Cleveland Clinic Mellen Center for Multiple Sclerosis

Mellen Center Approaches: Rituximab

**Q: What is rituximab?**

A: 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.

**Q: How does rituximab work?**

A: 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.

**Q: What experience is there with rituximab in MS?**

A: 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 post-treatment 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.

**Q: What are the side-effects of rituximab?**

A: 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

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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.

Q: What evaluations are needed prior to treatment with rituximab?

A: 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.

Q: How is rituximab administered?

A: 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.

Q: When should the next course of rituximab be administered?

A: 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 1 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.

Q: What testing is needed prior to subsequent rituximab infusions?

A: 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.

Q: Can vaccines be given while on rituximab?

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A: 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.

**Q: Does anti-rituximab antibodies develop and do they reduce efficacy?**

A: 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.

**Q: For what MS patients is rituximab indicated?**

A: 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.

**Q: For what is rituximab currently indicated?**

A: 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.

**Q: Is rituximab FDA approved for MS?**

A: 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.

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

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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

References:


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RITUXAN ORDER SHEET

Pretreatment Labs

____ CBC with diff
____ electrolytes, with creatine
____ hepatic panel, with Hepatitis B screen
____ HCG testing (women only)
____ peripheral CD19 cell INDFCM (for individual flow cytometry marker); in the comments type “anti-CD 19 cell count”

Pretreatment medications:
____ Acetaminophen 1000 mg PO x1; repeat q4h prn fever, rash, rigors
____ Diphenhydramine 50 mg IVP or PO x1, may repeat q4h prn fever, rash, rigors
____ Methylprednisolone 100 mg IV push over 3 minutes

____ Rituxan 1000 mg IV in 250 ml NS
____ Repeat above treatment in two weeks

Initial infusion: Start at 50mg/hr; if there is no reaction, then increase the rate 50mg/hr every 30 minutes, to a maximum of 400mg/hr.

Subsequent infusions: Start at 100mg/hr; if there is no reaction, then increase the rate by 100mg/hr every 30 minutes, to a maximum of 400mg/hr.

<table>
<thead>
<tr>
<th>Infusion instructions</th>
<th>Fever</th>
<th>Rigors</th>
<th>Congestion/edema</th>
<th>Hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease by ½</td>
<td>&gt;38.0 C</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>Stop infusion &amp; KVO 0.9% NS</td>
<td>&gt;39.0 C</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild-Moderate</td>
</tr>
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Infusion may be re-initiated at dose one level less if symptoms resolve with additional Benadryl 50mg IVP and Hydrocortisone 100mg IVP.

_________________________ MD
Mellen Center for Multiple Sclerosis Protocol: Rituximab (Rituxan) Induction

Indication: This protocol is used for patients with multiple sclerosis who demonstrate persistent inflammatory disease activity despite treatment with traditional MS therapies such as beta-interferons, glatiramer acetate, natalizumab, pulse methylprednisolone, cyclophosphamide, and mitoxantrone. The regimen described below is intended for multiple sclerosis patients only. Because of potentially severe cardiopulmonary infusion reactions, infusion should be monitored by medical team familiar with rituximab.

Pretreatment Assessment: 1) Neurologic assessment to obtain baseline exam and to determine the need for this protocol. 2) CBC w/diff, electrolytes, hepatic panel, hepatitis B panel, peripheral CD19 count, serum HCG (women only) 3) Consider holding antihypertensives on morning of infusion.

Treatment: Treatment consists of a single IV infusion of rituximab, which is then repeated after two weeks. To help reduce infusion reactions, methylprednisolone is given prior to rituximab infusion. This protocol is then repeated every six months. Pre-infusion laboratories are empiric – there is no specific liver or electrolyte toxicities. Anti-CD19 antibody is done before each infusion, although the infusion proceeds regardless of the results.

1) Baseline vital signs
2) Acetaminophen (Tylenol) 500-1000 mg PO and/or diphenhydramine (Benadryl) 25-50 mg PO/IVP. Each may be repeated every 4 hours.
3) Methylprednisolone, 100 mg IVP push over 3 minutes.
4) Rituximab, 1000 mg IV infusion in NS:
   Initial Infusion:
   a. 50 mg/hr x 30min
   b. 100 mg/hr x 30 min
   c. 150 mg/hr x 30 min
   d. 200 mg/hr x 30 min
   e. 250 mg/hr x 30 min
   f. 300 mg/hr x 30 min
   g. 350 mg/hr x 30 min
   h. 400 mg/hr until complete
   Subsequent infusion (if the first infusion was well-tolerated):
   a. 100 mg/hr x 30min
   b. 200 mg/hr x 30 min
   c. 300 mg/hr x 30 min
   d. 400 mg/hr until complete

Note: If hypersensitivity reaction develops (hypotension, angioedema, shortness of breath/bronchospasm), the infusion should be temporarily slowed or interrupted, and, if necessary, additional treatment (i.e. acetaminophen, diphenhydramine, hydrocortisone) should be given. In most cases, treatment can be resumed at a 50% reduction in rate once symptoms have resolved, as directed by a physician. Patients with pre-existing cardiac and pulmonary conditions should receive careful monitoring.

Common side-effects: fever, chills/rigors, nausea, asthenia, headache. These usually respond to acetaminophen and/or diphenhydramine.
Mellen Center for Multiple Sclerosis Protocol: Rituximab (Rituxan) Induction

Protocol for Nursing Staff

1. Check BP, pulse, temperature prior to treatment and record in chart; repeat all vitals with each change in infusion rate.

2. Administer Acetaminophen and diphenhydramine

3. Record all current medications; assess side-effects of previous infusion, if any

4. Start IV with NS 150 ml bag

5. Infuse methylprednisolone IV push over 3 minutes

6. Infuse rituximab as follows:

   **Initial Infusion:**
   a. 50 mg/hr x 30min
   b. 100 mg/hr x 30 min
   c. 150 mg/hr x 30 min
   d. 200 mg/hr x 30 min
   e. 250 mg/hr x 30 min
   f. 300 mg/hr x 30 min
   g. 350 mg/hr x 30 min
   h. 400 mg/hr until complete
      (infusion should take ~ 5 hours)

   **Subsequent infusion (if the first infusion was well-tolerated):**
   a. 100 mg/hr x 30min
   b. 200 mg/hr x 30 min
   c. 300 mg/hr x 30 min
   d. 400 mg/hr until complete
      (infusion should take ~ 4 hours)

7. Record BP and pulse after treatment

8. D/C IV

Note: Wear chemotherapy gloves while handling rituximab and associated tubing. Dispose of equipment in chemotherapy waste container. Label any specimens obtained during treatment with biohazard labels.