICER decreased to $7245/QALY. If utility of the CR health state increased to 0.98, the calculated ICER decreased to $7245/QALY; whereas, if the utility decreased to 0.81, the ICER increased to $9784/QALY. There were minimal changes in the calculated ICER in the remaining one-way sensitivity analyses, including when the cost of cyclosporine varied by ±20%.

At a willingness-to-pay threshold of $8500/QALY and above, treatment with rituximab was favored in probabilistic analysis
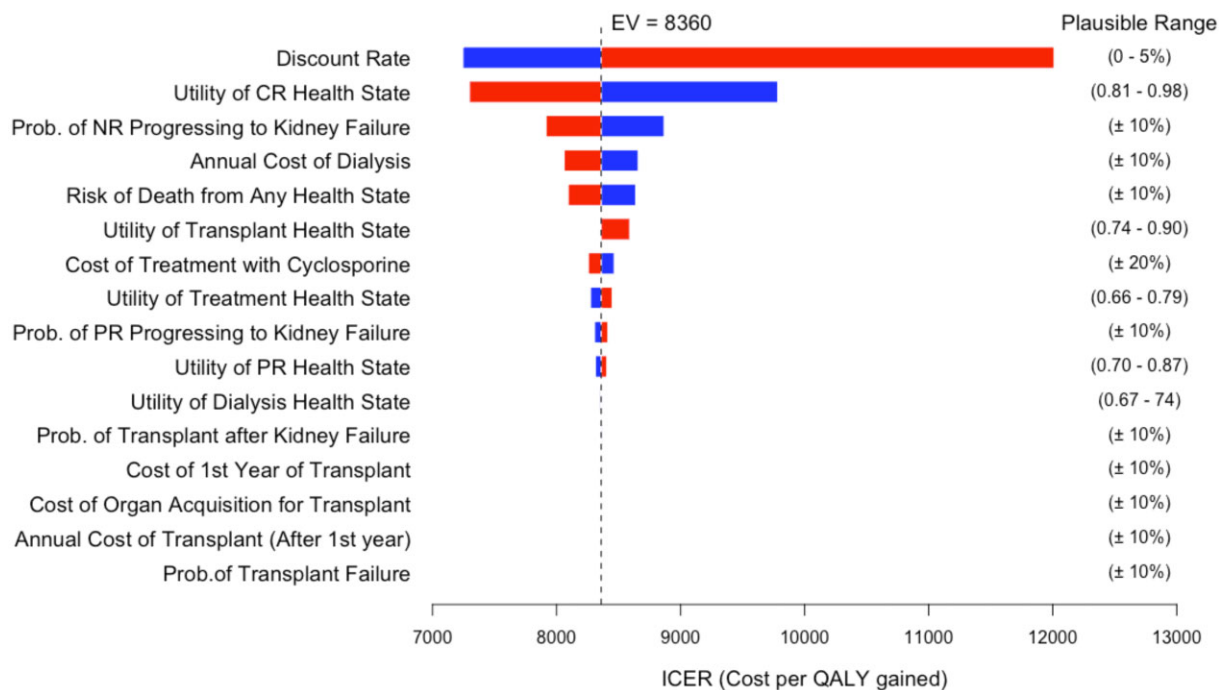
Figure 2: Tornado diagram of results of one-way sensitivity analyses from Markov model. This graph demonstrates the range of ICERs given the plausible ranges for each input variable. The estimated value (EV) of the ICER from the overall deterministic Markov model is shown on the graph with a dashed line. Prob., probability.

(Fig. 3). Rituximab therapy was the favored strategy in 100% of iterations at a willingness-to-pay threshold of $20 000/QALY.

In scenarios where the creatinine clearance of patients treated with cyclosporine was modeled to be 18 ml/min/1.73 m² lower than those treated with rituximab, as observed in the MENTOR study, the ICER improved modestly from $8373/QALY to $6995/QALY (Table 5). At the extremes of the confidence interval for the observed change in creatinine clearance (5–31 ml/min/1.73 m²), the ICER was estimated to be $8012–6007/QALY. In the scenario where the alternative therapy would be offered to patients who failed initial therapy with either cyclosporine or rituximab, the strategy of initial treatment with rituximab was dominant (less costly and greater benefit) compared with initial cyclosporine strategy.

When the price of rituximab in the model was lowered to account for the reduced cost of rituximab biosimilars, the ICER of rituximab compared with cyclosporine improved substantially (Fig. 4) with the largest improvement observed with the current price of rituximab in Canada, and the UK where the treatment with rituximab dominated treatment with cyclosporine (i.e. rituximab was less expensive and more effective). The threshold for cost neutrality was reached if the 1 g cost of rituximab decreased to ~$3800.

DISCUSSION

We had hypothesized that rituximab would be a cost-effective treatment option compared to cyclosporine for the treatment of primary membranous nephropathy in adults. In this analysis, we found that treatment with rituximab would result in improved quality-adjusted life years with an acceptable cost-effectiveness ratio (ICER of $8373/QALY) when referenced to commonly cited willingness-to-pay thresholds [15, 16, 17]. In scenarios of reduced drug acquisition costs that may occur with biosimilars, rituximab

was even more attractive and in some scenarios was dominant (less costly and more effective) compared with cyclosporine. Therefore, rituximab is preferred from the health-care payer perspective compared to cyclosporine.

This is the first economic evaluation to our knowledge that compares rituximab to cyclosporine for the treatment of membranous nephropathy. This analysis is based on the results directly obtained from a randomized controlled trial, which allowed for accurate model inputs of cost and outcomes for the first 24 months of the model. Further, quality of life data for health states of CR, PR, and NR were captured prospectively in the MENTOR study allowing for robust utility estimates for these health states. We were also able to incorporate the observation from the MENTOR study that patients treated with cyclosporine had a lower CrCl at the end of the study follow-up in a sensitivity analysis. Despite a lower CrCl potentially leading to an increased risk of kidney failure in patients treated with cyclosporine, incorporating this observation into our model only marginally improved the ICER in favor of rituximab to $6007/QALY, suggesting that the cost-effectiveness of rituximab is not substantially affected by the assumptions regarding kidney function following treatment, but rather the ability to achieve and maintain remission. Additionally, in a more realistic scenario that likely better approximates usual clinical care in which the alternative therapy would be offered to patients who failed initial therapy with either cyclosporine or rituximab, a strategy of starting treatment with rituximab was cost-saving compared to a strategy of starting treatment with cyclosporine. This further supports the use of rituximab as a potential first-line therapy for patients with primary membranous nephropathy who require immunosuppression.

There are several limitations to our analysis. First, the MENTOR study only captured 24 months of follow-up data, and therefore previously published analyses of retrospective data was used to inform model inputs beyond 24 months. When we limited the

Table 5: Model the results of scenario analyses including incremental cost, incremental QALY's and ICER of rituximab compared to cyclosporine therapy for the treatment of membranous nephropathy.

Scenario	Incremental Cost ($)	Incremental QALYs	ICER ($/QALY)
Base-case results	**28 007**	**3.34**	**8373**
Lower creatinine clearance (CrCl) in cyclosporine arm			
CrCl ↓18 ml/min/1.73 m²	25 906	3.70	6995
CrCl ↓5 ml/min/1.73 m²	27 477	3.43	8012
CrCl ↓31 ml/min/1.73 m²	24 037	4.00	6007
Alternative treatment offered	−102	3.21	dominant

time horizon of the model to 24 months, we did not find that rituximab was cost effective with a calculated ICER of $238 589/QALY. This is because none of the patients in the 24 months of the MENTOR study progressed to kidney failure or died, and therefore the benefit of rituximab compared to cyclosporine on health outcomes are not observed over this shorter time horizon. However, our model results indicate the cost-effectiveness of rituximab therapy over a lifetime time horizon is primarily derived from a reduction in the risk of progression to kidney failure that results from better induction and maintenance of both overall remission and CR compared to cyclosporine. While a lifetime horizon is most appropriate, [8, 18] there is uncertainty in extrapolating trial outcomes; if the association of remission and progression to kidney failure differs from existing literature, the result may be altered. Furthermore, the patient population represented in the MENTOR trial were particularly high risk, with median baseline proteinuria of 8.9 g/day, serum albumin of 2.5 g/dl, 74% with positive serum PLA2R antibody (medial level on EURIMMUN assay of 165 RU/ml), and 29–31% having received previous immunosuppression treatment. [5, 19] Therefore, the results of this study may not be applicable to lower risk populations. Additionally, in the MENTOR trial serious adverse events occurred in 31% of patients treated with cyclosporine compared with 17% in those treated with rituximab. [5] This finding was not statistically significant and therefore not included in our model, however, if the rate of adverse events is truly lower in patients treated with rituximab, then the cost-effectiveness of rituximab would be underestimated in our current model. Finally, the MENTOR study only included the treatment options of cyclosporine or rituximab. As such, we were not able to compare the cost-effectiveness of rituximab to alkylating agents, such as cyclophosphamide to rituximab. However, a recent economic evaluation that compared rituximab to cyclophosphamide for the treatment of primary membranous nephropathy and also found that rituximab was a cost-effective treatment option despite the high initial treatment cost with a ICER of £10 246/QALY (∼$12 214 in 2022) [20].

While the upfront cost of rituximab could be regarded as a limitation for routine use, in recent years biosimilar rituximab has become widely available. It is generally thought that these agents have equal efficacy for the treatment of primary membranous nephropathy; our analysis suggests that the lower costs of these
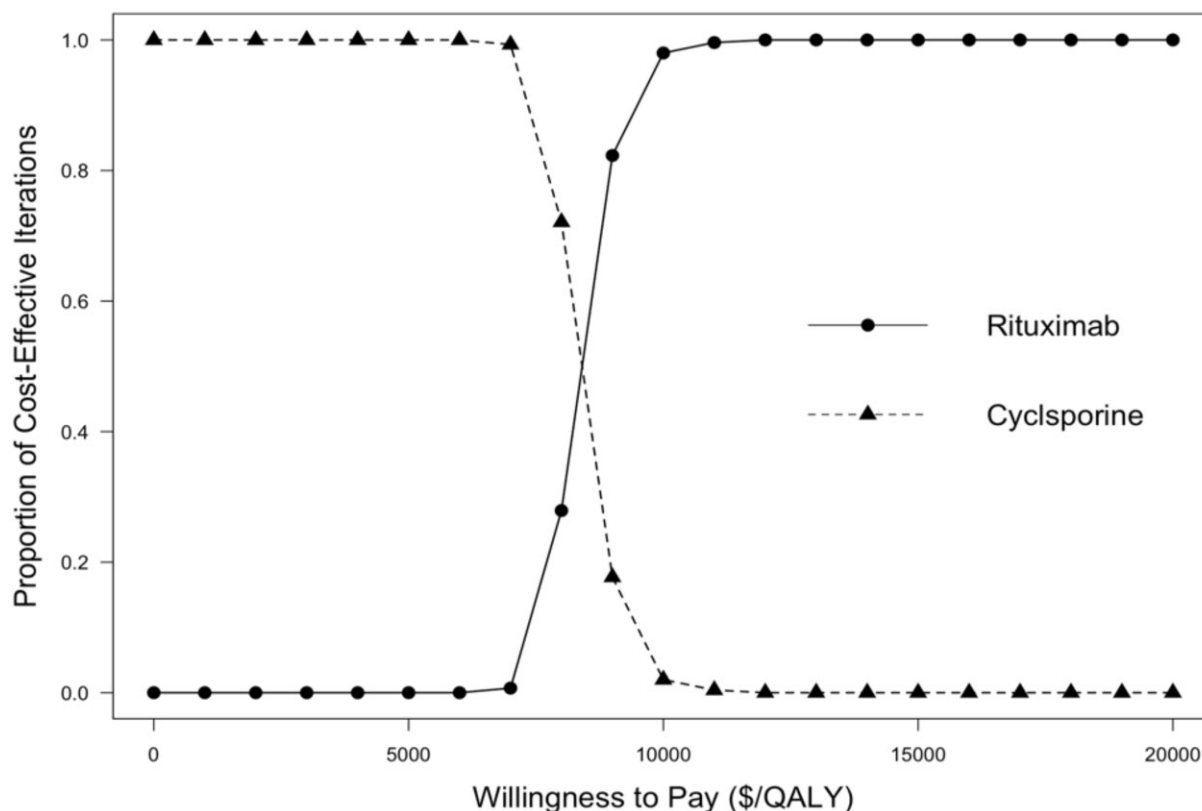
Figure 3: Cost-effectiveness acceptability curve of the results of the probabilistic sensitivity analysis for the incremental cost-effectiveness of rituximab (RTX) compared with cyclosporine (CsA) for the treatment of primary membranous nephropathy. This graph shows the proportion of iterations where rituximab (circles, solid line) and cyclosporine (triangles, dashed line) were cost effective according to varying willingness-to-pay thresholds. See the Supplementary Figure for these results presented as a scatter plot on the cost-effectiveness plane.
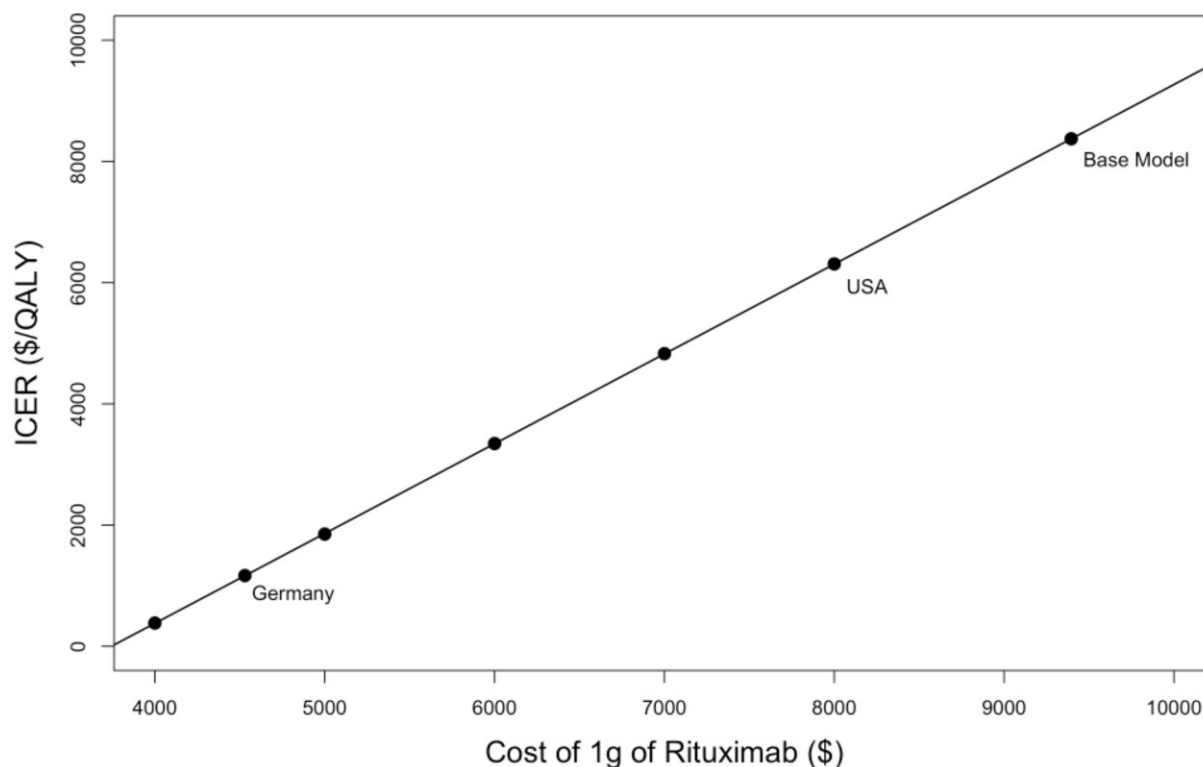
Figure 4: ICER as a function of the cost of 1 g of rituximab. For reference, the ICER assuming costs of generic biosimilars in Germany and the USA are labeled. Costs of generic biosimilars in Canada and the UK are not shown as these resulted in a dominant ICER where treatment with rituximab was less expensive than treatment with cyclosporine and more effective.

agents would dramatically improve the cost-effectiveness of rituximab, and might even result in cost savings in settings where the cost of biosimilars is much lower (i.e. Canada and the UK).

In summary, this trial based economic evaluation found that rituximab was cost effective compared to cyclosporine for the treatment of primary membranous nephropathy in adults, despite the high cost of rituximab therapy. The use of biosimilars may result in cost savings in some countries given the lower drug acquisition costs. These findings can be used by health-care payers to support policy decisions to implement the 2021 KIDOG guideline recommendations of rituximab as a cost-effective first-line therapy for the treatment of patients with primary membranous nephropathy.

SUPPLEMENTARY DATA

Supplementary data are available at *Nephrology Dialysis Transplantation* online.

AUTHORS' CONTRIBUTIONS

M.K., S.K., and H.S. were involved in the conceptualization, study design, analysis, and writing of this paper. S.J.B. and D.C.C. were involved in the conceptualization, study design, and writing of this paper. F.C.F. was involved in the conceptualization and writing of this paper.

DATA AVAILABILITY STATEMENT

Much of the data presented in this paper are derived from the MENTOR study data, which are not publicly available. Summary data have been included in the paper's tables and Supplementary Materials.

CONFLICT OF INTEREST STATEMENT

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