USE OF RITUXIMAB IN AUTO-IMMUNE CONDITIONS

SAFETY SCREENING AND MONITORING INFORMATION FOR CLINICIANS

Before the use of rituximab, patients need to be screened for infection, their ability to fight infection (including immunisation status) and any contraindications to use. During therapy with rituximab, patients must be monitored for adverse effects, especially infection.

There are three infections of particular concern with rituximab[1]:

Hepatitis B (HB)	*Pneumocystis jiroveci* pneumonia (PJP)	Progressive Multifocal Leukoencephalopathy (PML)

Patients with low concentrations of Immunoglobulin G (IgG) before commencing rituximab are at particular risk of infection due to previous immunosuppression or the underlying condition for which they are receiving rituximab. Infection risk also depends on past and current immunosuppression, especially corticosteroid treatment.[1]

It is important to treat suspected infections early. If the infection is serious, resistant to treatment or recurrent, check full blood counts, IgG concentrations and contact the patient's specialist for advice.[1]

Below is a summary of key safety screening and monitoring that should be performed in **all** patients receiving rituximab as immunosuppressive therapy. There is no consensus about how to screen and this document serves as guidance only. Please use in conjunction with relevant local protocols and resources listed in *References and Resources*.[2-10]

BEFORE STARTING RITUXIMAB THERAPY

- Assess precautions and contraindications for rituximab use including hypersensitivity, severe immunosuppression, use with other cytokine modulators, and presence of malignancy, cardiovascular and lung diseases, pregnancy and lactation. [Consult Australian Medicines Handbook (AMH) and Rituximab PI].[6, 8, 11]
- Screen the patient for active and latent infections, especially:
  - Hepatitis B (further information below)
  - Hepatitis C
  - HIV
  - Tuberculosis (TB) (Note: screening requirements determined by local TB epidemiology)
- Seek specialist advice in any patient currently suffering from or with a history of any of the above infections
- Check patient's vaccination status. Vaccination may be recommended prior to initiating rituximab in non-emergency cases- seek specialist advice; further information below.
- Measure plasma immunoglobulins [1, 3], full blood count, liver function tests and creatinine.[11]
- Consider prophylaxis for *Pneumocystis jiroveci* pneumonia; further information below.[7]

HEPATITIS B

Consult a liver disease specialist to discuss antiviral prophylaxis in patients with positive HB serology before commencing rituximab therapy. Monitor and manage according to guidelines to prevent HB reactivation. [1, 2, 6]

There is a high risk of reactivation of Hepatitis B Virus (HBV) infection in patients receiving rituximab for non-malignant (and malignant) medical conditions.[7] Therefore, it is important to note that:

- Rituximab should not be initiated in patients with severe active HB
- Hepatitis B virus (HBV) screening should be performed in all patients before the initiation of rituximab therapy. At a minimum, this should include HB surface antigen (HBsAg) status and Hepatitis B core antigen (anti-HBc) status.[6]
- If required, antiviral prophylactic treatment should begin at least one week before the start of rituximab therapy and generally continued for 12 months after stopping rituximab therapy.[1, 6]
- Entecavir or tenofovir are generally recommended for antiviral prophylaxis.*
- Repeat investigations may be warranted for subsequent rituximab dosing (e.g. risk of exposure to viral hepatitis).

* For doses see eTG: Treatment of chronic hepatitis B [3]

PNEUMOCYSTIS JIROVECI PNEUMONIA (PJP)

PJP prophylaxis (usually trimethoprim + sulfamethoxazole) may be considered in patients receiving rituximab with any of the following factors that increase the risk of PJP infection:

- high glucocorticoid dose (≥ 20mg prednisolone daily [or equivalent] for more than 4 weeks)
- co-administration of steroid-sparing or other immunosuppressive therapy
- presence of T-cell defects
- malignancy
- significant lymphopenia.

Expert advice should be sought regarding PJP prophylaxis before the start of rituximab therapy.[7]

THROUGHOUT RITUXIMAB THERAPY

In conjunction with local protocol requirements, the following monitoring is recommended:

- measures of therapeutic response and disease activity including measurement of circulating $CD19^+$ B cells;
- full blood count and plasma immunoglobulins before each treatment cycle;[6]
- infections (note, in some people B-cell recovery may take up to 2 years);
- progressive multifocal leukoencephalopathy (PML), (see below);[4, 12]
- other adverse effects;
- vaccination status (ensure this remains up-to-date) including those with travel plans, (see below).

Always reassess precautions and contraindications to rituximab therapy including pregnancy testing (if appropriate) prior to repeat dosing.[8]

PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PML)

Use of rituximab may be associated with an increased risk of PML, an opportunistic viral infection of the brain, caused by reactivation of the JC virus, which usually leads to death or severe disability.[12] Patients must be monitored for any new or worsening neurological symptoms or signs suggestive of PML. If these occur, rituximab should be immediately stopped until a diagnosis of PML has been excluded. Continue monitoring for at least 12 months after the last dose.

VACCINATIONS

- Immunisation responses are compromised after rituximab treatment so, if possible, vaccination with non-live vaccines should occur at least 4 weeks prior to treatment. Live vaccines are contraindicated for severely immunocompromised patients.[1]
- Given the varying circumstances of individual patients initiating off-label rituximab, it is recommended specialist advice about the most appropriate vaccinations for individual patients (e.g. seasonal influenza, pneumococcus and, in those at risk, hepatitis A and B) is sought.[1] Specialist advice regarding recommended vaccinations and timing should also be sought for patients who have already received rituximab, as vaccine responses may be blunted until B cell recovery occurs (often 6-12 months). The National Centre for Immunisation Research and Surveillance [telephone (612) 9845 1433] can provide advice for individual cases.
- Patients should be made aware of issues related to the effect of rituximab on immunisation status and requirements and ramifications if the severity of their condition compromises immunisation recommendations.
- Advice from infectious diseases or travel medicine specialists regarding vaccination, prevention and treatment of infections are recommended for patients planning to travel.

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