Ontario Renal Network

Rituximab Protocol

For adult patients with glomerulonephritis

Ontario

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GN Drug Access Task Group

- Melissa Lan, Renal Pharmacist of University Health Network (primary author)
- Jenny Ng, Renal Pharmacist of Sunnybrook Hospital (Task Group co-chair)
- Dr. Todd Fairhead, Director, Glomerulonephritis Clinic of the Ottawa Hospital & Assistant Professor, Division of Nephrology, Department of Medicine, University of Ottawa (Task Group co-chair)
- Lisa Zhu, Renal Pharmacist of Sunnybrook Hospital
- Brandi Grozell, Nurse Practitioner of Sunnybrook Hospital
- Alison Shipley, Renal Pharmacist of St. Joseph's Healthcare Hamilton
- Anna Babej, Renal Pharmacist of Trillium Health Partners
- Clara Korenvain, Renal Pharmacist of London Health Sciences Centre
- Kiet-Nghi Cao, Renal Pharmacist of The Ottawa Hospital
- Lewis Liu, Renal Pharmacist, Kingston Health Sciences Centre
- Rohini Naipaul, Senior Pharmacist, Cancer Care Ontario

The Glomerulonephritis and Specialty Clinics Priority Panel

- Dr. Michelle Hladunewich, ORN Provincial Medical Lead, Professor of Medicine, University of Toronto, Physician in Chief, Sunnybrook Health Sciences Centre
- Dr. Phil Boll, ORN Provincial Medical Lead and Nephrologist of Trillium Health Partners
- Dr. Daniel Cattran, Nephrologist of University Health Network and Professor of Medicine, University of Toronto and Senior Scientist, Toronto General Research Institute
- Dr. Norman Muirhead, Nephrologist of London Health Sciences Centre and Professor of Medicine, Western University
- Dr. Azim Gangji, Nephrologist of St. Joseph's Healthcare Hamilton and Assistant Professor of Medicine, Division of Nephrology, Department of Medicine, McMaster University
- Dr. Ian MacDonald, Nephrologist of Health Sciences North
- Dr. Todd Fairhead, Director, Glomerulonephritis Clinic of the Ottawa Hospital and Assistant Professor, Division of Nephrology, Department of Medicine, University of Ottawa
- Jenny Ng, Renal Pharmacist of Sunnybrook Health Sciences Centre
- Susanne Jeffery, Nurse Practitioner of Kingston Health Sciences Centre
- Sandra Grgas, Regional Director, Toronto Central & Clinical Director of University Health Network
- Stephanie Winn, Regional Director, North East and Director of Nephrology, Health Sciences North

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Protocol Development

The information contained in this protocol was derived from published evidence, clinical expert opinion, and existing institutional guidelines (University Health Network and Sunnybrook Health Sciences Centre).

Description

Rituximab (RITUXAN®) is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20.[1]

Indications

- To induce remission in patients with the following types of glomerulonephritis (GN) and who have organ and/or life-threatening disease:
    - Membranous Nephropathy (MN)[2]
    - Focal Segmental Glomerulosclerosis (FSGS)[3, 4]
    - Minimal Change Disease (MCD)[5]
    - Membranoproliferative glomerulonephritis (MPGN) with IgG deposits +/- complement)[6, 7]

- To induce or maintain remission in patients with the following types of Anti-Neutrophilic Cytoplasmic Autoantibody (ANCA)-associated vasculitides and who have organ and/or life-threatening disease:[1, 8, 9]
    - Granulomatosis with polyangitis (GPA)
    - Microscopic polyangitis (MPA)

Contraindications

- Known type 1 hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or to any component of this product[1]
- Patients who have or have had progressive multifocal leukoencephalopathy[1]
- Severe, active infection[1]

Precautions/Warnings

- Active infection[1]
- Reactivation of chronic, latent infections such as hepatitis B or tuberculosis[1]
- Malignancy concerns

Pregnancy and Lactation

Rituximab should not be administered to pregnant women unless the possible benefit outweighs the potential risk. It is recommended that women of childbearing age employ effective contraceptive methods during and for up to 12 months after treatment with rituximab.[1]

- The information available on use of rituximab during pregnancy is limited, but does not suggest an increased risk for major congenital malformations above the baseline risk in the general population.[10, 11]

- For infants exposed in utero to rituximab close to delivery, blood analysis to rule out hematological abnormalities is recommended as rituximab may affect fetal and neonatal B-cell development, potentially leading to increased susceptibility to infections.[12]
- The Canadian Immunization Guidelines (CIG) recommend that infants exposed to monoclonal antibodies in the womb should receive all inactivated vaccines according to the routine schedule. However, it is noted the immune response during the first few months may be suboptimal, depending on the monoclonal used and the gestational period during which it was administered.[13] ORN recommends adopting this recommendation for infants exposed in utero to rituximab for GN patients.
- The CIG makes the following relevant statements regarding the use of monoclonal antibodies during breastfeeding:
  Monoclonal antibodies administered to the mother during breastfeeding are thought to have very little or no impact on the infant. Transfer of monoclonal antibodies through breast milk is limited, and the minimal quantities that are ingested are likely to be broken down in the infant's gastrointestinal tract. Infants of breastfeeding women receiving monoclonal antibody treatment post-partum can therefore be immunized with both live and inactivated vaccines according to routine schedules, unless the infant was also exposed to monoclonal antibody in the womb.[12]

Screening

Refer to the **Recommendations for Malignancy Screening for Adult Patients with Glomerulonephritis prior to Immunosuppressive Therapy** on the Ontario Renal Network website (under development).

Immunizations

Refer to the **Considerations for Immunization for Adult Patients with Glomerulonephritis [hyperlink]** document on the Ontario Renal Network website.

Dosing and Duration

1. Treatment of GN (MN, FSGS, MCD, MPGN)

Doses vary across studies and indications.[2, 4, 5, 6] ORN recommends the following dosing regimen:

Rituximab 1000 mg IV q 2 weeks for 2 doses

2. Treatment of ANCA-associated vasculitides (GPA, MPA)

Protocol 1 (Rituximab for ANCA-associated Vasculitis (RAVE) Study Protocol):[14]
Rituximab 375 mg/m^2 x patient BSA (m^2) IV weekly for 4 doses

(This protocol is currently covered by the Ministry's Exceptional Access Program (EAP) for patients who meet specific clinical criteria)[15]

Note: The formula for calculating BSA in the RAVE clinical trial was: BSA in m^2= (Weight in kg) ^0.425 x (Height in cm) ^0.725 x 0.007184. Note: Do not round until the end of calculation.

OR

Protocol 2 [8]

Rituximab 1000 mg IV q 2 weeks for 2 doses

*No dosing adjustment has been provided in manufacturer's labelling (has not been studied) in renal or hepatic impairment.[1]

3. Maintenance therapy for ANCA-associated vasculitides (GPA, MPA)

Rituximab 500 mg IV q 6 months x 2 years

- Initiate 4 to 6 months after rituximab induction treatment providing remission has been achieved.
- Initiate after oral cyclophosphamide induction treatment providing remission has been achieved, white blood cell count is greater than 4000 cells/µL, and absolute neutrophil count is greater than 1500 cells/µL. In some patients, maintenance therapy can be started the day after oral cyclophosphamide is stopped.
- Initiate 2 to 4 weeks after IV cyclophosphamide induction treatment if remission is achieved, white blood cell count is greater than 4000 cells/µL, and absolute neutrophil count is greater than 1500 cells/µL.

Preparation using Rituxan®

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% sodium chloride injection USP or 5% dextrose injection USP.[1]

Use appropriate aseptic technique. Rituximab vials do not contain any preservative or bacteriostatic agent.[1]

Rituximab does not meet the criteria for inclusion on the National Institute for Occupational Safety and Health (NIOSH) list of antineoplastic and other hazardous drugs in healthcare settings. It does not represent an occupational hazard to health care workers. No personal protective precautions are required during administration and disposal.[16]

Rituximab in 0.9% sodium chloride solution is physically and chemically stable for 30 days at 2 – 8°C plus an additional 24 hours at ≤ 30°C. Rituximab in 5% dextrose solution is physically and chemically stable for 24 hours at 2 – 8°C plus an additional 12 hours at room temperature.[1]

Administration

Anti-hypertensives:

Consider holding anti-hypertensive agent(s) on morning of rituximab infusion due to potential for hypotension during infusion.

Pre-medications:

- Acetaminophen 650 mg given PO 15-30 minutes prior to rituximab
- Diphenhydramine 50 mg given PO 15-30 minutes prior to rituximab *or* diphenhydramine 50 mg IV in 50 mL 0.9% sodium chloride injection USP or 5% dextrose injection USP given 15-30 minutes prior to rituximab
- Methylprednisolone sodium succinate 100 mg IV in 50 mL 0.9% sodium chloride injection USP or 5% dextrose injection USP given 15-30 minutes prior to rituximab

PRN medications for infusion reactions:

- Acetaminophen 325-650 mg PO q 4-6 hours PRN for pain, fever, chills
- Dimenhydrinate 25-50 mg PO / IV q 4 hours PRN for nausea, vomiting
- Diphenhydramine 25-50 mg PO / IM / IV q 4-6 hours PRN for itching, urticaria, pruritus, hives
- Epinephrine (1:1000) 0.01 mL/kg (maximum 0.5 mL) SC / IM q 10-15 minutes PRN x 2 doses for severe anaphylactic reaction
- Hydrocortisone sodium succinate 100 mg IV *or* methylprednisolone sodium succinate100 mg IV PRN x 1 dose for severe allergic/anaphylactic reaction (choice of steroid and dose varies according to hospital protocols)
- Oxygen via mask/nasal prongs PRN for shortness of breath, wheezing
- Salbutamol 200 mcg (2 puffs) q 4-6 hours via aerochamber *or* salbutamol 2.5 mg nebules plus nebulizer PRN for dyspnea, wheezing

First infusion or patients with prior infusion reaction:

Infuse rituximab intravenously at a rate of 50 mg/hr for the first 30 to 60 minutes, increasing by 50 mg/hr every 30 minutes as tolerated, for a maximum rate of 400 mg/hr.[1]

Subsequent infusions:

Infused rituximab intravenously at a rate 100 mg/hr for the first 30 to 60 minutes, increasing by 100 mg/hr every 30 minutes to a maximum rate of 400 mg/hr as tolerated.[1]

For infusion reactions:

Hold IV infusion and contact physician for further advice. If patient's symptoms improve, re-start infusion at half the previous infusion rate then increase infusion rate and monitor as outlined above, as tolerated.

Plasma exchange and dialysis:

- Rituximab is removed by plasma exchange.[17] For patients receiving plasma exchange, administer rituximab after plasma exchange.
- Rituximab is not removed by hemodialysis.

Monitoring

Rituximab infusion monitoring

Vital signs to be monitored pre-infusion, every 15 to 30 minutes for the first hour of the infusion, before each infusion rate increase, at completion of infusion, and 15 to 30 minutes post-infusion.

- Blood pressure
- Heart rate
- Respiratory rate
- O_2 saturation
- Temperature
- Infusion reactions symptoms (i.e. fever, rigors, chills)

Suggested post-rituximab infusion efficacy and safety monitoring

Monitor CBC and hepatic enzymes at baseline, approximately 4 weeks after completing the rituximab course and then regularly at 1 to 3-month intervals thereafter.

Suggest to monitor absolute CD19/20+ B cell count/percentage at baseline, approximately 4 weeks after completing the rituximab course to confirm CD19/20+ B cell depletion, and thereafter to guide clinical decision-making.

- Absolute CD 19/20+ B cell depletion target: Less than 15 cells/μL^2 or <1%
- Absolute CD 19/20+ B cell reconstitution target**:** Greater than or equal to 15 cells/μL^2 or greater than or equal to 1%

Pneumocystis Pneumonia (PCP)

Refer to the **PCP Prophylaxis Recommendations for Adult Patients with Glomerulonephritis** on the Ontario Renal Network website (under development).

Cost and Coverage

Refer to **Medications for Glomerulonephritis** on the Ontario Renal Network website for information on funding options for rituximab.

Drug Benefit Prices for products reimbursed under the Ministry's Exception Access Program as of April 30, 2019:

Rituximab (Rituxan®) 10 mg/mL, 50 mL vial: $2411.54CAD
Rituximab (Rituxan®) 10 mg/mL, 10 mL vial: $482.31 CAD

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