

## Mellen Center Approaches: Rituximab

### What is rituximab?

Rituximab (trade name Rituxan) is a chimeric murine/human monoclonal antibody directed at CD20, which is a transmembrane protein expressed on the surface of circulating B-cells and their progenitors.

### How does rituximab work?

Infusion of rituximab leads to rapid lysis of B-cells via antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis. After treatment, B-cells are typically undetectable in circulating blood for 3-6 months.

### What experience is there with rituximab in MS?

Rituximab was evaluated in a 24-week, placebo-controlled, phase II clinical trial of relapsing remitting MS. Treatment involved one course of two infusions of rituximab or placebo given two weeks apart, and then patients were followed clinically and with monthly MRI. The total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 (the primary outcome) were reduced by 91% ( $p < 0.0001$ ). In addition, the proportion of patients with relapses by Week 24 was reduced by 58% ( $p = 0.02$ ) in the rituximab-treated group, and the annualized relapse rate was reduced by 56% ( $p = 0.04$ ).

In an open-label, 48-week phase I trial in relapsing remitting MS, two courses of rituximab (two infusions given two weeks apart, and then repeated after 24 weeks) were evaluated primarily for safety. At 48 weeks, gadolinium-enhancing lesions were reduced by 96% compared to baseline, and 81% of patients were relapse-free.

A phase III trial of rituximab in 439 primary progressive MS patients found that rituximab was not effective in slowing the progression of disability. However, a subgroup analysis showed that patients <51 years of age or with gadolinium enhancing lesions at baseline had benefit from rituximab.

A retrospective study evaluated the efficacy of rituximab in 25 patients with neuromyelitis optica (Devic's disease). At a median follow-up of 19 months, the median annualized posttreatment relapse rate was lower than the pretreatment rate (0 vs. 1.7,  $p < 0.001$ ), and disability improved or stabilized in 20 of the 25 patients.

### What are the side-effects of rituximab?

Infusion reactions are common with rituximab and include fever, chills, rigors, nausea, pruritis, rash, asthenia, and hypotension. These infusion reactions are thought to be related to cytokine release related to B-cell lysis. When severe, this systemic inflammatory response syndrome (SIRS) can sometimes be fatal. These side-effects can be reduced by pre-treatment with acetaminophen, diphenhydramine, and methylprednisolone (100mg).

In addition, rituximab is associated with an increased risk of infections, including urinary tract infections and sinusitis. Although no opportunistic infections have been reported in the MS trials, some have been reported in clinical trials of other disorders, including progressive multifocal leukoencephalopathy (PML). Two patients in the neuromyelitis optica retrospective study died, although it is unclear if their deaths were related to rituximab or their underlying disease.

### What evaluations are needed prior to treatment with rituximab?

We generally recommend a neurologic assessment as a baseline examination and blood studies for CBC with differential, electrolytes, hepatic panel, hepatitis B panel, peripheral CD19 count, and serum beta-HCG. Because of the potential for hypotension during the first infusion, one can consider holding a patient's chronic antihypertensive medication on the morning of infusion.

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## Mellen Center Approaches: Rituximab, continued

### How is rituximab administered?

Rituximab is administered as an IV infusion over 4.5-6 hours. To help reduce infusion reactions, the dose is started low and gradually increased. Acetaminophen, diphenhydramine, and intravenous methylprednisolone are given prior to rituximab. See Mellen Center Rituximab treatment protocol for complete details on rituximab administration. The same treatment is repeated two weeks later, although the rate of infusion can be escalated more quickly than the first infusion.

### When should the next course of rituximab be administered?

The FDA-approved administration regimen for rheumatoid arthritis is a 2-infusion course (with each infusion separated by 2 weeks), and then repeat the 2-infusion course every six months. The Phase I safety trial followed this regimen. We typically evaluate efficacy about 6 months after treatment initiation using both clinical and imaging assessments.

Some clinicians have used a single 1000 mg infusion for follow-up courses. The efficacy of this regimen is not known.

### What testing is needed prior to subsequent rituximab infusions?

No laboratory testing is needed between the 2 infusions that are separated by 2 weeks. For subsequent courses of rituximab, we obtain CBC with differential, hepatic panel, and consider beta-HCG. No testing of B-cell levels is needed, since no clinical decision will be made based upon the B-cell counts.

### Can vaccines be given while on rituximab?

Because rituximab may reduce the generation of new antibodies, the efficacy of vaccines is probably reduced during rituximab therapy. Therefore, clinically indicated vaccines should be given one month or more before starting rituximab. If vaccines are needed during rituximab treatment, they ideally should be given about 1 month prior to the next treatment course.

### Does anti-rituximab antibodies develop and do they reduce efficacy?

Patients can develop anti-rituximab antibodies, although it is not clear that they impact efficacy of rituximab. The presence of antibodies appears to affect neither the reduction in B-cells following infusion nor the side-effects.

### For what MS patients is rituximab indicated?

Rituximab may be a reasonable treatment option for relapsing MS patients who have not tolerated or had sub-optimal therapeutic response to standard MS therapies, which may include one or more of the injectible and oral therapies and natalizumab (Tysabri). Rituximab also may be a reasonable treatment option in patients with rapidly progressive MS (very frequent relapses, poor recovery from relapses, extensive enhancing lesions on MRI, etc) Although no cases of PML related to rituximab have been reported in MS patients, the clinical experience in MS patients is very limited and there have been cases of PML reported in association with rituximab therapy in other diseases including rheumatoid arthritis. In addition, there may be other rare complications of rituximab in MS patients which has not yet been recognized. At this time, rituximab is not considered a first-line therapy for either relapsing MS or neuromyelitis optica. Insurance coverage for rituximab is sometimes limited, in part because there is no FDA approval.

### For what is rituximab currently indicated?

Currently, rituximab is FDA-approved for CD-20-positive non-Hodgkin's lymphoma, CD-20-positive chronic lymphocytic leukemia, and rheumatoid arthritis. Dosing regimens vary depending upon the indication, previous treatments, and ongoing chemotherapy treatment.

### Is rituximab FDA approved for MS?

Although the phase I and II trial results were very encouraging, the manufacturers of rituximab have decided not to pursue FDA approval for rituximab. Instead, they are pursuing approval of a more humanized version of rituximab, called ocrelizumab. After a positive Phase II trial of ocrelizumab in MS was reported in 2010, ocrelizumab entered Phase III trials in 2011.

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## Mellen Center Approaches: Rituximab, continued

*NOTE: RITUXIMAB is not FDA approved for MS and may not be covered by insurance. Because of the potential high cost of this medicine it may be prudent to have the patient check whether this would be covered by insurance before beginning a course of this medicine.*

Attachments: Mellen Center Rituxan Order Sheet  
Mellen Center Rituxan Protocol

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