
Article:
Hamilton, P, Kanigicherla, D, Venning, M et al. (2 more authors) (2018) Rituximab versus the modified Ponticelli regimen in the treatment of primary membranous nephropathy: a Health Economic Model. Nephrology Dialysis Transplantation, 33 (12). pp. 2145-2155. ISSN 0931-0509

https://doi.org/10.1093/ndt/gfy049

Rituximab versus the modified Ponticelli regime in the treatment of Primary Membranous Nephropathy: A health economic model

Patrick Hamilton[1], Durga Kanigicherla[1], Michael Venning[1], Paul Brenchley[1], David Meads[2]

1 Manchester Institute of Nephrology & Transplantation
Manchester Royal Infirmary
Oxford Road
Manchester
M14 9WL

2 Academic Unit of Health Economics
Leeds Institute of Health Sciences
Charles Thackrah Building
University of Leeds
101 Clarendon Road
Leeds
LS2 9LJ

Corresponding Author
Dr Patrick Hamilton MB ChB MRCP (UK)
patrick.hamilton@cmft.nhs.uk
0161 276 7987

Manuscript	4445
Abstract	245
Acknowledgements	93
References	59
Tables	6
Figures	4
Supplementary material	4 tables

Summary

Treatment for primary membranous nephropathy has remains still cyclophosphamide-based (the Ponticelli regimes), since the 1980s despite its high side-effect burden. Newer therapies such as Rituximab show promise but are expensive. We undertook a cost-effectiveness analysis of overall administration costings; based on UK NHS prices to compare Rituximab with than the modified Ponticelli regime, the current standard of care.

Background

Membranous Nephropathy is among the most common causes of nephrotic syndrome worldwide, with a high healthcare burden. Treatment using the modified Ponticelli regimes (mPR) has remained the standard of care for decades, but newer therapies such as Rituximab offer promising results with reduced side effects. The cost of this treatment however, is perceived as a barrier to widespread use; especially in resource limited healthcare systems.

Methods

We developed a decision-analytic model to estimate the cost-effectiveness of Rituximab versus the mPR from the perspective of the National Health Service in the UK over a one-year, five-year and lifetime horizon. Primary outcome is the cost-effectiveness of Rituximab vs. mPR at five-years post-treatment. Secondary outcomes are cost-effectiveness at 1 and 10 years post-treatment and over a lifetime.

Results

At one-year post-treatment, Rituximab therapy dominates mPR. At five-years post treatment, Rituximab therapy is cheaper than the Ponticelli regime but at a loss of 0.014 QALYs with an ICER of £95,494.13. Over a lifetime, Rituximab remains the cheaper option with an incremental cost of -£5251.03 but with a reduced quality of life (incremental QALY of -0.512) giving an ICER of £10,246.09.

Conclusions

Our analysis indicates that Rituximab has the potential to be a cost-effective treatment in the short and medium term despite the high single dose cost. This evaluation suggests that further research is warranted and highlights the need for a high quality clinical trial to confirm the efficacy and cost-effectiveness of Rituximab versus the current standard of care.

Introduction

Membranous nephropathy (MN) is one of the most common causes of adult nephrotic syndrome worldwide with a high healthcare burden in which approximately 20% of patients progress to end stage renal disease (ESRD)[1,2].

MN has two distinct entities with primary MN (PMN) now considered to be an autoimmune disease since the discovery of the M-type of phospholipase A2 receptor 1 (anti-PLA_2R) antibodies[3-7].

In PMN, disease activity and prognosis is still measured by proteinuria level and renal excretory function with the risk of renal decline falling in the presence of a reduction in proteinuria[6,10-14]. A key marker of treatment efficacy in PMN is therefore control of proteinuria, with or without immunosuppression[9]. Such immunosuppression is generally a combination of alkylating agents and steroids, as used in studies by Ponticelli et al[15-18]. This regime of rotating high dose intravenous steroids and immunosuppression was first described in 1984 and has been the mainstay of treatment since[15]. Initially using Methylprednisolone and Chlorambucil, it was later modified to include Methylprednisolone and Cyclophosphamide[15-18]. Despite its treatment success, the modified Ponticelli regime (mPR) bares a significant side effect profile, including an increased risk of infection, osteoporosis, diabetes mellitus, weight gain, haemorrhagic cystitis, infertility and malignancy[16]. This led many researchers to search for alternative therapies including tacrolimus and Mycophenolate Mofetil but with little evidence to show any improvement in outcomes[19-23].

Rituximab has been used extensively in cancer therapy since the late 1990s and more recently for autoimmune diseases. A number of case series and studies have demonstrated potential in PMN but so far randomised controlled trials (RCT) have been scarce[24-28]. This, combined with the high cost of the medication itself, has restricted its widespread use in resource limited, evidence based, healthcare systems such as the National Health Service in the UK (NHS).

We developed a decision-analytic model to estimate the cost-effectiveness of Rituximab therapy versus the standard of care, namely the modified Ponticelli regime for the treatment of primary MN.

Methods

A cost-effectiveness analysis was carried out using a stochastic cohort Markov model developed using standard methods[29], conducted from the perspective of current practice in the UK NHS at 2015 prices.

The primary outcome was the cost-effectiveness of Rituximab versus mPR at five-years post treatment. Secondary outcomes were cost-effectiveness at one and ten years post-treatment and over a lifetime. A literature search revealed no studies directly comparing Rituximab versus mPR and therefore data was taken from the only studies of sufficient size to afford representative outcome assessment as described below. The analysis employed the cost-utility framework where the main measure of benefit is the quality-adjusted life year (QALY) and with analysis outcomes presented in terms of incremental cost-effectiveness ratios (ICER) of cost per QALY gained.

Choice of comparator

Here we have used the mPR which is the standard of treatment as per the KDIGO guidelines having established that the majority of UK renal centres use versions of the mPR as described by Ponticelli et al and Jha et al[9,17,18,30].

Model Structure

The model was developed in consultation with an expert panel including physicians, health economists and clinical scientists, and was identical for each treatment arm (see figure 1).

For the treatment phase, all patients were assumed to experience active disease and costs were calculated from the papers described below. Following the treatment phase, patients could transition to (persistent) active disease, partial remission or complete remission. Health states then included sustained remission, relapse, ESRD (conservative management, haemo- or peritoneal dialysis and renal transplant) or death. Following the initial treatment phase, patients transitioned between health states on three-monthly cycles over a lifetime horizon.

PMN is generally considered a disease of middle age with the median age of patients with PMN at diagnosis is 53 years old; we therefore extended the lifetime over an additional 47 years corresponding to a maximum survival of 100 years old[31].

Parameter values

Model parameter values and effectiveness of the interventions were based on the most robust data available for each arm; Jha et al for the mPR arm and Ruggenenti et al for the Rituximab arm[18,26]. Jha et al was a prospective RCT comparing the mPR with supportive care, in biopsy proven adults (>16 years old) with nephrotic syndrome for more than 6 months duration and less than 2 months of treatment with either steroids or immunosuppression. There was a total of 93 patients completing the study, 47 receiving the mPR with oral cyclophosphamide and IV Methylprednisolone.

Ruggenenti et al published an observational study describing 100 consecutive patients, considered to be at a high risk of progressing to ESRD or to develop significant cardiovascular complications of their nephrotic syndrome, treated with Rituximab and no control group. It involved two distinct regimes; initially patients received Rituximab in four weekly doses of 375mg/m^2. However, as many patients on this regime were found to be B cell deplete after only the first dose of Rituximab, all subsequent patients from 2005 onwards were changed to a titrated regime. Prior to inclusion in the trial, 32 patients had received treatment with alternative immunosuppression. 20 of these did achieve partial remission prior to relapsing and necessitating treatment. The remaining 12 never achieved remission prior to starting Rituximab. Of the 100 patients described in the study, 71 received a single 375mg/m^2 dose of Rituximab and only received a second dose if their serum B cells were more than 5 cells/mm^3. The cost of treatment in the Rituximab arm was therefore calculated using the same proportion of treatments (with corresponding outcomes) as in this study. This resulted in 29% of the total cost of treatment being taken as the cost of the initial four doses of 375mg/m^2 Rituximab regime and 71% as the cost of the B-cell titration regime.

These papers were also chosen for their similar observational period allowing for a similar evaluation of care; however partial and complete remission were defined slightly differently (table 1), Jha et al having more stringent remission criteria. In practice, there is a cohort of patients that spontaneously remit but the majority will remain nephrotic and therefore require treatment. Both these studies, as in clinical practice, have included patients with biopsy proven membranous nephropathy and significant proteinuria warranting immunosuppression. Both studies have a male predominance reflecting clinical practice and the mean age at presentation was older in the study as described by Ruggenenti et al. Jha et al was carried out in India and Ruggenenti et al was carried out in Italy, two differing healthcare systems. However, both studies were carried out using standard methods and are comparable to use in the UK[18,26]. See table 1.

Probabilities

Transition probabilities from the treatment phase to active disease, complete remission, partial remission, relapse and death were taken from the literature as above (Jha et al and Ruggenenti et al[18,26]). Here there was an assumption of constant hazards based on survival at a single time point. If a patient developed ESRD they transitioned into the renal replacement pathway, which includes conservative management. Transition probabilities after ESRD have been obtained from the UK Renal Registry (2014)[32]. Death rates were taken as those described in the study arms. At the end of the study follow up, UK Office of National Statistics (ONS) data was used to provide a baseline mortality rate[33]. For patients in active disease, the death rate obtained from the ONS data was added to the transition probability from the studies. Once in partial or complete remission, death rate was taken as that in the ONS only. Death rates once in ESRD were taken from the UK Renal Registry.

Costs

Healthcare resource use included all healthcare contact, hospital stays, medication and serious adverse event (SAEs) episodes described in each publication. The cost of relapse was taken as the cost of treatment but without SAEs. Costs for each hospital/healthcare contact and SAEs were taken from the NHS reference costs 2014 to 2015[34]. Standard Deviation estimated using S = Q3–Q1 / 1.35 [35]. The cost of medication was taken from the Drugs and Pharmaceutical electronic market information (eMit) or from the British National Formulary 2015 if not available[36,37]. For medications for which the dose is based on Body Surface Area we used 1.79m^2 [38]. Maintenance therapy was not costed. Standard deviation of costs is not provided by the BNF so these were taken to be half the mean. (Table 2, 3 & 4). See supplementary material for table with disaggregated costs of treatment stage for reference case and regimes used in sensitivity analysis.

Utility/Quality of life

For many patients, the presenting symptoms that bring them to the notice of healthcare professionals, and ultimately to the diagnosis of PMN, is that of the nephrotic syndrome, namely oedema, increasing shortness of breath and fatigue. Currently there is limited data available on the quality of life (or utility) for patients with PMN, therefore utility values for

active disease were taken as that of active nephrotic syndrome, given these are the main symptoms a patient will experience when their disease is active[39]. For patients with partial or complete remission we used age and sex matched EQ-5D UK population norms[40]. Once patients reached ESRD, utility values were estimated using SF-6D values from Wyld et al. converted to utility scores[41,42]. (Table 5).

Cost-effectiveness analysis

All costs are presented as mean cost per patient. Expected costs and QALYs were estimated for each arm and, where appropriate, ICERs calculated (derived from the incremental cost of treating with Rituximab and the incremental QALY). ICERs below the £20,000 threshold would indicate that Rituximab is considered cost-effective as set by National Institute for Health and Care Excellence (NICE) standards[43]. Following NICE guidelines, half cycle correction was conducted and a discount rate of 3.5% per annum was applied to all outcomes incurred beyond one year[43].

Incremental Net Monetary Benefit (INMB)

INMB's were calculated using the incremental QALY, the incremental cost and the Lambda, which in this case is £20,000, as per NICE guidelines[43]. A positive value indicates that Rituximab therapy is cost effective and therefore the preferred option when compared with the mPR.

Deterministic Sensitivity Analysis

We performed one-way sensitivity analysis on a range of parameters to assess the impact of each parameter on the outcome of the model at five-years post treatment as described by the INMB. For sensitivity analysis of the costs, these were altered, the quality of life and transition probabilities remaining unchanged. For sensitivity analysis of the transition probabilities, the costs remained unchanged. Exact alterations to costs and probabilities are given below.

Rituximab regimes

The study described by Ruggenenti et al used to inform the Rituximab arm in our model utilised two different regimes as described in the methods section. We therefore carried out a sensitivity analysis based on all patients in the Rituximab arm receiving the original regime consisting of four weekly infusions of 375mg/m^2 Rituximab. We then carried out the analysis

based on all patients in the Rituximab arm receiving the B cell titrated regime ie a single 375mg/m^2 dose of Rituximab with a second dose if their serum B cells were subsequently more than 5 cells/mm^3. For both of these, the costs in the Ponticelli arm remained unchanged. Further sensitivity analysis was carried out using the recently reported RCT described by Dahan et al[27]. Here patients in the treatment arm were given 2 doses of 375mg/m^2 Rituximab on days 1 and 8. For this analysis, only the costs in Rituximab arm of the model were changed and all outcomes remained the same.

Ponticelli regimes

The mPR uses low cost medications but requires multiple hospital admissions to receive steroid infusions. Therefore, to assess the impact that drug delivery has on the overall cost we performed a sensitivity analysis with patients only receiving oral prednisolone and no IV Methylprednisolone, with cyclophosphamide remaining unchanged. We also assessed how a change in the cyclophosphamide regime may affect the overall cost by carrying out a sensitivity analysis using pulsed monthly cyclophosphamide for 6 months with adjunctive oral prednisolone (with no IV methylprednisolone) as described by Kanigicherla et al[44]. The costs for the Rituximab arm remained unchanged for both of these analyses.

Other

To assess how the cost of drug delivery itself affects the model outcomes we performed a sensitivity analysis with an increase and decrease in the cost of the delivery of an infusion in a day-care setting by 20% and on the cost of the medication itself (Rituximab and Cyclophosphamide). For the cost of infusion delivery, the cost was altered in both arms. For the cost of medication, the cost was altered in each arm and analysed separately.

In order to provide consistency, the cost of cancer in the original analysis was taken as the cost for the least severe form of the disease as per the NHS reference costs[34]. To assess whether the cost of cancer impacts on the results we used the cost for the most severe form of the various cancers as reported in the NHS reference costs[34] for the sensitivity analysis.

Given the known uncertainty in the quality of life measures available we performed a sensitivity analysis on this by altering the utility value of partial remission to be the same as active disease instead of complete remission. This was changed in both arms simultaneously.

Transition probabilities

To investigate the impact of the transition probabilities on outcomes, we performed a number of analysis including altering the death rate to be equal in both arms, the chance of developing ESRD and needing RRT to be equal in both arms and the rate of relapse to be equal in both arms. We analysed the effect of treatment efficacy by altering the transition probabilities of going from the treatment phase to either active disease, partial remission or complete remission by making them equal in both arms. We then altered the chance of transitioning from active disease to remission so that it was equal in both arms. We altered all transition probabilities to be equal in both arms with no change to costs or utility values. We also increased and decreased the probability, by 20%, of going into remission in the Rituximab arm and keeping the Ponticelli arm unchanged. We then performed the same analysis by altering the transition probability in the Ponticelli arm and kept the Rituximab arm unchanged.

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted with 10,000 Monte Carlo simulations based on random draws of all parameter values simultaneously from probability distributions. This provided 10,000 estimates of costs and QALYs, which were used to generate 10,000 ICERs and incremental net monetary benefit (INMB) estimates and allowed us to estimate the level of parameter uncertainty in the analysis. These simulated analyses were plotted on a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC)[45]. The CEAC indicates the probability that Rituximab is cost-effective versus mPR across a range of willingness to pay per QALY gain thresholds[46]. The higher the probability, the lower the uncertainty is in the model and decision.

Validation

We employed a number of tests to ensure the model was valid as possible although given the nature of the disease and lack of clinical trials, we were unable to perform a full validation. Validation was carried out using recognised techniques[47]. Face validation was carried out with each aspect of the model design, data sources, formulae and eventual results reviewed and discussed by a panel of experts including clinicians, clinical scientists and health economists. Internal validation was performed using deterministic sensitivity analysis and testing whether changes in model inputs led to changes in outputs in the expected direction - for example by increasing the SAE / AE risks for Rituximab we expected the cost-effectiveness of that intervention would be reduced. Verification of the code was performed by one clinician and two separate and independent health economists.

As there are no other health economic or epidemiological models or RCTs in this area, cross validation, external validation and predictive validation were not possible.

Results

Incremental Cost-Effectiveness Ratio

At five-years post treatment, Rituximab therapy is cheaper than the Ponticelli regime but at a loss of 0.014 QALYs. Here the ICER is £95,494.13 (incremental cost -£1,355.82 and incremental QALY -0.014). At one-year post-treatment, Rituximab therapy dominates mPR. At 10 years post-treatment, Rituximab remains the cheaper option with an incremental cost of -£2,201.37. With an incremental QALY of -0.091 the ICER is £24,256.91. Over a lifetime the ICER was £10,246.09, obtained from the incremental per-patient cost of -£5,251.03 and incremental QALY of -0.512. See supplementary material for frequency of patients in each disease state at five-years post-treatment with corresponding costs and QALYs. See table 6.

Figure 2 - cost-effectiveness plane showing incremental costs versus incremental QALY at one-year, five-year and over a lifetime. Threshold line at £20,000 per QALY for 10,000 PSA simulations. At one-year and five-year post treatment the majority of simulated ICERs are in the right-hand side of the plane indicating Rituximab is more effective. There is a majority of patients in the lower half of the plane indicating that at five-years post treatment, Rituximab therapy is cheaper. The vast majority are below the £20,000 per QALY threshold set by NICE as the acceptable limit for the cost-effectiveness[43]. Over a lifetime the majority of patients are in the left lower quadrant showing that Rituximab therapy is cheaper but less effective.

Cost

At five-years post treatment the cost for the mPR was -£13,116.65 and the cost for the Rituximab regime was £11,760.83, showing that the mPR is more expensive than Rituximab with an incremental cost of -£1,355.82. At one-year post-treatment, the cost of mPR and Rituximab was £8,676.10 and £7,927.90 respectively giving and incremental cost of -£748.20. At ten-years post-treatment, the cost of mPR was £17,834.30 and for Rituximab was £15,632.93, indicating that Rituximab continues to be cheaper with an incremental cost of -£2,201.37. Over a lifetime the cost of mPR is £29,943.80 compared to £24,692.77 for the mPR; an incremental cost of -£5,251.03. See table 6.

QALY

The QALY gains for mPR and Rituximab were 3.712 and 3.697 respectively at five-years post treatment, 0.952 and 0.954 respectively at one-year, 6.603 and 6.513 respectively at ten-years, and 14.162 and 13.650 respectively over a lifetime. Therefore, at one year Rituximab

confers QALY benefits over mPR but this is reversed by five-years and continues over a lifetime.

Incremental Net Monetary Benefit

At one-year, five-year and ten-year post treatment the incremental net monetary benefit (INMB) of Rituximab therapy is £785.44, £1,071.86 and £386.32 respectively, indicating Rituximab is more cost-effective. Over a lifetime the INMB is -£4,998.79 showing mPR is the more cost-effective option. See table 6.

Deterministic Sensitivity Analysis

Constrained to address outcomes with a mixed-protocol Rituximab analysis the sensitivity analysis confirms that a major driver of cost for Rituximab was the number of infusions required. The original four-dose regime is too expensive at five-years post treatment but for the B cell titrating regime and the regime described by Dahan et al[27], at five-years post treatment, Rituximab is the cost-effective option. The other major drivers of cost-effectiveness in the Rituximab arm were death rate and the probability of reaching remission. For the mPR arm the main driver of the cost appears to be the frequency of infusions with removal of the cost of IV methylprednisolone resulting in the mPR being more cost-effective at five-years post treatment. The use of pulsed monthly IV cyclophosphamide alongside daily oral Prednisolone (again without IV Methylprednisolone) also resulted in the mPR being the most cost-effective at five-years post treatment. See figure 3 for full tornado plot of sensitivity analysis.

Cost effectiveness acceptability curve

Figure 4 - CEAC for the comparison based on the 10,000 PSA simulations. It shows the likelihood that Rituximab is cost-effective compared to mPR over a range of willingness-to-pay (WTP) per QALY gain threshold values (Lambda). At a lambda of £20,000 Rituximab has a 64% chance of being the cost-effective option at five-years post treatment. At a threshold of £30,000 this falls to 61%. This reflects the fact that Rituximab is the cheaper option at this time point but with a slightly reduced QALY.

Threshold analysis

In order for Rituximab to be the most cost-effective option over a lifetime, threshold analysis shows that the transition probability for treatment to active disease, partial remission and complete remission would have to change from 0.51250 to 0.61706, from 0.28500 to 0.22387 and from 0.20250 to 0.15907 respectively. Alternatively, the transition probability for active disease to death and partial remission to death for Rituximab would have to change from 0.00315 to 0.00136 and from 0.00680 to 0.00225 respectively.

Threshold analysis to determine the cost at which Rituximab represents the cost-effective option over a lifetime showed that due to the disparity in QoL there is no price at which it is cost-effective over a lifetime.

Discussion

The NHS, as with healthcare systems around the world, endeavours to provide the best care possible, with limited resources, for its aging population and increasingly complex patients. This has resulted in NICE, the regulatory body, considering not only the health benefits of therapies but also their economic impact.

Rituximab has become increasingly important in the treatment of a range of autoimmune conditions[48-58]. Its attraction lies in its more directed immunoregulation and reduced side effect profile as compared to other immunosuppressants. Its single dose cost however, has limited its use in conditions such as MN, especially where there is a paucity of evidence from RCTs available.

With this lack of RCTs but with good evidence that Rituximab can provide a benefit for patients in a number of trials and case series[24-28], we constructed a Markov model to assess its cost-effectiveness when compared to the standard of care, i.e. the mPR. Using costs from the UK NHS we found that at every time point analysed Rituximab was the cheapest option and this was especially true if using the B-cell titration regime. At one year post-treatment, the QALY was better using Rituximab than the mPR, but over a life-time this reduced with the mPR providing an increment of approximately half a QALY. However, Rituximab may still represent value for money given the cost savings are so high for every QALY lost.

It appears that the main driver of cost for the mPR is the frequency of infusions, adding cost to an inexpensive medication such as Methylprednisolone. This is also true for Rituximab, with the original regime, in which patients have four doses, proving less cost-effective[25]. In the B-cell titration regime[24], patients continue to have a good response to treatment but with fewer infusions making it consistently more cost-effective.

The reduction in quality of life for Rituximab over time is in part associated with the slightly increased risk of death and to a lesser extent the higher risk of relapse after Rituximab. Our model, however, is a conservative estimate for the quality of life benefits from Rituximab, as we do not take into account late complications associated with the therapies. It is well documented that there is an increased risk of malignancy many years after treatment with Cyclophosphamide[59]. Rituximab in contrast, appears to have fewer complications and no indication of an increased risk of malignancy. Our model does not capture the quality of life associated with the provision of treatment, such as early onset side effects, notably nausea in cyclophosphamide, or with the number of visits. With the reduced side effect profile and reduced hospital visits needed for Rituximab therapy one could deduce that this would contribute to an improved quality of life although this is not possible to prove in this model.

This is the most comprehensive estimate of the cost-effectiveness of treatment for PMN to date but it does come with limitations. The spread of results on the scatterplot for the PSA at the lifetime horizon indicates significant uncertainty in the results with the robustness of data available degenerating over time. This highlights the need for further good quality long-term prospective research comparing these therapies. Another limitation is that this evaluation was based on a naive comparison, if other single arm or cohort study data becomes available it may be that an indirect comparison would then be feasible.

Due to the paucity of RCTs investigating the efficacy of Rituximab in PMN we opted to base the Rituximab arm on the largest data series available for its use in this condition. This is a prospective observational study with all the limitations this confers on the data such as patient selection and centre bias but it remains the most robust data available.

This and the Jha study used to inform the model are international studies (Italy and India) but for precision our model is costed to the UK health system. At present, there are no large-scale clinical trials published using Rituximab in a UK population, and there have been no large clinical trials in the UK using Cyclophosphamide for the treatment of PMN.

Another limitation has been the assignment of utility values to the disease. There is good validated data for population norms but renal specific quality of life data is scarce. This meant for active disease and RRT we had to convert SF-36 scores to utility values using standard methods[39-42].

PMN can be a slowly progressing disease with many patients following a relapsing and remitting pattern over a number of years. Here we used only the rates for transition to ESRD and RRT as described in the two papers. This is likely to have underestimated the degree to which patients progressed to ESRD over a lifetime due to the relatively short follow up time of the studies. Given the uncertainty already apparent in the model over a lifetime, it adds further evidence for the need for long term RCTs in PMN.

This model has only included the cost of therapy at a tertiary level. It was beyond the scope of the study to assess the overall societal cost and there is likely to be significant cost to patients, families and carers in the form of lost days of work, travel costs, equipment costs. The cost of primary healthcare contact has also not been included in this model.

Conclusion

Rituximab has shown promise as a therapy for PMN in a number of studies but the high cost of the medication has proven to be a barrier to its widespread acceptance. Here we have constructed the most detailed economic model yet for the treatment of PMN and show that Rituximab is not more expensive than the gold standard treatment and is cheaper over a lifetime. This work highlights the uncertainty surrounding PMN treatment with the small number of RCTs available to guide practitioners and commissioning bodies. Based on the evidence available, the longer-term effectiveness of Rituximab in PMN needs further evaluation, and importantly, long-term trials comparing Rituximab with cyclophosphamide-based therapy should be undertaken to help establish the most cost-effective management of the condition.

Acknowledgements

This research was supported financially by Kidneys for Life Charity (charity no 505256). PB acknowledges support from Medical Research Council Project grant MR/J010847/1, and EU Framework 7 Programme Grant 305608, "EURenOmics". We also acknowledge support from the Manchester Academic Healthcare Science Centre (MAHSC) (186/200). MV received consultancy fees from Chemocentryx for work in vasculitis. Special thanks go to Dr Ian Jacob, Manchester Centre for Health Economics, University of Manchester, UK for discussions on the model. An abstract of this research was presented at the American Society of Nephrology in Chicago, November 2016.

Figure 1

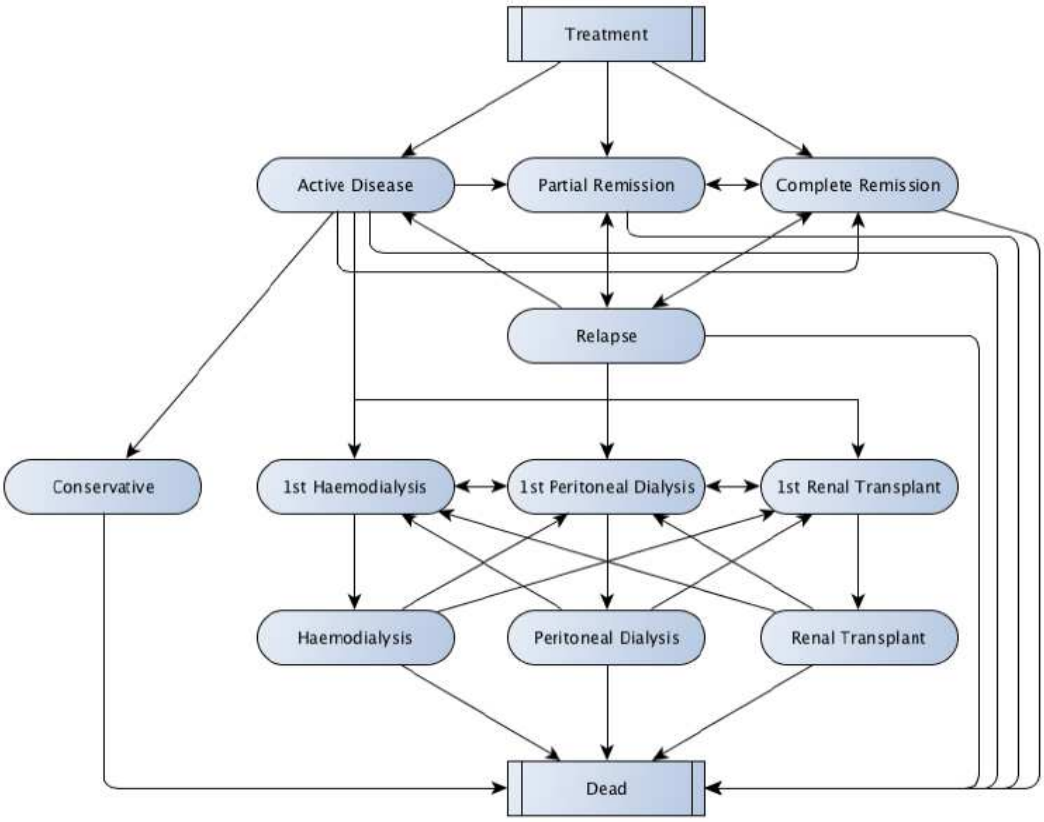

Figure 2

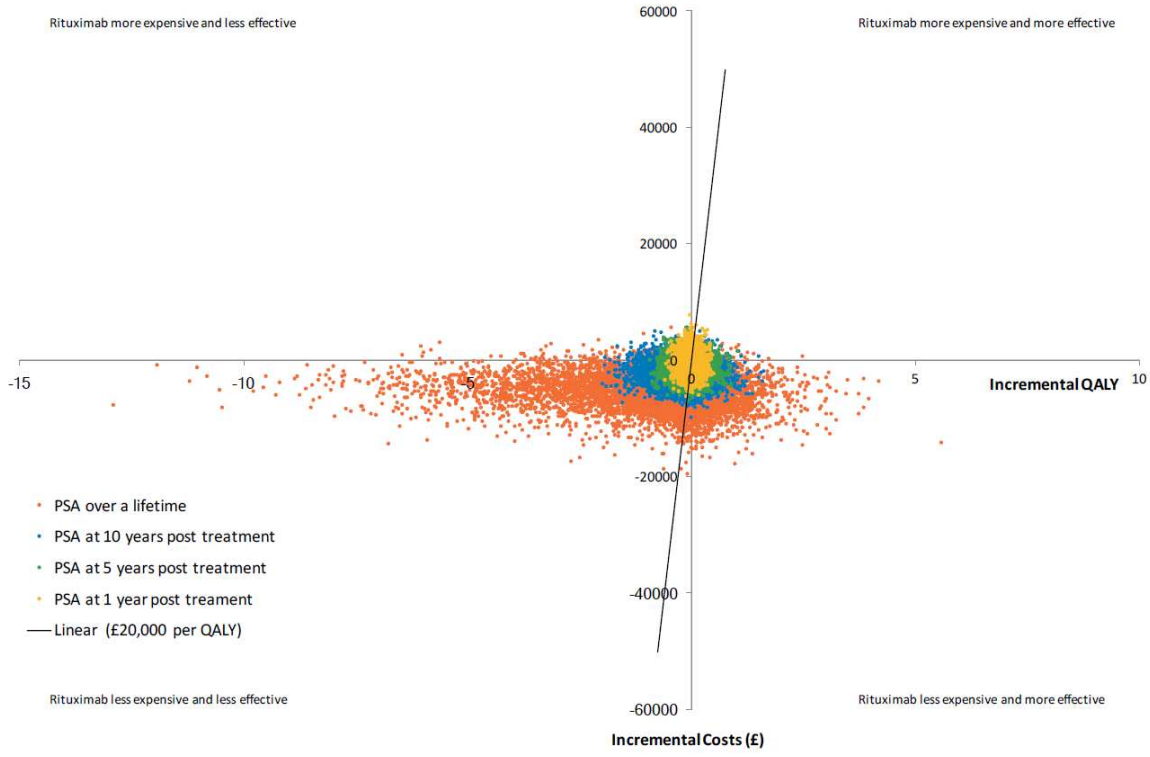

Figure 3

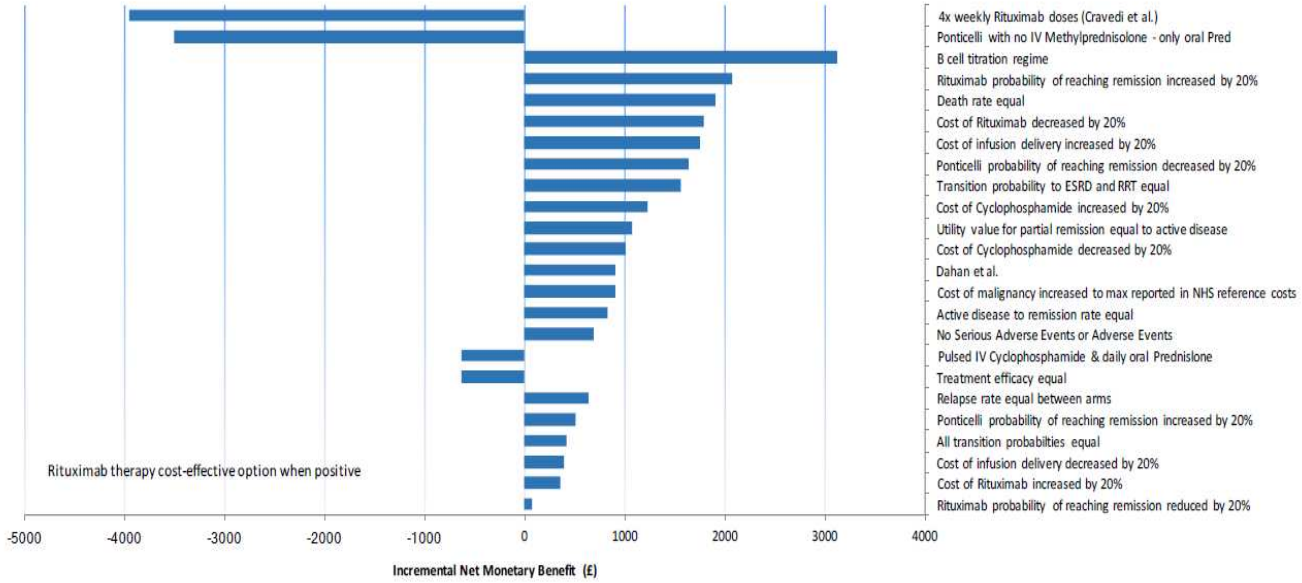

Figure 4

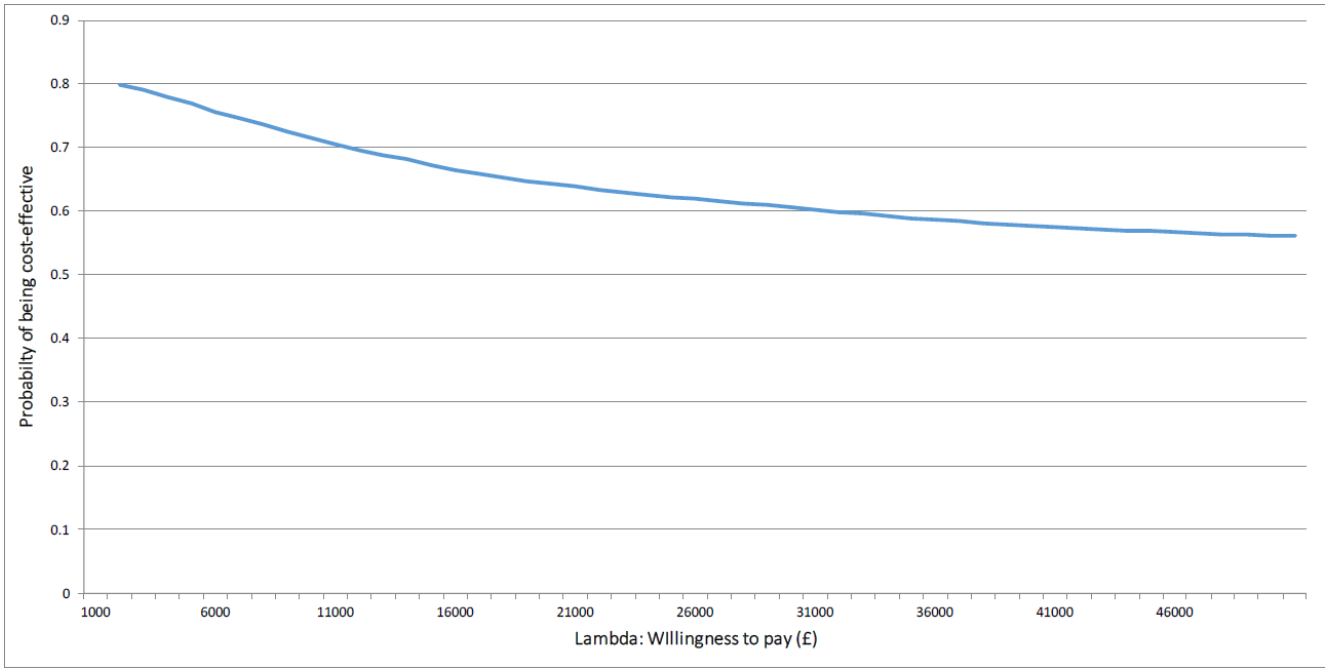

Table 1

	Jha et al.	Ruggenenti et al.
Country	India	Italy
Cohort size	47	100
Median follow up	11 years (range 10.5 – 11)	29 months (range 6 – 121)
Age in years – mean ± SD	38.0 ± 13.6	51.5 ± 5.9
Gender		
Male – n (%)	30 (63.8)	72 (72)
Female – n (%)	17 (36.2)	28 (28)
Disease state definitions		
Active disease	Proteinuria ≥ 3.5g/d or Proteinuria ≥ 2.5g/d & serum albumin < 2.5g/dl with oedema and hyperlipidaemia	Proteinuria ≥ 3.5g/d
Partial remission	Proteinuria < 2.0g/d or ≥ 50% reduction from baseline	Proteinuria < 3.0g/d & ≥ 50% reduction from baseline
Complete remission	Proteinuria < 0.2g/d	Proteinuria < 0.3g/d & ≥ 50% reduction from baseline
Relapse	Not defined	Proteinuria ≥ 3.5g/d after partial or complete remission
Adverse events – n (%)		
During infusion		
Allergy	0 (0)	8 (8)
Bronchial wheezing	0 (0)	10 (10)
Cutaneous rash	0 (0)	1 (1)
Hypotension	0 (0)	1 (1)
Stroke	0 (0)	3 (3)
TIA	0 (0)	2 (2)
Acute MI	1 (1)	3 (3)
Cancer	0 (0)	3 (3)
Respiratory tract infection	3 (6)	0 (0)
Urinary tract infection	5 (11)	0 (0)
Pyomyositis	1 (2)	0 (0)
Disseminated tuberculosis	1 (2)	0 (0)
Thrombosis	3 (0)	0 (0)
Deaths	1 (1)	4 (4)

Table 1 – Comparison of trials used for model

Table 2

Medication	Dose	Pack size	Treatment Dose	Mean Value (£)	SD (£)	Source
IV Methylprednisolone	1000mg	1 pack	1000mg	11.04	5.90	DFN009 eMIT
Prednisolone tablets	5mg	100 tablets	35mg	4.39	0.26	DFC045 eMIT
PO Cyclophosphamide	50mg	100	140mg	82.00	41.00	BNF
IV Cyclophosphamide	1000mg	1 vial		9.41	5.56	DHA014 eMIT
Rituximab	10mg/ml	10mL vial	375mg/m^2	174.63	87.32	BNF
		50mL vial		873.15	436.58	BNF
Basiliximab	20mg	1 vial		842.38	421.19	BNF
IV Hydrocortisone	100mg/mL	1mL amp	100mg	1.08	0.54	BNF
		5mL amp	500mg	4.89	2.45	BNF
Paracetamol	500mg	100 tablets	1000mg	0.52	0.29	DDM003 eMIT
Ondansetron	8mg	10 tablets	8mg	1.06	5.89	DDF029 eMIT
IV Chlorphenamine	10mg/1ml	5 ampoules	10mg	22.80	3.52	DCI002 eMIT
PO Mesna	400mg	10 tablets	400mg	42.90	21.45	BNF
IV Mesna	100mg/ml	4mL vial	200mg	3.95	1.98	BNF
Normal Saline	1000ml	1 bag	1000ml	0.80	0.40	BNF

Table 2 – Cost of medication. All medications oral unless otherwise stated. All doses based on weight of 70kg patient. All prices based on dose and pack size. SD – Standard deviation. eMIT – Department of Health electronic market information tool accessed on 30th June 2016 and costs correct to December 2015[36]. Prices given in eMIT are excluding VAT therefore taken as 20%. BNF – British National Formulary accessed on 30th April 2015[37]. Standard Deviations for BNF meds taken as Mean / 2 as they are not provided.

Table 3

Health Service	Mean Value	LQR	UQR	SD	Source
Delivery of Chemo (1st)					
Simple Parenteral	257.00	136.00	311.00	129.63	SB12Z NHS ref costs
Complex & Infusional	414.00	250.00	521.00	200.74	SB14Z NHS ref costs
Subsequent chemo	362.00	230.00	413.00	135.56	SB15Z NHS ref costs
AVF, Graft or Shunt DC	1910.66	1334.41	2342.81	746.96	YQ42Z NHS ref costs
PD associated procedure DC	1268.00	503.00	1815.00	971.85	LA05Z NHS ref costs
Nephrology clinic	160.00	110.00	185.00	55.56	WF01A 361 NHS ref costs
Transplant clinic	358.00	220.00	493.00	202.22	WF01A 102 NHS ref costs
Haemodialysis					
CKD via AVF at base	166.00	143.00	176.00	24.44	RENALCKD LD02A NHS ref costs
Peritoneal Dialysis					
Automated PD	71.00	50.00	67.00	12.59	RENALCKD LD12A NHS ref costs
Renal Transplant					
Cadaver NHB	12,845.93	10,179.00	14,250.00	3015.56	LA01A NHS ref costs
Cadaver HB	12,434.09	12,904.00	14,450.00	1145.19	LA02A NHS ref costs
Live donor	13,828.19	9996.00	17,756.00	5748.15	LA03A NHS ref costs
Pre-transplant work-up					
Live donor	1205.75	958.00	1559.00	445.19	LA11Z NHS ref costs
B Cell subsets	5.00	2.00	7.00	3.70	DAPS06 NHS ref costs

Table 3 – Cost of healthcare provision. All costs given in British Pound Sterling. NHS ref costs – National Health Service reference costs 2014 – 2015[34]. LQR – Lower Quartile Range. UQR – Upper Quartile Range. IP – Inpatient. OP – outpatient. DC – Day case. AVF – Arterioventricular Fistula. PD – Peritoneal Dialysis. AKI – Acute Kidney Injury. CKD – Chronic Kidney Injury. NHB – Non-Heart Beating donor. HB – Heart beating donor. Sat – Satellite unit. CAPD – Continuous Ambulatory Peritoneal Dialysis. Complex & Infusional – Complex Parenteral and prolonged infusion treatment. Standard Deviation estimated using S = Q3 – Q1 / 1.35 from Cochrane Handbook from Systematic Reviews and Interventions 2008[35].

Table 4

Complication	Mean	LQR	UQR	SD	Source	Notes/Assumptions
			Jha et al			
Respiratory tract infections	1540.00	1255.00	1685.00	318.52	DZ22Q NHS ref costs	Unspecified acute LRTI (0-1)
Urinary tract infections	1503.00	1233.00	1659.00	315.56	LA04S NHS ref costs	Kidney/UTI – no intervention (0-1)
Gluteal Abscess	1358.00	960.00	1557.00	442.22	HD26G NHS ref costs	MSK signs or symptoms (0-3)
Bacterial Meningitis	2339.00	1561.00	2638.00	797.78	AA22G NHS ref costs	Nervous system infections (0-4)
Pulmonary Tuberculosis	2650.00	1702.00	3131.00	1058.52	DZ14J NHS ref costs	Pulmonary, pleural, other Tb
Septicaemia	1993.00	1586.00	2224.00	472.59	WJ06J NHS ref costs	Sepsis (0-1)
Deep vein thrombosis	1362.00	992.00	1491.00	369.63	YQ51E NHS ref costs	DVT (0-2)
			Ruggenenti et al			
Acute MI	1505.00	1205.00	1701.00	367.41	EB10E NHS ref costs	Actual/Suspected MI (0-3)
Stroke	2348.00	1803.00	2597.00	588.15	AA35F NHS ref costs	Stroke (0-3)
TIA	1253.00	978.00	1393.00	307.41	AA29F NHS ref costs	TIA (0-4)
Lung cancer	3047.00	2063.00	3610.00	1145.93	DZ17R NHS ref costs	Resp. neoplasm (0-5)
Breast cancer	3357.00	1504.00	4554.00	2259.26	JA12F NHS ref costs	Malignant - intervention (0-2)
Prostate Carcinoma	2268.00	1469.00	2660.00	882.22	LB06M NHS ref costs	Prostate Ca – intervention (0-1)

Table 4 – Cost of AEs and SAEs. All costs given in British Pounds. NHS ref costs – National Health Service reference costs 2014 – 2015[34]. LQR – Lower Quartile Range. UQR – Upper Quartile Range. CC Score in parenthesis. TIA – Transient Ischaemic Attack. All costs taken as non-elective short stay. Standard Deviation estimated using SD = Q3 – Q1 / 1.35 from Cochrane Handbook from Systematic Reviews and Interventions 2008[35].

Table 5

Utility	Mean	Lower CI	Upper CI	SD / SE	Source	Notes
Complete remission	0.860	0.630	1.000	0.230	Kind et al.	Age & Sex matched
Partial remission	0.860	0.630	1.000	0.230	Kind et al.	
Active disease	0.738	0.422	1.000	0.317	Liborio et al.	SF36 converted to EQ5D
ESRD	0.800	0.650	0.940	0.030	Wyld et al.	CKD (pre-treatment)
Conservative	0.620	0.360	0.890	0.090	Wyld et al.	SF36 converted to EQ5D
Haemodialysis	0.680	0.530	0.820	0.020	Wyld et al.	SF36 converted to EQ5D
Peritoneal dialysis	0.710	0.590	0.820	0.020	Wyld et al.	SF36 converted to EQ5D
Renal transplant	0.820	0.740	0.900	0.040	Wyld et al.	SF36 converted to EQ5D
Dead	0.000	0.000	0.000	0.000		

Table 5 – Quality of life utility values. ESRD – End-stage renal disease. Partial remission and Complete Remission taken as the same.

Table 6

	Deterministic Sensitivity Analysis				Probabilistic Sensitivity Analysis			
	Incremental Cost	Incremental QALY	ICER	INMB	Incremental Cost	Incremental QALY	ICER	INMB
One-year	-£748.20	0.002	Rituximab Dominates	£785.44	-£761.19	0.001	Rituximab Dominates	£777.54
Five-years	-£1,355.82	-0.014	£95,494.13	£1,071.86	-£1,383.61	-0.014	£101,665.93	£1,111.42
Ten-years	-£2,201.37	-0.091	£24,256.91	£386.32	-£2,217.16	-0.092	£24,222.17	£386.47
Lifetime	-£5,251.03	-0.512	£10,246.09	-£4,998.79	-£5,228.58	-0.612	£2,198.07	-£7,016.21

Table 6 - Results for both probabilistic and deterministic sensitivity analysis at one, five and ten years post treatment and over a lifetime. Lambda taken as £20,000.
QALY – Quality-adjusted life year. ICER – Incremental cost-effectiveness ratio. INMB – Incremental net monetary benefit.

References

1. McGrogan A, Franssen CFM, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant. 2011 Feb; 26(2):414-30. doi: 10.1093/ndt/gfq665

2. Schieppati A, Mosconi L, Perna A. Prognosis of untreated patients with idiopathic membranous nephropathy. N Engl J Med. 1993 Jul 8;329(2):85-9.

3. Beck LH Jr., Bonegio RGB, Lambeau G et al. M-Type Phospholipase A 2Receptor as Target Antigen in Idiopathic Membranous Nephropathy. N Engl J Med. 2009 Jul 2;361(1):11–21.

4. Stanescu HC, Arcos-Burgos M, Medlar A et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. N Engl J Med. 2011 Feb 17;364(7):616–26.

5. Coenen MJH, Hofstra JM, Debiec H et al. Phospholipase A2 Receptor (PLA2R1) Sequence Variants in Idiopathic Membranous Nephropathy. J Am Soc Nephrol. 2013 Mar 29;24(4):677–83.

6. Kanigicherla D, Gummadova J, McKenzie EA et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. Kidney International. Nature Publishing Group; 2013 May;83(5):940–8.

7. Hofstra JM, Debiec H, Short CD et al. Antiphospholipase A2 Receptor Antibody Titer and Subclass in Idiopathic Membranous Nephropathy. J Am Soc Nephrol. 2012 Oct;23(10):1735-43.

8. Hofstra JM, Wetzels JFM. Management of patients with membranous nephropathy. Nephrol Dial Transplant. Oxford University Press; 2012 Jan 1;27(1):6–9.

9. Eknoyan G, Eckardt KU, Kasiske BL. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney Int; 2012.

10. Hofstra JM, Laurence H Beck J, Beck DM et al. Anti-Phospholipase A2 Receptor Antibodies Correlate with Clinical Status in Idiopathic Membranous Nephropathy. Clinical Journal of the American Society of Nephrology. American Society of Nephrology; 2011 Jun 1;6(6):1286–91.

11. Bech AP, Hofstra JM, Brenchley PE et al. Association of Anti-PLA2R Antibodies with Outcomes after Immunosuppressive Therapy in Idiopathic Membranous Nephropathy. Clinical Journal of the American Society of Nephrology. 2014 Aug 7;9(8):1386–92.

12. Ruggenenti P, Debiec H, Ruggiero B et al. Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy. J Am Soc Nephrol. American Society of Nephrology; 2015 Mar 24;:ASN.2014070640.

13. Beck LH, Fervenza FC, Beck DM et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol. American Society of Nephrology; 2011 Aug;22(8):1543–50.

14. Hoxha E, Thiele I, Zahner G et al. Phospholipase A2 Receptor Autoantibodies and Clinical Outcome in Patients with Primary Membranous Nephropathy. J Am Soc Nephrol. American Society of Nephrology; 2014 Jun 1;25(6):1357–66.

15. Ponticelli C, Zucchelli P, Imbasciati E, Cagnoli L, Pozzi C, Passerini P, Grassi C, Limido D, Pasquali S, Volpini T, et al. Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. N Engl J Med. 1984 Apr 12;310(15):946-50. PubMed PMID: 6366560.

16. Ponticelli C, Zucchelli P, Passerini P et al. A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. Kidney International. 1995 Nov;48(5):1600–4.

17. Ponticelli C, Altieri P, Scolari F et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol. American Society of Nephrology; 1998 Mar;9(3):444–50.

18. Jha V, Ganguli A, Saha TK et al. A randomized, controlled trial of steroids and cyclophosphamide in adults with nephrotic syndrome caused by idiopathic membranous nephropathy. J Am Soc Nephrol. American Society of Nephrology; 2007 Jun;18(6):1899–904.

19. Dussol B, Morange S, Burtey S et al. Mycophenolate mofetil monotherapy in membranous nephropathy: a 1-year randomized controlled trial. Am J Kidney Dis. Elsevier; 2008 Oct;52(4):699–705.

20. Chan TM, Lin AW, Tang SC et al. Prospective controlled study on mycophenolate mofetil and prednisolone in the treatment of membranous nephropathy with nephrotic syndrome. Nephrology (Carlton). Blackwell Publishing Asia; 2007 Dec;12(6):576–81.

21. Praga M, Barrio V, Juárez GF et al. Tacrolimus monotherapy in membranous nephropathy: A randomized controlled trial. Kidney International. Elsevier Masson SAS; 2007 May 1;71(9):924–30.

22. Wetzels JFM. Tacrolimus in membranous nephropathy. Kidney International. 2008 Jan;73(2):238.

23. Yuan H, Liu N, Sun G-D et al. Effect of prolonged tacrolimus treatment in idiopathic membranous nephropathy with nephrotic syndrome. Pharmacology. 2013;91(5-6):259–66.

24. Cravedi P, Ruggenenti P, Sghirlanzoni MC et al. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. American Society of Nephrology; 2007 Sep;2(5):932–7.

25. Remuzzi G, Chiurchiu C, Abbate M et al. Rituximab for idiopathic membranous

nephropathy. Lancet. Elsevier; 2002;360(9337):923–4.

26. Ruggenenti P, Cravedi P, Chianca A et al. Rituximab in Idiopathic Membranous Nephropathy. J Am Soc Nephrol. 2012 Jul 31;23(8):1416–25.

27. Dahan K, Debiec H, Plaisier E et al. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J Am Soc Nephrol. 2016 Jun 27;:ASN.2016040449.

28. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, Michel PA, Mihout F, Dussol B, Matignon M, Mousson C, Simon T, Ronco P; GEMRITUX Study Group. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J Am Soc Nephrol. 2017 Jan;28(1):348-358. doi: 10.1681/ASN.2016040449. PubMed PMID: 27352623; PubMed Central PMCID: PMC5198292.

29. Sonnenberg FA, Beck JR. Markov Models in Medical Decision Making A Practical Guide. Medical Decision Making. SAGE Publications; 1993 Dec 1;13(4):322–38.

30. Kanigicherla DAK, Hamilton P, Venning MC et al. Results of survey on management of Membranous Nephropathy in the United Kingdom *on behalf of the UK MN RADAR steering group. Nephrol Dial Transplant. Oxford University Press; 2015 May 1;30(suppl 3):iii108–8.

31. Kanigicherla DAK, Short CD, Roberts SA et al. Long-term outcomes of persistent disease and relapse in primary membranous nephropathy. Nephrology Dialysis Transplantation. Oxford University Press; 2016 Jan 13;:gfv435.

32. Gilg J, Pruthi R, Fogarty D. UK Renal Registry 17th Annual Report: Chapter 1 UK Renal Replacement Therapy Incidence in 2013: National and Centre-specific Analyses. Nephron. Karger Publishers; 2015 Jan 22;129(Suppl. 1):1–29.

33. Office of National Statistics. Historic and Projected Mortality Rates (qx) from the 2010-based UK Life Tables: Principal Projection, 1951-2060.

34. NHS Reference Costs 2014 to 2015. https://www.gov.uk/government/publications/ nhs-reference-costs-2014-to-2015

35. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd; 2008. 1 p.

36. Drugs and pharmaceutical electronic market information (eMit). https://www.gov.uk/ government/publications/drugs-and-pharmaceutical-electronic-market-information- emit. Accessed December 2015.

37. Joint Formulary Committee. British National Formulary. 69th ed. London: BMJ Group and Pharmaceutical Press; March 2015

38. Sacco JJ, Botten J, Macbeth F et al. The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. Shea BJ, editor. PLoS ONE. Public Library of Science; 2010 Jan 28;5(1):e8933.

39. Wyld M, Morton RL, Hayen A et al. A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Chronic Kidney Disease Treatments. Turner N, editor. PLoS Med. 2012 Sep 11;9(9):e1001307–10.

40. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. 1999.

41. Ara R, Brazier J. Deriving an Algorithm to Convert the Eight Mean SF-36 Dimension Scores into a Mean EQ-5D Preference-Based Score from Published Studies (Where Patient Level Data Are Not Available). Value in Health. 2008 Dec;11(7):1131–43.

42. Libório AB, Santos JPL, Minete NFA et al. Proteinuria is associated with quality of life and depression in adults with primary glomerulopathy and preserved renal function. Abe H, editor. PLoS ONE. Public Library of Science; 2012;7(5):e37763.

43. NICE. Process and methods guides: guide to the methods of technology appraisal 2013. 2013.

44. Kanigicherla DA, Hamilton P, Czapla K, Brenchley PE. Intravenous Pulse cyclophosphamide and steroids induce immunological and clinical remission in New-incident and relapsing Primary Membranous Nephropathy. Nephrology (Carlton). 2016 Oct 24.

45. Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ. Wiley Subscription Services, Inc., A Wiley Company; 1998 Dec 1;7(8):723–40.

46. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. Health Econ. John Wiley & Sons, Ltd; 2004 May;13(5):405–15.

47. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB; ISPOR-SMDM Modeling Good Research Practices Task Force. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012 Sep-Oct;32(5):733-43.

48. Stone JH, Merkel PA, Spiera R et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363(3):221–32.

49. Jones RB, Tervaert JWC, Hauser T et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010 Jul 15;363(3):211–20.

50. Buch MH, Smolen JS, Betteridge N et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. BMJ Publishing Group Ltd and European League Against Rheumatism; 2011. pp. 909–20.

51. Walsh M, Jayne D. Rituximab in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis and systemic lupus erythematosus: past, present and future. Kidney International. 2007 Jul 4;72(6):676–82.

52. Keogh KA, Ytterberg SR, Fervenza FC et al. Rituximab for Refractory Wegener's Granulomatosis. Am J Respir Crit Care Med. 2006 Jan 15;173(2):180–7.

53. Pillebout E, Rocha F, Fardet L et al. Successful outcome using rituximab as the only immunomodulation in Henoch-Schonlein purpura: case report. Nephrology Dialysis Transplantation. Oxford University Press; 2011 Jun;26(6):2044–6.

54. Gürcan HM, Keskin DB, Stern JNH et al. A review of the current use of rituximab in autoimmune diseases. International Immunopharmacology. 2009 Jan;9(1):10–25.

55. Jones RB, Ferraro AJ, Chaudhry AN et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2009 Jul;60(7):2156–68.

56. Pindi Sala T, Michot J-M, Snanoudj R et al. Successful outcome of a corticodependent henoch-schönlein purpura adult with rituximab. Case Reports in Medicine. Hindawi Publishing Corporation; 2014;2014(8152):619218–4.

57. Smith KGC, Jones RB, Burns SM et al. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. Arthritis Rheum. 2006;54(9):2970–82.

58. Stasi R, Stipa E, Del Poeta G et al. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology. 2006 Aug 27;45(11):1432–6.

59. van den Brand JAJG, van Dijk PR, Hofstra JM et al. Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. American Society of Nephrology; 2014 Jun 6;9(6):1066–73.