

# Rituximab in autoimmune diseases

## SUMMARY

Rituximab is a monoclonal antibody that depletes B cells from the circulation. It was originally used to treat lymphoma but is increasingly used for the treatment of autoimmune diseases.

Rituximab was found to be effective in randomised controlled trials for rheumatoid arthritis, granulomatosis with polyangiitis and other antineutrophil cytoplasmic antibody-associated vasculitides. However, evidence of efficacy is very limited for many other autoimmune conditions.

Before starting rituximab, it is important to check the patient's baseline immunoglobulins and immunisation status. Patients should also be screened for latent infections and other contraindications.

## Introduction

Rituximab was first developed for the treatment of non-Hodgkin lymphoma, and is also used in chronic lymphocytic leukaemia. It is increasingly being prescribed for the treatment of autoimmune diseases. While we know that rituximab works by removing B lymphocytes from the circulation, exactly how this leads to clinical improvement in many of the conditions that rituximab is used to treat is still to be determined.

## Mechanism of action

Rituximab is a chimeric monoclonal antibody that binds to the CD20 surface marker expressed on B cells. This includes precursor B cells (pre-B cells) and mature and memory B cells.<sup>1</sup> Following antibody binding, B cells die by a number of mechanisms including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis.<sup>2</sup> Although the loss of B cells from the circulation is transient (usually for about six months), the duration of depletion can be highly variable among individuals.

Rituximab was developed to remove malignant, clonal B cells expressing CD20 in conditions such as lymphoma. Empirically, it makes sense to use it to remove malignant B-cell clones but how does it work in diseases where the B cells are not malignant?

While rituximab decreases concentrations of antibodies that are pathogenic (or presumed pathogenic), levels of other protective antibodies are maintained, such as those to tetanus toxoid.<sup>1</sup> Rituximab does not reduce plasma cells, which secrete antibodies, because they do not express CD20. Instead, the efficacy of rituximab in autoimmune disease is thought to be due to the decrease in the rate of new plasma cell synthesis (as CD20+ B cells

are a required intermediary) or to the disruption of another role of B cells in the immune system, such as the role of B cells as antigen-presenting cells to T cells.

## Indications for use

In Australia, rituximab is available on the Pharmaceutical Benefits Scheme (PBS) for a number of different types of non-Hodgkin lymphoma and for CD20+ chronic lymphocytic leukemia. It has been shown to be effective in rheumatoid arthritis<sup>3-5</sup> and is subsidised for severe disease.

Evidence from randomised controlled studies has also shown benefit in granulomatosis with polyangiitis and other antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides.<sup>6-8</sup> This led to the approval of rituximab by the Therapeutic Goods Administration in 2013 for ANCA-associated vasculitis. In January 2016, rituximab was added to the PBS for induction of remission (and for re-induction of remission) for granulomatosis with polyangiitis and microscopic polyangiitis, two forms of ANCA-positive vasculitis.

A six-month survey in Australian hospitals, published in 2013, found more than 300 instances of 'off-label' use of rituximab.<sup>9</sup> It was prescribed in over 50 conditions, including autoimmune conditions listed in the Table.<sup>10-17</sup> For most of these conditions, there is only evidence from case reports and case series. For others, randomised controlled studies failed to show benefit for rituximab, or contradictory case studies exist.<sup>9</sup> Randomised controlled studies of systemic lupus erythematosus failed to show a benefit for rituximab despite promising earlier reports. The addition of rituximab to standard immunosuppressive therapy did not show a difference in the outcomes for non-renal and renal lupus erythematosus<sup>10,11</sup> but this may have been due to problems with study design

## Katrina L Randall

Immunologist  
Department of Immunology  
Canberra Hospital  
Senior lecturer  
ANU Medical School  
Canberra

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Table Off-label use of rituximab in autoimmune diseases

Condition	Evidence of benefit (if any)
Systemic lupus erythematosus (non-renal and renal)	Randomised controlled trials failed to show benefit when rituximab was added to standard therapy <sup>10,11</sup>
Antiphospholipid syndrome	Case reports and case series including meta-analysis of case series showed benefit <sup>12</sup>
Blistering diseases of the skin, such as pemphigus and cicatricial pemphigoid	Case reports and case series including meta-analysis of case series showed benefit <sup>13,14</sup>
Neurological diseases such as myasthenia gravis and neuromyelitis optica	Case reports and case series showed benefit <sup>15,16</sup>
Immune thrombocytopenia	Randomised controlled trial failed to show benefit <sup>17</sup> despite promising data from case studies

such as the choice of treatment regimen and study outcome measures. In particular, in the study of lupus nephritis, rituximab reduced the need for rescue medication with cyclophosphamide, despite not showing an overall benefit.<sup>10</sup>

A recent randomised controlled trial in immune thrombocytopenia failed to show a difference between rituximab and placebo in the primary outcome measure, despite promising data from case studies.<sup>17</sup>

### Contraindications

Patients with acute or chronic infections should not be treated with rituximab and it is also contraindicated in severe congestive heart failure (New York Heart Association Class IV). Known hypersensitivity to rituximab or other mouse-derived proteins is also a relative contraindication, and rituximab should not be given in pregnancy.<sup>1</sup>

### Dosing and administration

The optimal dose of rituximab is poorly defined because of limited studies exploring dose response for many conditions. Rituximab is used in hospitals as it is given as an intravenous infusion, although a subcutaneous formulation is also being evaluated. There are two different intravenous dosing strategies – 375 mg/m<sup>2</sup> weekly for four weeks (lymphoma protocol) and 1000 mg fortnightly (independent of body weight) for two doses (rheumatoid arthritis protocol). For some conditions and in some hospitals, the fortnightly strategy is modified to a low-dose strategy which involves two 500 mg doses given 1–2 weeks apart.<sup>18</sup>

Infusion-related reactions to rituximab are common (30% with the first infusion). Premedication with paracetamol and corticosteroid (usually 100 mg of hydrocortisone) is used to minimise these.<sup>1</sup>

### Treatment-related infections

As with other immunosuppressants, the main concern with rituximab is infection. While studies have shown that antibodies to vaccine-preventable diseases, such as tetanus, remain normal after treatment, repeated courses of rituximab can be associated with hypogammaglobulinaemia (particularly decreases in total IgG).<sup>19,20</sup> Some studies have shown no increase in infection in patients with rheumatoid arthritis treated with rituximab compared to placebo.<sup>1</sup> A German analysis of data from patients treated with rituximab for autoimmune diseases (excluding rheumatoid arthritis) estimated the rate of serious infections to be 5.3/100 patient years. However as this is registry data, we do not know the rate of serious infection in the 'normal population' or in patients with autoimmune disease not treated with rituximab.<sup>21</sup> Patients with low concentrations of IgG before commencing rituximab are at particular risk of infection due to previous immunosuppression or to the underlying condition for which they are being treated.<sup>22</sup> Risk may also depend on past and current immunosuppression, in particular corticosteroid treatment. Neutropenia has also been described 3–6 months after treatment with rituximab at a rate of 1.5/100 patient years and can be associated with serious infection.<sup>23</sup>

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

There are three particular infections of concern with rituximab – progressive multifocal leucoencephalopathy, hepatitis B and *Pneumocystis jirovecii* pneumonia. Patient information about the risks associated with rituximab is available at <http://rheumatology.org.au>.

### Progressive multifocal leucoencephalopathy

In day-to-day practice, the infection that concerns patients the most is the risk of progressive multifocal leucoencephalopathy. This is caused by reactivation of JC virus and can lead to severe disability or death. It is estimated that there is less than a 1:20 000 chance of developing progressive multifocal leucoencephalopathy when rituximab is used for the treatment of rheumatoid arthritis.<sup>1</sup> There is a slightly higher risk for patients with systemic lupus erythematosus, but this may be confounded by the fact that these patients can develop progressive multifocal leucoencephalopathy independently of rituximab treatment.<sup>24</sup>

Patients, GPs and treating physicians need to investigate and exclude progressive multifocal

leucoencephalopathy for any new or worsening neurological symptoms, particularly visual disturbance, ataxia, confusion and abnormal gait.

### Hepatitis B virus

There are reports of the reactivation of hepatitis B virus after treatment with rituximab. A study of these case reports relating to rituximab for lymphoma found an overall mortality rate of 80% from hepatitis B reactivation.<sup>25</sup> However, this high rate could have been due to publication bias. It is important to check hepatitis B serology (including hepatitis B core antibody) in all patients before starting rituximab treatment. For those with positive serology indicating a past or chronic infection, discuss antiviral prophylactic treatment with a specialist.

### Pneumocystis jirovecii pneumonia

Another infection of concern with rituximab is *Pneumocystis jirovecii* pneumonia.<sup>26</sup> This is an opportunistic infection usually associated with low CD4 T-cell counts. Prophylaxis is generally started when CD4 counts are less than 200 cells/microlitre of blood. However, infections have been described in patients, after rituximab, with CD4 counts greater than 200/microlitre,<sup>26</sup> indicating that this threshold may not be valid in the absence of B cells. The mechanism of susceptibility after the use of rituximab is not known, but may be due to decreased B-cell help for T cells.

The exact incidence of infection in patients with autoimmune disease treated with rituximab is unknown. Rates of 1.5–6% have been reported when rituximab is used for the treatment of lymphoma.<sup>27</sup> Infection is most commonly described when rituximab is used together with other medicines but has also been described with rituximab on its own.<sup>26</sup> Primary prophylaxis with trimethoprim/sulfamethoxazole may therefore be considered when prescribing rituximab.

### Immunisation

As immunisation responses are compromised after treatment with rituximab,<sup>28</sup> it is recommended that any required immunisations are given before treatment.<sup>1</sup> Current guidelines recommend pneumococcus and influenza vaccination for patients with autoimmune disease, and hepatitis A and B vaccinations in at-risk groups.<sup>29</sup> A four-week gap between vaccination with non-live vaccines and

commencement of rituximab is recommended, but the optimal interval is an area of ongoing research.<sup>1</sup>

Live vaccines are contraindicated in those who have had treatment with rituximab or are being considered for it.

As it is assumed that a protective response to tetanus toxoid booster vaccination may not occur after rituximab treatment, for a tetanus-prone wound, passive immunisation with tetanus antibodies is advised for 24 weeks after rituximab treatment.<sup>29</sup> However if the patient is persistently B-cell lymphopenic, passive immunisation may need to be considered even after this time.

### Monitoring and re-treatment

Patients are usually found to have depleted B cells after one dose of rituximab. This is confirmed by checking B- and T-cell lymphocyte subsets through a different surface marker – CD19 – to ensure that rituximab is not just blocking access to the surface marker for the detection antibody. Most clinicians would also follow the titre of the pathogenic (or presumed pathogenic) antibody specific for the disease that is being treated.

The optimum timing and safety and efficacy of any re-treatment with rituximab is still an area of active research.<sup>1</sup> This is reflected in current variable practices, which include patients starting re-treatment:

- when their B cells return before any disease manifestations
- after B cells return and symptoms develop
- after a certain number of months even if there are no detectable B cells in the blood.

### Conclusion

Rituximab is being used more widely for the treatment of autoimmune diseases, in many cases as an off-label drug. It works by transiently depleting B cells from the circulation. While it is used increasingly for autoimmune disease, with case studies and case series describing efficacy, for most conditions there have been no randomised controlled studies. Patients need to be appropriately screened before the use of rituximab, and monitored for adverse effects, particularly infection. ◀

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