CADTH
ACMTS

Proposed Project Scope

Rituximab to Treat Primary Membranous Nephropathy

10 February 2020

for Stakeholder Feedback

BACKGROUND AND RATIONALE

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

The incidence of MN is 1.2/ 100,000 persons per year worldwide.[2] Approximately 80% of patients with MN have anti-phospholipase A2 receptor (anti-PLA2R) antibodies and are classified as primary (or idiopathic) MN; whereas 20% of patients have secondary MN due to a malignancy, an infection (e.g., hepatitis B or C), drugs (e.g., penicillamine, NSAIDs), an autoimmune disease (e.g., systemic lupus erythematosus), or a non-identified autoantibody.[1,2]

Spontaneous remission of primary MN is seen in up to 30% of patients,[1,2,5] and 30% to 40% of patients will progress to ESDR.[1] The occurrence of remission is more common in patients with low antibody levels.[1,2] Those with high levels of antibodies have higher risks of relapses, lower responses to therapy, and longer time to remission.[1,2]

The Toronto Risk Score is a validated tool that can predict the risk of progression to ESRD in patients with primary MN.[1] Low risk patients will have normal serum creatinine/ creatinine clearance and proteinuria ≤4 g /24 hours over a six-month observation period. Medium risk patients will have normal and stable renal function and with proteinuria of 5 to 8 g/ 24 hours over a six-month observation period. Those at high risk will have persistent proteinuria >8 g/ 24 hours.[1]

The treatment goal of patients with primary MN is to achieve proteinuria remission to prevent renal damage.[2] Treatments include supportive therapies for hypertension, hyperlipidemia, edema, and for preventing thromboembolism.[1,2] There is evidence to show that immunosuppressive therapy reduces proteinuria, all-cause mortality and progression to ESRD. Alkylating drugs (cyclophosphamide or chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus) are immunosuppressive therapies recommended to treat patients with primary MN as described in the guidelines *The Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines for Glomerulonephritis 2012* (KDIGO).[6]

The 2012 KDIGO guidelines recommend using the Ponticelli regimen as initial treatment: in the first month, intravenous methylprednisolone 1g is administered daily for three doses, then oral methylprednisolone (0.5 mg/ kg per day) is administered for 27 days. In the second month, oral cyclophosphamide[a] (2 mg/ kg per day) is administered for 30 days. Months 3 and 5 are a repeat of the treatment regimen administered in the first month. Months 4 and 6 repeats the treatment regimen of the second month.[6]

Alternatively, calcineurin inhibitors may be administered for six months in patients who are not candidates for cyclophosphamide. The recommended dosing administration for cyclosporine is 3.5 to 5.0 mg/ kg per day given orally in two equally divided doses 12 hours apart, with prednisone 0.15 mg/ kg per day, for 6 months. Alternatively, tacrolimus is administered at a dosage of 0.05 to 0.075 mg/ kg per day given orally in two divided doses 12 hours apart, without

[a] Initially the Ponticelli regimen consisted of oral chlorambucil 0.15 to 0.2 mg/ kg per day and methylprednisolone, but the preference now is to use cyclophosphamide and methylprednisolone.

prednisone, for 6 to 12 months. The guidelines make further recommendations in case of resistance to treatment, relapses, and children.[6]

The use of these medications are associated with serious adverse events. Patients administered cyclophosphamide are at risk of malignancy, infertility, infection, bone marrow suppression, liver toxicity, and cardiovascular events.[1,2] Serious adverse events seen in patients on calcineurin inhibitors include hypertension and nephrotoxicity.[1]

Other treatments for which there is evidence of efficacy include adrenocorticotropic hormone (ACTH), azathioprine, mycophenolate mofetil, and rituximab.[1,2]

Rituximab is a monoclonal antibody directed against the CD20 receptor. It induces the depletion of CD20 positive B-cells. Its use in primary MN was first reported in a case series in 2002 and subsequently in three single arm trials and one RCT that compared rituximab with supportive therapies.[2]

Rituximab does not have Health Canada approval for the indication of primary MN, and as a such is used off-label. Recently, three phase III RCTs have been conducted to evaluate rituximab compared with other immunosuppressive treatments in primary MN; one RTC has published results and the other two RCT are completed but not yet published.

In July 2019, the MENTOR study on remission of proteinuria in 130 patients with primary MN was published.[7] It compared intravenous (IV) rituximab (two infusions, 1 g each, administered 14 days apart; repeated at 6 months in case of partial response) or oral cyclosporine (starting at a dose of 3.5 mg/ kg per day for 12 months). Results demonstrated that:

- Rituximab was noninferior to cyclosporine in inducing proteinuria remission
- Rituximab was superior to cyclosporine in maintaining proteinuria remission.[7]

A critical appraisal of the MENTOR study is posted on the CADTH website.[8]

The STARMEN study (ClinicalTrials.gov Identifier NCT019551870) investigated the use of cyclical cyclophosphamide-corticosteroid combination treatment for 6 months (Ponticelli regimen) compared with sequential tacrolimus-rituximab. The initial dose of oral tacrolimus was 0.05 mg/ kg per day, adjusted to achieve blood trough levels of 5 to 7 ng/mL for 6 months. At the end of Month 6, the tacrolimus dosage was reduced by 25% per month, with a complete withdrawal at the end of Month 9. Rituximab was administered as a single dose of 1 g IV given at Day 180, before the onset of the tacrolimus dose reduction. The trial was conducted in 86 patients with primary MN.[9] The study completion date was in June 2019.

The RI-CYCLO study (ClinicalTrials.gov NCT NCT03018535) evaluated rituximab 1 g administered on days 1 and 15, compared with 6 months of cyclical cyclophosphamide-corticosteroid combination treatment (Ponticelli regimen) in 76 adults with a diagnosis of primary MN.[10] The study completion date was in December 2019.

Several meta-analyses of RCTs have been published evaluating immunosuppressive therapies in primary MN, but none included rituximab.[11-19]

An economic evaluation published in 2018 evaluated the cost-effectiveness of rituximab compared with the Ponticelli regimen. The evaluation was conducted from the perspective of the UK National Health Service using 2015 prices and based on an RCT by Jha et al[20] that compared the Ponticelli regimen to supportive care, and on an observational study by Ruggenenti et al[21] that included 100 consecutive patients treated with rituximab and no control

group. The results of the economic evaluation showed that, at five-years post treatment, rituximab was cheaper than the Ponticelli regimen but at a loss of 0.014 quality adjusted life years (QALYs), with an incremental cost effectiveness ratio (ICER) of £95,494.[22]

Policy Issue

The KDIGO 2012 guidelines did not consider rituximab as a possible treatment for primary MN. The publication of the MENTOR study creates a paradigm shift and clinician requests to use rituximab as a treatment for primary MN have increased. Whereas MENTOR compared rituximab to cyclosporine, its comparative efficacy and safety to cyclophosphamide remains unknown.

CADTH will undertake a series of projects to review the available evidence on the use of rituximab for primary MN with the perspective of trying to determine its place in therapy and cost effectiveness relative to cyclophosphamide and the calcineurin inhibitors.

Table I: Policy Questions

1. Which patient population(s) for primary membranous nephropathy would be most appropriate to access treatment with rituximab?
2. What policies would provide access to rituximab for treating primary membranous nephropathy to the most appropriate patient population(s)?

Table II: Drug Products Available in Canada

Product	Manufacturer
Cyclophosphamide (Procytox)	Baxter Corporation
Cyclosporine (generics)	Various manufacturers
Rituximab (Rituxan, Truxima*)	Hoffmann-LA Roche Limited; Celltrion Healthcare Co Ltd
Tacrolimus (generics)	Various manufacturers

*Truxima is a newly marketed biosimilar (Notice of Compliance received on December 11, 2019)

PROJECT DESCRIPTION

Table IV: Proposed Project Scope

Population	Adults and children with primary membranous nephropathy
Intervention	Rituximab
Comparators	• Cyclophosphamide with corticosteroids • Calcineurin inhibitors (cyclosporine or tacrolimus) with or without corticosteroids
Outcomes	• Clinical effectiveness (e.g., remission, partial remission, time to treatment failure, end-stage renal disease, biomarker-assessed renal function improvement, serum albumin, autoantibody levels, health-related quality of life) • Safety (e.g., nephrotoxicity, cancer, infections) • Cost effectiveness
Study Design	• Randomized controlled trials

Research Questions
1. What is the internal and external validity of the MENTOR study? 2. What are the efficacy and safety of rituximab compared with current treatments in patients with primary membranous nephropathy? 3. What is the cost-effectiveness of rituximab compared with current treatments in patients with primary membranous nephropathy? 4. What criteria and conditions would provide access to rituximab for the most appropriate patient population for treatment of primary membranous nephropathy? 5. Which policy option is preferred?

KEY PROJECT COMPONENTS

Table V: Project Components

Product Type	Description	Research Question
1. Technology Review – FCA*	Focused critical appraisal of the MENTOR study	What is the internal and external validity of the MENTOR study?
2. Health Technology Assessment – Systematic Review	Systematic review/ network meta-analysis	What are the efficacy and safety of rituximab compared with current treatments in patients with primary membranous nephropathy?
3. Health Technology Assessment – Health Economics	De novo economic evaluation	What is the cost-effectiveness of rituximab compared with current treatments in patients with primary membranous nephropathy?
4. Technology Review – OU 360	Policy options paper	What criteria and conditions would provide access to rituximab for the most appropriate patient population for treatment of primary membranous nephropathy?
5. Implementation Advice Panel	Provide advice on which policy option is preferred	Which policy option is preferred?

*completed and posted on the CADTH website

STATUS OF THE DOCUMENT

This proposed project scope will be posted for 10 business days for stakeholder feedback. The feedback will be considered as we finalize the project plan. A list of included studies for the Systematic Review and a project protocol may be posted on CADTH's website if required. Of note, this project is not a Therapeutic Review and as such there will be no CDEC recommendations made.

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