NHS England

Evidence review:
Rituximab for Membranous Glomerular Nephritis

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Contents

1. Introduction 4
2. Summary of results 4
3. Research questions 5
4. Methodology 5
5. Results 7
6. Appendix One 11
7. Appendix Two 24

1. Introduction

Membranous nephritis (MN) remains a leading cause of nephrotic syndrome (NS) in adults (Glassock et al. 2003, Swaminathan et al. 2006). About one quarter of cases are felt to be secondary to a predisposing disease (e.g. systemic lupus erythematosus), an infection (e.g. hepatitis B), or medical therapy (e.g. non-steroidal anti-inflammatory drugs). In most other cases, an underlying aetiology for the lesion is unknown and the disorder is termed idiopathic. There are several closely related terms used to describe the condition.

The treatment of MN depends on the patient presentation and disease progression after diagnosis is made by biopsy (Fervenza et al. 2008). In general, most patients are given a trial of conservative therapy with renin-angiotensin system (RAS) blockade. If partial or complete remission is not achieved with 6 months of conservative management, immunomodulatory therapy is then initiated. The two leading immunomodulatory therapies used are alkylating agents (cyclophosphamide or chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus), both typically given alongside oral or intravenous corticosteroids (Perna et al. 2004, Cattran et al. 2005,). Recently, rituximab has surfaced as a potential treatment option for MN. This review aims to establish the evidence base on the clinical efficacy, safety and cost-effectiveness of rituximab for MN.

2. Summary of results

There is emerging evidence showing there may be benefit in the use of rituximab for the treatment of idiopathic membranous glomerular nephritis (IMN) in native kidney patients. However, this is based on weak study designs (majority of studies are cases series from a single centre) with small sample sizes lacking controls patients who are given other immunosuppressive drugs or conservative therapy alone. Therefore, from the studies, spontaneous remission rather than therapeutic effect of the rituximab cannot be formally ruled out. In addition, there were significant variations in treatment protocols across studies. There are also indications that a significant number of patients in studies followed up for 12 months and above relapsed requiring a second course of rituximab. From the studies, rituximab appears to be safe. There was no cost-effectiveness data reported compared to current treatment. In conclusion, rituximab may prove to be a viable treatment option for IMN, although the current data do not support using this drug in non-research settings. Findings from robust randomised control trials comparing rituximab with immunosuppressive drugs and conservative therapy alone are needed to confirm its potential therapeutic benefit.

3. Research questions

The research question is the clinical and cost effectiveness of rituximab in the treatment of membranous glomerular nephritis

Population: patients with membranous glomerular nephritis but not including patients with secondary membranous nephropathy e.g. secondary to SLE or Lupus, or patients with recurrent idiopathic membranous nephropathy after kidney transplantation

Intervention: rituximab

Comparator: conventional standard of care including immune-modulatory treatments: ciclosporin, tacrolimus, chlorambucil, cyclophosphamide

Outcome: renal function, quality of life, adverse events.

4. Methodology

Data was gathered from published literature. Articles were retrieved by electronic search strategy. Searches were carried out in MEDLINE, Cochrane, NHS Evidence and CRD databases. The search terms used were 'membranous glomerulopathy', 'membranous glomerulonephritis', membranous nephropathy', 'rituximab', 'ciclosporin', 'tacrolimus', 'chlorambucil', 'cyclophosphamide' and their combinations.

A single reviewer reviewed abstracts retrieved from the databases and selected articles using the inclusion and exclusion criteria listed below. Reference tracking was undertaken (reference lists of all full text papers were scanned and judgment used to decide whether to pursue these further for inclusion).

i. Inclusion criteria

- Articles published between January 2000 and July 2013
- Articles in the English language only were considered
- Primary research studies reporting clinical effectiveness, safety and/or cost-effectiveness of the rituximab in biopsy-proven idiopathic MN

ii. Exclusion criteria

- Case reports
- Studies reporting use of rituximab in secondary MN
- Studies reporting use of rituximab to treat MN in transplanted kidneys

Each included study was critically appraised and assigned a level of evidence (see Table 1) and where possible graded (see Table 2) using the Scottish Intercollegiate Guidelines Network (SIGN) framework.

Table1: Scottish Intercollegiate Guideline Network (SIGN) levels of evidence

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs (including cluster RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–*	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of, or individual high quality non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a very low risk of confounding, bias or chance
2+	Well conducted, non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a low risk of confounding, bias or chance
2–*	Non-randomised intervention studies (controlled non-randomised trial, controlled before-and-after, interrupted time series), comparative cohort and correlation studies with a high risk of confounding, bias or chance
3	Non-analytical studies (eg case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence (–) should not be used as basis for making recommendations.
Source: adapted from SIGN (2001).

Table 2: Scottish Intercollegiate Guideline Network (SIGN) Grades of Evidence

Grades of recommendations
Grade 'A' At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population ***or*** A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results.
Grade 'B' A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 1++ or 1+

Grade 'C' A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results ***or*** Extrapolated evidence from studies rated as 2++
Grade 'D' Evidence level 3 or 4 ***or*** Extrapolated evidence from studies rated as 2+

Source: Adapted from the Scottish Intercollegiate Guidelines Network (SIGN), 2001

5. Results

A total of 12 studies were found which met the inclusion criteria. Of the 11 studies, 10 were case series and 2 were cohort studies (see Table 3 in the Appendix). All 12 studies reported clinical efficacy of which 10 also reported on safety of rituximab to treatment patients with MN. No cost-effectiveness or evaluations were found (with the exception of Cravedi et al 2007 wherein the authors evaluated whether titrating rituximab to circulating CD20 B cells compared to standard 4 weekly infusions limit costs of treatment).

Study characteristics and their results and have been summarised in Table 4 in the Appendix The findings of the studies have been categorised based on the research questions in this report into 2 categories- clinical effectiveness & safety.

Summary of evidence

12 studies were found in total (10 case series- SIGN Level 3, and 2 cohort studies- SIGN Level 2-). All of these studies reported clinical effectiveness of rituximab in the treatment of idiopathic membranous glomerular nephritis in native kidney patients. Of these 10 also reported on safety. The study by Ruggenenti et al. 2003 was a longer follow up of patients from Remuzzi et al (2003). It also seems that the following studies- Ruggenenti et al 2006, Ruggenenti et al 2008 and Ruggenetti et al 2012 also included patients previously reported, however this is unclear. No cost-effectiveness studies were found (with the exception of Cravedi et al 2007 wherein the authors evaluated whether titrating rituximab to circulating CD20 B cells compared to standard 4 weekly infusions limited the costs of treatment).

The majority of studies included had small sample sizes ranging from 7-28 patients apart from one study that had a sample of a 100 patients. The study entry characteristics of patients such as proteinuria levels, prior treatments and their durations etc. also varied between studies. It should also be noted that the majority of the studies included patients that came from one centre (all except studies by Fervenza et al, Segarra et al, El Reshaid et al and Kong et al)

5 studies followed a protocol which gave rituximab at a dose of 375 mg/m^2 once weekly for 4 weeks. The remaining 7 studies followed different protocols- Fervenza et al.(2008) followed a protocol where 1 g rituximab was administered on days 1 and 15, patients who had proteinuria >3 g per 24 h and 415 CD19þ B cells per ml at 6 months were treated again with a second identical course of rituximab (10/15 patients in the study, underwent retreatment with rituximab; Segarra et al (2009) followed a protocol in which second relapses occurring after CD-19 cell recovery were re-treated with a second trial of rituximab at the minimum dose necessary to achieve the depletion of CD-19 cells; Feverna et al. (2010) where patients received re-treatment at 6 months regardless of proteinuria response; Cravedi et al (2011) followed a protocol in which five patients and their matched reference patients received the standard four-dose rituximab protocol, whereas the remaining 6 patients and matched reference patients received the B-cell-driven protocol; El Reshaid et al. (2012) protocol included the use of 4 weekly slow infusions of 500 mg of rituximab diluted in 450 mL of normal saline leading to a concentration of 1 mg/mL; Ruggenenti et al. (2012) followed a protocol in which a second dose of 375 mg/m2 infusion only when >5 circulating B cells per mm^3 were detected the morning after completion of the first rituximab administration. Patients in the study by Cravedi et al. 2007 included patients who received 375 mg/m^2 once weekly for 4 weeks (n=24) as well as rituximab therapy titrated to circulating CD20 B cells (n=12). This study reported B cell titrated protocol to be as effectively as a protocol providing 375 mg/m^2 once weekly for 4 weeks (achieves B cell depletion and idiopathic membranous nephropathy remission) but is fourfold less expensive, allowing for more than €10,000 (approximately $13,000) in savings per patient at 12 months follow up.

In majority of the studies, rituximab was typically used as a second-line immunosuppressive therapy after treatment failure of steroids alone or steroids used in conjunction with either cyclosporine or an alkylating agent. The only exceptions were Remuzzi et al. (2002), Ruggenenti et al. (2003), Cravedi et al. (2011) and Ruggenenti et al. (2012). In Remuzzi et al. (2002), Ruggenenti et al. (2003) (study was a longer term follow up study of Remuzzi et al 2002) rituximab was the first-line immunosuppressant used for refractory nephrotic syndrome after at least 6 months of angiotensin-converting enzyme inhibitor therapy. In the studies by Cravedi et al. (2011) & Ruggenenti et al. (2012), the samples included patients who received rituximab as first and second line therapy. These studies compared first line and second line therapies and reported similar outcomes in both groups (Cravedi et al 2011, Ruggenenti et al 2012).

The main clinical efficacy outcomes reported by the studies were a decrease in proteinuria or the achievement of remission (complete or partial) following rituximab therapy. In the studies reporting proteinuria, they reported a decrease at 3 months of 44%, at 6 months a decrease of 66%, and at 12 months a decrease ranging 48%- 66%. Patient remission at 12 months follow up and reported in the studies ranged from 45%-75%. In one study all patients (n=28) relapsed from 12 months onwards, requiring retreatment (El Reshaid et al 2012). Another study reported 88% patients (n=16/18) achieved remission at 24 months follow up, however, all patients in the study received re-treatments at 6 months (Fervenza et al 2010). Ruggenenti et al 2012 reported 65% remission in patients (n=65/100) at median of 29 months follow up and 28% (18/65) of these had a relapsed at a median follow up of 42 months and were given a second course of rituximab. Another study that reported all patients (n=13) in CR or PR at 30 months were in remission (3/13 patients were given second course of treatment to treat relapses) (Segarra et al 2009).

In the 10 studies that reported adverse events, rituximab was generally well tolerated and overall most studies reported no significant adverse events of rituximab therapy (Table 4). The few reported side effects were typically mild, transient, and thought to be owing to an infusion reaction. Rituximab, when administered in these reports, was given with pre-medications (including steroids) to limit such effects. However, two serious adverse events were noted in these studies. The first, a laryngospasm reported by Ruggenenti et al (2003). The second was a lung neoplasm not detected on chest x-ray done 1 year before enrolment in the study of Fervenza et al (2008) this patient was withdrawn from the study and died.

Overall, there is emerging evidence showing there may be benefit in the use of rituximab for the treatment of idiopathic membranous glomerular nephritis in native kidney patients. However, this is based on weak study designs (majority of studies are cases series from a single centre) with small sample sizes lacking controls given other immunosuppressive drugs or conservative therapy alone. Therefore, from the studies, spontaneous remission rather than therapeutic effect of the rituximab cannot be formally ruled out. In addition, there were significant variations in treatment protocols across studies. There is also indication that a significant number of patients in studies followed up for 12 months and above relapsed requiring a second course of rituximab. From the studies, rituximab appears to be safe. There was no cost-effectiveness data reported compared to current treatment. In conclusion, rituximab may prove to be a viable treatment option for IMN, although the current data do not support using this drug in non-research settings. Findings from robust randomised control trials comparing rituximab with immunosuppressive drugs and conservative therapy alone are needed to confirm its potential therapeutic benefit.

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6. Appendix One

Table 1: Study designs by Intervention

Study type	Reference
Case Series	Remuzzi et al 2002
	Ruggenetti et al 2003
	Ruggenetti et al 2006
	Feverna et al 2008
	Ruggenetti et al 2008
	Segarra et al 2009
	Feverna et al 2010
	El Reshaid et al 2012
	Ruggenetti et al 2012

	Kong et al 2013
Cohort Studies	Cravedi et al 2007
	Cravedi et al 2011

Table 4: Studies Reporting Clinical Effectiveness and Safety of Rituximab for Membranous Nephritis

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics Eight patients who had idiopathic membranous nephropathy with persistent nephrotic syndrome. Intervention Patients received four weekly infusions of rituximab (375 mg/m^2). All patients also received similar conservative treatment that included loop diuretics to control oedema, full-dose ACE inhibitor therapy combined with beta-blockers and calcium channel blockers as deemed appropriate to control BP and proteinuria, and statins to control hypercholesterolemia.	Urinary protein, albuminuria and albumin fractional clearance change at 4 weeks and 20 weeks post treatment	Clinical efficacy • At weeks 4 and 20, urinary protein decreased from mean (SE) 8.6 g/24 h (1.4) to 3.8 (0.8) and 3.7 (0.9), respectively ($p<0.0001$). • At week 20, albuminuria and albumin fractional clearance decreased by 70% and 65%, and serum albumin increased by 31%. CD20 B lymphocytes fell below normal ranges up to study end. Safety *See Ruggenenti et al 2003*	Remuzzi et al 2002	• Case Series • Small sample size (n=8) • Short follow up (20 weeks) • First line therapy (treatment before RTX- Full-dose ACE-I for mean 29.7 mo) • Longer term follow- up of patients reported in Ruggenenti et al 2003

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 8 idiopathic MN patients with persistent (>6 mo) urinary protein excretion >3.5 g/24 h) unresponsive to prolonged ACE inhibitor therapy. Intervention Patients received four weekly infusions of rituximab (375 mg/m^2). All patients also received similar conservative treatment that included loop diuretics to control oedema, full-dose ACE inhibitor therapy combined with beta-blockers and calcium channel blockers as deemed appropriate to control BP and proteinuria, and statins to control hypercholesterolemia.	Complete remission (CR), partial remission (PR), non-responders (NR), or relapse of NS following treatment at 12 months	Clinical efficacy At 12 months: • 2 patients achieved CR (proteinuria < 0.5g/24 h) • 4 patients achieved PR (proteinuria < 3.5 g/24 h or proteinuria reduction >50% versus basal) • Proteinuria decreased by 66%, from 8.6 ± 4.2 to 3.0 ± 2.5 (P <0.005) g/24 h • Albumin fractional clearance and serum albumin increased by 41% versus from 2.7 + 0.5 to 3.5 +0.4 (P < 0.05) mg/dl. Safety • Episode of larynx spasm (n=1). • Episode of skin rash (n=1). • Generalized chills during infusion which were reduced by lowering rate of infusion (n=1).	Ruggenenti et al 2003	• Case Series • Small sample size (n=8). • Short follow up (12 months) • 4 weekly RTX infusions • First line therapy (treatment before RTX- Full-dose ACE-I for mean 29.7 mo) • CR or PR achieved in 75% patients • Proteinuria decreased by 66% (significant) • No significant safety concerns except and episode of larynx spasm • Study report the long-term follow- up of patients from Remuzzi et al 2002

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 14 patients with IMN with proteinuria >3.5 g/24 h unresponsive to prolonged ACE inhibitor therapy. Intervention Patients received four weekly intravenous infusions of rituximab (375 mg/m2). All patients also received similar conservative treatment that included loop diuretics to control oedema, full-dose ACE inhibitor therapy combined with beta-blockers and calcium channel blockers as deemed appropriate to control BP and proteinuria, and statins to control hypercholesterolemia.	Proteinuria at 3 months after treatment as compared with baseline	Clinical efficacy At 3 months: • Proteinuria decreased in all patients from 8.9 + 5.3 to 4.9 + 3.9 g/24 h ($P < 0.001$). • Serum albumin increased from 2.2 +0.6 to 2.8 + 0.5 mg/dl ($P < 0.01$). • Changes in serum albumin and cholesterol were inversely correlated ($P < 0.02$, $r = -0.44$).	Ruggenetti et al 2006	• Case Series • Small sample size (n=14) • Short follow up (3 months) • 4 weekly RTX infusions • Second line therapy (Before treatment with RTX- no immunomodulatory therapies were given in one year prior; ACE-I was given for at least 6 mo) • 8 patients were previously reported in Ruggenetti et al 2003? • Proteinuria decreased by 44% and serum albumin increased by 21 % (both significant) at 3 months

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
2-	<u>Study design</u> Matched cohort study <u>Patients, characteristics and intervention</u> 36 idiopathic MN (IMN) patients were included- 12 IMN patients who received a B cell–driven treatment rituximab therapy compared to a 24 matched reference patients given the standard protocol of four weekly doses of 375 mg/m^2	Evaluation of whether titrating rituximab to circulating CD20 B cells compared to four weekly doses of 375 mg/m^2	<u>Clinical efficacy</u> On follow-up at 12 months • Proteinuria progressively and similarly decreased in both groups • Similar proportion of patients and reference patients achieved complete (n = 2 [17%] versus 2 [8%]) or partial (n = 6 [50%] versus 14 [58%]) remission. The proportion of non-responders (n =4 [33%] versus 8 [33%]) was the same in the two groups. <u>Safety</u> • Severe reaction of nausea, vomiting, sweating, and hypotension at 1st & 2nd infusions (n=1 in the standard protocol group) • Mild adverse reactions (nausea, chills, sweating, and face rush) during the first Infusion (n=1 B cell–driven and n=4 in standard protocol groups) • One of the four patients of the standard protocol group a second course was planned due to reoccurrence of disease but, a few minutes after the start of the first infusion, treatment had to be stopped because of systemic rash second infusion was attempted after 1 week of premedication with oral • Steroids and antihistamines, but, again, it had to be stopped after a few minutes because of a systemic rash. Subsequent analyses revealed that the patient had developed antichimeric antibodies.	Cravedi et al. 2007	• Cohort study • Small sample size (n=36) • Second line therapy (Before treatment with RTX- no immunomodulatory therapies were given in one year prior; ACE-I was given for at least 6 mo) • Similar outcomes in both groups • No significant safety concerns except 1 patient developed antichimeric antibodies.

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patients characteristics 15 severely nephrotic patients with proteinuria refractory to angiotensin-converting enzyme inhibition and/or receptor blockade. At entry the mean serum creatinine was 1.47± 0.5 mg per 100 ml and the mean creatinine clearance was 85.27 ± 28 ml per min per 1.73m^2 Intervention Patients also received rituximab (RTX; 1 g, intravenous on days 1 and 15. Patients who had proteinuria >3 g per 24 h and 415 CD19þ B cells per ml at 6 months were retreated with a second identical course of rituximab. All patients also received a similar conservative treatment regimen that included loop diuretics to control oedema, an HMG-CoA reductase inhibitor, and an ACEi combined with an ARB if tolerated. b-Blockers and non-dihydropyridine calcium channel blockers, in that order, were added when required to control systolic blood pressures	Complete remission (CR), partial remission (PR), non-responders (NR) or relapse of NS following treatment at 12 months	Clinical efficacy At 12 months follow up: • CR (proteinuria <0.3 g per 24 h) was achieved in two patients. • PR (<50% peak value and <3 g per 24 h) was achieved in six patients. • The mean drop in proteinuria from baseline to 12 months was 6.274.8 g or a 48% reduction (P =0.0003). Safety • Itching, rigors, and a skin rash during infusion (n=3). • Sore or scratchy throat during infusion (n=3). • Muscle pain after infusion that resolved with the use of non-steroidal medication (n=1). • Small patches of hair loss and thinning (n=2) • Community acquired pneumonia 3 months after the first infusion that resolved with oral antibiotic treatment (n=1). • Fatigue and voice loss soon after the infusion ended, but recovered spontaneously (n=1) • Reactivation of herpes zoster (n=1) • Diagnosed with adenocarcinoma of the lung 3 months after the first infusion (n=1).	Fervenza et al 2008	• Case Series • Small sample size (n=15) • ACE-I + ARB for at least 4 mo (n =15); Seven patients had failed previous immunosuppressive treatment - prednisone alone (n = 2); prednisone and alkylating agent (n=2); cyclosporine (n= 2); MMF (n = 1). • Short follow up (12 months) • 10 patients who had proteinuria >3 g per 24 h and 415 CD19þ B cells per ml were retreated at 6 months • Only 45% responded to treatment at 12 months (CR or PR) • Proteinuria decreased by 48% at 12 months (significant) • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 7 IMN patients Intervention 4 weekly rituximab (375 mg/m^2) infusions.	Sodium fractional clearance, Renal plasma flow	At median of 21 months • Sodium fractional clearance decreased from 1.56 to 13.25 • Renal plasma flow decreased from 440.8 to 276.6 ml/min per 1.73 m	Ruggenenti et al 2008	• Case Series • Small sample size (n=7) • Second line therapy • Before treatment with RTX ACE-I given for at least 6 mo
3	Study design Case Series Patient characteristics 13 patients with IMN who showed evidence of long-term dependence on treatment with CNI (either cyclosporine or tacrolimus) and with GFR higher than 60 ml/min Intervention All patients received one intravenous infusion of rituximab (375 mg/m2) per week for 4 consecutive weeks. Relapses occurring after CD-19 cell recovery were retreated with a second trial of rituximab at the minimum dose necessary to achieve the depletion of CD-19 cells. One month after the last infusion of rituximab, both steroids and MMF were discontinued and the dose of CNI was tapered down at a rate of 30% every month until either discontinuation was achieved or evidence of relapse of nephrotic proteinuria (proteinuria >3.5g/d) was noted.	Percentage of patients with CNI withdrawal and no evidence of relapse and the percentage of patients with complete or partial remission 30 months after CNI withdrawal	Clinical efficacy • Proteinuria decreased significantly (2.5 ± 0,76 basal versus 0.85 ± 0.17 at 6 mo; P =0.0003). • CNIs and other immunosuppressant drugs could be withdrawn in all patients with no evidence of relapse. • Three patients suffered a relapse of nephrotic proteinuria 19, 23, and 28 month after rituximab treatment; all were successfully treated with a second course of rituximab. At 30 month, all patients were in remission. Safety • No side effects related to the rituximab administration were observed, and no opportunistic infection or other adverse events related to persistent immunosuppression were observed throughout the whole follow-up.	Segarra et al 2009	• Case Series • Small sample size (n=13) • Second line therapy • 3 patients were given second course of RTX • Proteinuria decreased by 66% at 6 months (significant) • All patients were in remission at 30 months follow up. • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patients characteristics 24 patients with MN and proteinuria >5 g/24 h Intervention Patients received rituximab (375 mg/m^2 X 4), with re-treatment at 6 months regardless of proteinuria response. All patients also received a similar conservative treatment regimen that included loop diuretics to control oedema, an hepatic hydroxymethyl glutaryl–CoA reductase inhibitor, and an ACEI combined with an ARB if tolerated.	Complete remission (CR), partial remission (PR), non-responders (NR), limited response (LR) or relapse of NS following treatment at 24 months	Clinical efficacy At 24 months (n=18/24): • CR (proteinuria <0.3 g/24 h) was achieved in 4 patients • PR (proteinuria <3.5 g/24 h and a >50% reduction in peak proteinuria along with serum albumin >3 g/dl) was achieved in 12 patients • 1 patient had a LR (>50% reduction in proteinuria but >3.5 g/24 h) • 1 patient relapsed • 6 patients were lost to follow up • In the cohort, proteinuria decreased from a baseline of 11.9 ± 4.9 g/24 h to 4.2 ± 3.8 g/24 h at 12 months and 2.0 U1.7 g/24 h at 24 months (both *P* <0.001). Safety • Itchy throat, nasal congestion, and face flushing during first infusion (n=3) • Flu-like symptoms 24 hours after the first infusion (n=4). Minor skin rash (n=2) • Metallic taste after each infusion (n=1) • Hospitalized for possible community-acquired • pneumonia 2.5 months after the first set of infusions; this resolved with oral antibiotic treatment(n=1) • Myocardial infarction 5 months after the first set of infusions (n=1)	Fervenza et al 2010	• Case Series • Small sample size (n=24) • Second line therapy (no immunomodulatory therapies were given in 6 months before treatment) • 16/18 achieved CR or PR (88%) • Proteinuria decreased by 65% at 12 months (significant) • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
2-	Study design Matched cohort study Patients and their characteristics 22 idiopathic MN (IMN) patients were included- 11 IMN patients who received second-line rituximab therapy and 11 matched reference patients given first-line rituximab therapy. Intervention The study compared 11 idiopathic MN patients who received second-line rituximab therapy for persisting NS or relapsing after previous treatment with steroids alone or combined with alkylating agents, cyclosporine, or immunoglobulin G, with those of 11 age- (± 5 years), gender- and proteinuria- (± 1 g/24h) matched reference patients given first-line rituximab therapy. From 2001 up to October 2005, patients received four weekly rituximab doses (375 mg/m 2 each). Since November 2005, the standard protocol has been replaced with a treatment protocol titrated to the number of circulating B cells. The same treatment and follow-up protocol was applied to patients and matched reference patients. All patients also received symptomatic treatment to control oedema, hypertension, and dyslipidemia, according to predefined guidelines that were identical for patients and reference patients.	Complete remission (CR), partial remission (PR), non-responders (NR) or relapse of NS following treatment at 1 & 2 years	Clinical efficacy Complete remission (when 24-hour proteinuria was < 0.3 g in at least two consecutive evaluations) • 2 patients vs. 3 reference patients achieved complete remission Partial remission (when 24-hour proteinuria had declined to < 3.5 g and by at least 50% vs. baseline in at least two consecutive evaluations) • 5 subjects per cohort achieved partial remission Relapse (whenever 24-hour proteinuria increased to 6 3.5 g after a period of partial or complete remission) • 1 patient and 1 reference patient had a relapse of the NS 15 and 10 months after rituximab therapy, respectively. Safety A transient facial rash during infusion was observed in 1 patient and in 1 reference patient who had received the four-dose regimen.	Cravedi et al 2011	• Cohort study • Small sample size (n=22) • Two treatment protocols were used (Five patients and their matched reference patients received the standard four-dose rituximab protocol, whereas the remaining 6 patients and matched reference patients received the B-cell-driven protocol). • Similar outcomes in both groups • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 83 patients with corticosteroid-resistant and calcineurin-inhibitors ± cellcept refractory idiopathic nephrotic syndrome who had required previous treatment for a minimum of two years were included. 32 patients with Minimal change disease (MCD), 18 with focal segmental glomerulosclerosis (FSGS) and 28 with membranous glomerulopathy (MG). Intervention Protocol included the use of 4 weekly slow infusions of rituximab (500 mg of rituximab was diluted in 450 mL of normal saline leading to a concentration of 1 mg/mL). After the 4th week, the dose of C-I + cellcept were tapered off and discontinued by 8 weeks.	Complete remission (CR), partial remission (PR), non-responders (NR) or relapse of NS following treatment	Clinical efficacy At 12 months: MCD group (n=32) At 12 months: • In this group 29 achieved CR and 2 PR . 1 of the previous NR did not respond. • Excluding two patients who required retreatment, the others remained in CR (17 patients up to 28 months and six up to 36 months). FSGS group (n=18) At 12 months: • 17 of the 18 patients achieved PR • 1 patient remained NR MG group (n=28) From 8-12 months • 12 had achieved CR • 14 had achieved PR • 2 patients failed to respond • From 12 months onwards, all patients relapse. Requiring retreatment. Safety • Most patients had infusion-related symptoms included itching, mild hypotension and broncho-spasm during the first infusion. • Rituximab was not tolerated despite pre-medication with corticosteroids, diphenhydramine and acetaminophen as well as slow infusion rate and patients excluded from the study (n=5). • Bloody diarrhoea two months post-infusion (n=1) • Transient increase of alkaline phosphatase to twice the upper limit of normal but normalized later (n=2).	El Reshaid et al 2012	• Case Series • Small MG sample size (n=28) • Short follow up (12 months) • Second line therapy • By 12 months, all patients relapsed in MG group • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 100 patients with IMN with persistent nephrotic syndrome despite at least 6-month therapy with full-dose ACE inhibitors and optimized conservative therapy Intervention Up to October 2005, patients received four weekly rituximab doses. Thereafter, patients received a second rituximab infusion only when >5 circulating B cells per mm^3 were detected the morning after completion of the first rituximab administration	Complete remission (CR), partial remission (PR), non-responders (NR), or relapse of NS following treatment	Clinical efficacy • 65 patients achieved complete or partial remission at median follow up of 29 months. Received rituximab first-line (47 of 68; 61%), second-line (18 of 32; 56%). • 27 of the patients with partial remission eventually achieved complete remission. • 18/65 patients achieving complete or partial remission had a relapse of proteinuria from 7 through 116 months (median 42 months) after rituximab administration. • 24 patients who were alive and free of dialysis after at least 4 years of follow-up achieved complete or partial remission. (complete or partial remission defined as 24-hour urinary protein excretion ,0.3 or 3.0 g with at least 50% reduction versus baseline), respectively) Safety • Transient, non-serious adverse events were observed during rituximab administration (n= 28) • Bronchial wheezing ,(n=10) • Cutaneous rash (n=1) • Episode of hypotension (n=1)	Ruggenenti et al 2012	• Case Series • 14 patients were previously reported in Ruggenenti et al 2003 & 2006? • First (n=68) & second (n=32) line therapy patients • 65% patients achieved CR or PR at 29 months • 28% patients had a relapse at median follow up of 42 months • No significant safety concerns

Clinical Effectiveness and Safety					
Level of Evidence	**Study design & Intervention**	**Outcome measure(s)**	**Results**	**Reference**	**Comments**
3	Study design Case Series Patient characteristics 24 adult patients who received rituximab (RTX) for IMN (n = 11), minimal change disease (MCD, n = 7), focal segmental glomerulosclerosis (FSGS, n = 4), and membranoproliferative glomerulonephritis (MPGN, n = 2)	Complete remission (CR), partial remission (PR), non-responders (NR), or relapse of NS following treatment	Clinical efficacy Median follow-up for all patients was 31.5 months • Rituximab therapy induced remission in 19/24 (79.2 %) patients (IMN: 63.6 %, MCD: 100 %, FSGS: 75 %, and MPGN: 100 %) • Disease recurrence in patients with ≥3 relapses pre-RTX therapy (MCD, n = 6 and FSGS, n = 1) decreased from 37.0 to 19.6 events per 1,000 patient-months. • All patients with steroid maintenance, discontinued or achieved at least a 50 % dose reduction at 3.0 months (IQR: 1.5-8.0) post-treatment. • One patient ceased CSA in addition to a 50 % steroid dose reduction 13 months post-RTX. Safety • Rituximab was well tolerated with a single serious infection (4.2 %) responsive to treatment.	Kong et al 2013	• Case Series • Small sample size (n=11) • Second line therapy • RTX induced remission in 63% patients at median follow up of 31.5 months • No significant safety concerns

7. Appendix Two

Literature Search Terms

Assumptions / limits applied to search:	
Original search terms:	'Membranous glomerulopathy', 'membranous glomerulonephritis', membranous nephropathy', 'rituximab', 'ciclosporin', 'tacrolimus', 'chlorambucil', 'cyclophosphamide' and their combinations.
Updated search terms - Population	Patients with membranous glomerulopathy
Updated search terms - Intervention	Rituximab
Updated search terms – Comparator	Supportive care.
Updated search terms – Outcome	*Critical to decision-making:* *Important to decision-making:*
Inclusion criteria	General inclusion criteria

	• Articles published between January 2000 and July 2013 • Articles in the English language only were considered
	Specific inclusion criteria
	• Primary research studies reporting clinical effectiveness, safety and/or cost-effectiveness of the rituximab in biopsy-proven idiopathic MN
Exclusion criteria	**General exclusion criteria**
	• Case reports • Studies reporting use of rituximab in secondary MN • Studies reporting use of rituximab to treat MN in transplanted kidneys
	Specific exclusion criteria