CADTH

Rituximab for the Treatment of Primary Membranous Nephropathy

Implementation Advice

Background

Representatives from public drug programs requested that a panel of clinical experts be convened to elaborate on the place of rituximab in the treatment of PMN to inform appropriate usage of this drug in the Canadian context. The panel was asked to focus their discussion on the following questions:

- Based on the available evidence, what is the place in therapy of rituximab to treat primary membranous nephropathy?
- What specific characteristics should patients possess or satisfy for access to rituximab?
- What is the most appropriate rituximab dosing regimen?
- What objective measures or outcomes, and at what time points, should be used to determine treatment success or failure in primary membranous nephropathy?
- Are there special populations that require other considerations?

Consultation Process and Objectives

The clinical expert panel was comprised of 3 Canadian specialists with expertise in the diagnosis and management of patients with diseases of the kidneys and one Canadian specialist with expertise in critical care medicine. The objective of the panel was to provide advice to the participating drug programs. A consensus-based approach was used, and input was sought using a questionnaire and a panel meeting. In addition to the clinical panellists and CADTH staff, representatives from public drug programs were invited to participate in the discussion and to provide input in advance of the meeting on the topics up for discussion.

There was consensus among the panel members that there is considerable unmet need in the discussed patient population, and the panel agreed that rituximab has the potential to meet some of these unmet needs. The criteria specified in this appendix reflect the panel members' conclusions based on the best available evidence and their clinical expertise in the diagnosis and management of primary membranous nephropathy.

The advice presented in this report is based on the evidence presented in the clinical review and the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 guidelines, as well as the experience and expertise of the implementation advice panel members.

Implementation Advice

Initiation, discontinuation, and administration or prescribing criteria and conditions for rituximab for treatment of PMN are shown in Table 14.

Table 14: Summary of Initiation, Discontinuation, and Administration Criteria for Rituximab

Criteria	Description
Definitions	**Complete remission:** Proteinuria < 0.3 g/day or protein-creatinine ratio < 30mg/mmol **Partial remission:** Reduction in proteinuria of at least 50% from baseline and final proteinuria between 0.3 g and 3.5 g per day **Relapse:** Recurrence of proteinuria (as per the initiation criteria) accompanied by a decrease in serum albumin to less than 30g/L in patients who have achieved a complete or partial remission following prior rituximab treatment **Nonresponse:** Lower than 25% reduction in proteinuria by 6 months after initial course
Initiation criteria	Eligibility for treatment with rituximab is based on criteria for moderate to high risk of developing progressive kidney injury or complications of nephrotic syndrome. **Initiation criteria** Rituximab may be used in patients 18 years of age or older if one of the following criteria are met: • proteinuria > 5g/day despite 6 months of conservative therapy with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker ○ a shorter observation period (less than 6 months) may be considered when proteinuria > 8g/day or high anti-PLA2R titres > 50 or eGFR < 60 ml/min/1.73m^2 • proteinuria > 3.5 g/day with life- or organ-threatening complications of nephrotic syndrome (i.e., venous thrombosis, arterial thrombosis, infection, or rapid decline in kidney function not otherwise explained) • biopsy-proven or serology (anti-PLA2R)-proven recurrence in a patient who has received a kidney transplant and has proteinuria > 3.5 g/day. **Initial treatment** • Rituximab 1g intravenously on day 0 and day 15 • If there is complete remission, no additional courses of rituximab are required **Additional courses** An additional course of rituximab may be administered using the same dosage and regimen at 6 months: • if proteinuria is reduced from baseline by at least 25% without complete remission • in case of a relapse.
Discontinuation criteria	• Rituximab can be discontinued when there is complete remission • Rituximab can be discontinued in nonresponders; re-treatment of nonresponders is not recommended

Prescribing conditions	Populations that require special consideration:
	• Rituximab may be used in lactating women.
	• Rituximab should be used with extreme caution in:
	  ○ pregnant women
	  ○ patients with latent or active hepatitis B.

eGFR = estimated glomerular filtration rate; PLA2R = phospholipase A2 receptor.

Clinical Panel Input Summary

Treatment Goals

The panel affirmed that the goals for treatment with rituximab and other therapies in primary membranous nephropathy are to achieve remission of proteinuria, maintain quality of life, prevent progressive loss of kidney function, prevent the need for renal replacement, and potentially prolong survival.

Place in Therapy

The panel discussed that there is uncertainty around the relative efficacy and harms of rituximab compared to other therapies for primary membranous nephropathy. There was consensus that the use of rituximab is associated with a lower risk of specific harms, relative to other drugs, due to a more favourable toxicity profile. The panel noted specific examples of toxicities associated with other treatment protocols, such as the use of higher doses of corticosteroids, higher risk of nephrotoxicity with calcineurin inhibitors, and cumulative toxicities related to cyclophosphamide protocols. The panel also acknowledged that there are risks to using rituximab, including serious infections; therefore, it should only be prescribed by clinicians with appropriate expertise.

The panel agreed that if rituximab is to be used as a first-line treatment, it may be used in patients newly diagnosed with primary membranous nephropathy, and is an alternative to CYC, calcineurin inhibitors, and cyclophosphamide in the first-line context. Rituximab is also a treatment option for patients who have had inadequate response to CYC, calcineurin inhibitors, or cyclophosphamide, or for patients in which continued treatment with those medications is not appropriate. Re-treatment with rituximab is an option in patients who had PR or CR and subsequently relapsed. Patients with recurrence of membranous nephropathy in a transplant kidney may also be considered for rituximab as first-line therapy; these patients are at risk of graft loss and are already immunosuppressed because of calcineurin inhibitor therapy.

Initiation Criteria

The panel agreed that the use of rituximab in patients with low risk of disease progression is not appropriate. Treatment with rituximab would be appropriate for patients (≥ 18 years of age) with moderate to high risk of progressive kidney disease based on proteinuria and estimated glomerular filtration rate.

The panel noted that the KDIGO guidelines recommend also using serum albumin and anti-phospholipase A2 receptor (PLA2R) titres to guide risk assessment, initiation, and continuation of treatment. While there is evidence that suggests a correlation between anti-PLA2R titres and resistance to treatment, laboratory tests for anti-PLA2R are not accessible in many Canadian centres and there is no consensus on how to use titre thresholds for treatment initiation. Additionally, the data that are available regarding anti-PLA2R titres in patients with primary membranous nephropathy do not provide sufficient evidence for informing treatment selection.

Discontinuation Criteria

The panel agreed that treatment with rituximab may be stopped when complete remission is achieved. Only one course of rituximab is required to determine whether or not a patient responds to therapy. In case of a nonresponse, re-treatment is not recommended.

Prescribing Conditions

The panel noted that the warnings and risks stated in the product monograph should be taken into account when prescribing rituximab. Rituximab may be used by those who are lactating, but careful consideration of risks to the fetus should be taken if prescribing for those who are pregnant. Special consideration should be given to risk of reactivation in patients with latent or active hepatitis B.