

Mellen Center Approach to Ocrelizumab (Ocrevus)

Q: What is mechanism of action of ocrelizumab?

A; Ocrelizumab is a novel humanized monoclonal anti-CD20 antibody constructed with recombinant DNA techniques and designed to selectively target CD20-expressing B-cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis are not known but involve immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Components of MS pathology potentially affected by this mechanism include reductions in: auto-antigen presentation, secretion of pro-inflammatory cytokines, production of auto-antibodies, and formation of meningeal lymphoid follicle-like structures.

Q: Which cell types does ocrelizumab deplete?

A: Ocrelizumab affects cell types in the middle of the B-cell lineage, including pre-B cells, mature and memory B cells, but not lymphoid stem cells or plasma cells. The capacity for B cell reconstitution and preexisting humoral immunity are thought to be preserved.

Q: What are the kinetics of ocrelizumab?

A: The average half-life of ocrelizumab in the body is approximately 28 days. Following administration, B-cells are rapidly depleted and can remain undetectable for a prolonged and variable period of time ranging from 6 months to more than 12 months.

Q: How can we apply prior experience with rituximab?

A: Significant anecdotal off-label experience with rituximab has accumulated in large MS centers around the world including the Mellen Center, for treating both MS and neuromyelitis optica (NMO). Uncontrolled case series have reported excellent efficacy and safety when rituximab has been used to treat MS. Though ocrelizumab targets the same immunologic mechanism and is administered in a similar fashion to rituximab, ocrelizumab is a different antibody. In vitro characterization of ocrelizumab demonstrated enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) and reduced complement-dependent cytotoxicity (CDC) as compared with rituximab. Ocrelizumab binds to a different, but overlapping, epitope of the extracellular domain of CD20 as compared with rituximab.

Q: Is ocrelizumab FDA-approved for use in MS?

A: As of March 2017, ocrelizumab is FDA approved to treat relapsing and primary progressive forms of MS.

Q: How is ocrelizumab administered?

A: Ocrelizumab is an infrequently administered intravenous medication, given in the outpatient (office or hospital-based infusion room) setting. In Phase III studies of RRMS, ocrelizumab was administered as follows:

Day 1: ocrelizumab 300mg IV x 1

Day 15: ocrelizumab 300mg IV x1

Followed by ocrelizumab 600mg IV x 1 every 6 months

In a Phase III study of ocrelizumab in PPMS, total dose and frequency was similar to the above protocol except follow-up doses every 6 months were divided as 300mg IV each separated by 14 days.

Q: Use in Relapsing forms of MS:

A: The efficacy of ocrelizumab was demonstrated in two double-blind, double-dummy, Phase 3 studies (OPERA I and OPERA II) evaluating the efficacy and safety of ocrelizumab vs IFN beta-1a SC in adult patients with RRMS. In those studies, treatment with ocrelizumab significantly reduced the relapse rate vs IFN beta-1a by 46% in OPERA I ($p < 0.0001$) and by 47% in OPERA II ($p < 0.0001$). Ocrelizumab treatment also significantly reduced the time to onset of disability progression vs IFN beta-1a, and suppressed new T2 lesions (by 77% in OPERA I and 83% in OPERA II) and gadolinium-enhancing lesions (by 94% in OPERA I and 95% in OPERA II).

We do not anticipate restricting use of ocrelizumab to patients who have experienced breakthrough disease on other disease modifying therapies.

Q: Use in Primary Progressive MS:

A: Ocrelizumab was evaluated for efficacy in PPMS in a randomized, double-blind, placebo-controlled Phase 3 trial (ORATORIO). A total of 732 patients were randomized to receive ocrelizumab 600 mg IV or placebo every 24 weeks. Treatment with ocrelizumab significantly reduced the risk of progression of clinical disability sustained for ≥ 12 weeks (as measured by the Expanded Disability Status Scale) by 24% compared with placebo ($p = 0.0321$). Ocrelizumab also significantly reduced the risk of progression of clinical disability sustained for ≥ 24 weeks by 25% vs placebo ($p = 0.0365$).

Subgroup analyses of patients in ORATORIO with ($n = 193$) vs without gadolinium-enhancing lesions ($n = 533$) at baseline showed that efficacy tended to be stronger in patients with baseline gad enhancement (HR for disability progression 0.65, 95% CI 0.40, 1.06) than without gad enhancement (HR 0.84, 95% CI 0.62, 1.13). This result is consistent with the results of other

disease modifying therapies tested in PPMS, the common theme of which is that younger patients and those with evidence of active inflammation in the form of new T2 or gadolinium-enhancing lesions are the most likely to benefit from therapy.

Q: What are the major adverse effects of ocrelizumab:

A: The most common adverse events observed in the Phase III studies of ocrelizumab were mild-to-moderate infusion-related reactions. The incidence of adverse events, including serious infections, was similar between ocrelizumab and placebo. Particular events of interest:

Infusion reactions:

Mild to moderate infusion reactions were observed in approximately 25% of patients at the time of first infusion. Moderate infusion reaction was defined as requiring minor local or noninvasive management (usually additional medication or change in infusion rate). The incidence of infusion reactions decreased substantially with subsequent infusions in the clinical trials (to 10% or less). Infusion reactions may typically include itching. Severe infusion reactions (requiring urgent medical management) occurred very rarely in the clinical trials. Ocrelizumab must be administered in physician office or inpatient setting by nurses who have experience and qualification to infuse the drug, under supervision by physicians who have experience managing infusion reactions.

Infections:

The rate of common infections was similar between ocrelizumab and placebo or Rebif, with upper respiratory infection, nasopharyngitis, urinary tract infection, occurring each up to 15% of the time in ocrelizumab vs. 10% of the time in the placebo group. No opportunistic infections were identified. Ocrelizumab should not be utilized in patients with active acute or chronic infections. Ocrelizumab might reactivate Hepatitis B infection. For this reason checking for Hepatitis B infection prior to initiating ocrelizumab is important.

Neoplasms:

Neoplasms occurred rarely across all treatment arms in all 3 Phase III clinical trials. The rates of events overall are consistent with what is expected in an MS patient population. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of the 668 females treated with interferon beta 1a or placebo. Longer-term data are required to effectively assess the impact of ocrelizumab on rates of malignancy. We recommend patients adhere to usual age-appropriate malignancy screening recommendations.

Q: How are infusion reactions typically managed?

A: Infusion reactions are expected related to the mechanism of action of ocrelizumab (cytolysis), and those standard infusion reactions may be differentiated from those with features of mast cell or basophil activation (signifying potential progression to anaphylaxis). Features such as itching cannot be used to differentiate between the two. Patients who develop a non-life-threatening mild to moderate SIR can usually be managed by temporary discontinuation of drug infusion alone. Once all symptoms have resolved, most patients will tolerate a slower infusion rate (one-half the rate at which the reaction occurred) with additional antihistamines plus acetaminophen. Patients with even mild symptoms of mast cell/basophil activation (eg, urticaria and dyspnea) should in most cases not resume infusion or be retreated, because reexposure to the causative agent could result in a fulminant and severe anaphylaxis.

Q: Pregnancy and ocrelizumab?

A: No definitive guidance is available on the effect of ocrelizumab on pregnancy. Theoretically, the drug could pass to the fetus and have an effect on the fetus. We will counsel woman to use effective contraceptive methods while on ocrelizumab and wait at least 5 months (based on the half-life of the drug) since their last ocrelizumab infusion before attempting to conceive.

Q: Should we monitor CD19 counts in a patient on ocrelizumab?

A: We do not expect to routinely monitor B-cell (CD19) counts in patients receiving ocrelizumab or altering the administration schedule based on CD19 counts. The return of B-cells may affect some patients' abilities to receive other therapies after ocrelizumab, so checking CD19 counts may occasionally be useful to monitor the return of B-cells after treatment.

Q: Is any routine monitoring required for patients on ocrelizumab?

A: We routinely check MRI scans of the brain at least every 12 months in patients on therapies for both safety and efficacy monitoring.

Q: Is PML a concern in patients treated with ocrelizumab?

A: Although no cases of PML related to ocrelizumab have been reported in MS patients, the experience is limited to patients enrolled in clinical trials. 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.

Q: Can vaccines be given while on ocrelizumab?

A: Live vaccines should be avoided for patients within 6 months of any ocrelizumab infusion, potentially longer based on B-cell reconstitution. 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. An ongoing study will assess the effectiveness of standard vaccines in patients being treated with ocrelizumab.

References:

1. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet* 2011;378:1779-1787.
2. Morschhauser F, Marlton P, Vitolo U et al. Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma. *Ann Oncol* (2010) 21 (9): 1870-1876.
3. DiLillo DJ, Hamaguchi Y, Ueda Y, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. *J Immunol* 2008; 180: 361-371.
4. Montalban X, Hemmer B, Rammohan K, et al. Efficacy and safety of ocrelizumab in primary progressive multiple sclerosis - results of the Phase III, double-blind, placebo-controlled ORATORIO study. Presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Barcelona, Spain; 2015. ECTRIMS Oral presentation #228.
5. Hauser SL, Comi GC, Hartung HP. Efficacy and safety of ocrelizumab in relapsing multiple sclerosis - results of the Phase III double-blind, interferon beta-1a-controlled OPERA I and II studies. Presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Barcelona, Spain; October 7–10, 2015. ECTRIMS Oral Presentation #190.

Mellen Center ocrelizumab treatment protocol (draft, MAR2016)

Pretreatment:

1. Testing
 - a. CBC with differential
 - b. Serum creatinine
 - c. LFTs,
 - d. Remote hepatitis panel
 - e. TSH
 - f. VZV IgG
 - g. Serum pregnancy test if female and of childbearing potential
 - h. PPD or Quantiferon in patients from regions endemic for TB or with suspected exposure
 - i. Brain MRI within 3 months prior to treatment, to serve as baseline
2. Patient instructions
 - a. Because of the possibility of hypotension during infusions, providers may choose to instruct patients to hold any antihypertensive medication on the morning of infusion
 - b. Patients will be expected to have a ride to and from their infusion, due to possibility of sedating antihistamines
3. Complete ocrelizumab startup forms
4. Complete patient education
5. Complete Mellen ocrelizumab checklist abstract
6. Complete and sign orders in Beacon
7. Review and sign Informed Consent

Nursing Protocol:

Nursing instruction: Cycle 1 start date may be adjusted to align with the first scheduled treatment

Day 1:

methylprednisolone 100mg IV x 1

acetaminophen 1000mg po x 1

diphenhydramine 50mg po x 1

ocrelizumab 300mg IV x 1 (see infusion rates)

Hypersensitivity protocol:

NaCl 0.9% iv infusion Dose: 500mL/hr Route: INTRAVENOUS AS NEEDED over 2 Hours for 1 dose. Comments: Inform physician Instructions: For Hypotension (SBP < 100) in the setting of Shortness of Breath, Bronchospasm or Hives: Stop Infusion and switch line to 0.9 NS at 500ml/hr. Notify Physician. Monitor vital signs q 5 min in acute phase reaction. As reaction resolves do vital signs q 15 min until stable. Consult Physician to determine if the medication may be resumed.

diphenhydrAMINE 50 mg injection (BENADRYL) Dose: 50mg Route: INTRAVENOUS AS NEEDED Instructions: Stop Infusion. Notify Physician. Consult Physician to determine if the medication may be resumed.

famotidine 20 mg injection (PEPCID) Dose: 20mg Route: INTRAVENOUS AS NEEDED for 1 doses Instructions: Stop Infusion. Notify Physician. Consult Physician to determine if the medication may be resumed.

hydrocortisone sodium succinate 100 mg injection (Solu-CORTEF) Dose: 100mg Route: INTRAVENOUS AS NEEDED Instructions: Stop Infusion. Notify Physician. Consult Physician to determine if the medication may be resumed.

Day 15:

methylprednisolone 100mg IV x 1

acetaminophen 1000mg po x 1

diphenhydramine 50mg po x 1

ocrelizumab 300mg IV x 1 (see infusion rates)

Hypersensitivity protocol:

NaCl 0.9% iv infusion Dose: 500mL/hr Route: INTRAVENOUS AS NEEDED over 2 Hours for 1 dose. Comments: Inform physician Instructions: For Hypotension (SBP < 100) in the setting of Shortness of Breath, Bronchospasm or Hives: Stop Infusion and switch line to 0.9 NS at 500ml/hr. Notify Physician. Monitor vital signs q 5 min in acute phase reaction. As reaction resolves do vital signs q 15 min until stable. Consult Physician to determine if the medication may be resumed.

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Subsequent cycles every 6 months:

methylprednisolone 100mg IV x 1

acetaminophen 1000mg po x 1

diphenhydramine 50mg po x 1

ocrelizumab 600mg IV x 1 (see infusion rates)

Hypersensitivity protocol:

NaCl 0.9% iv infusion Dose: 500mL/hr Route: INTRAVENOUS AS NEEDED over 2 Hours for 1 dose. Comments: Inform physician Instructions: For Hypotension (SBP < 100) in the setting of Shortness of Breath, Bronchospasm or Hives: Stop Infusion and switch line to 0.9 NS at 500ml/hr. Notify Physician. Monitor vital signs q 5 min in acute phase reaction. As reaction resolves do vital signs q 15 min until stable. Consult Physician to determine if the medication may be resumed.

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Table 1: Infusion rates

		Amount and Volume¹	Infusion Rate and Duration³
Initial Dose (two infusions)	Infusion 1	300 mg in 250 mL	<ul style="list-style-type: none"> • Start at 30 mL per hour • Increase by 30 mL per hour every 30 minutes • Maximum: 180 mL per hour • Duration: 2.5 hours or longer
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (one infusion)	One infusion every 6 months ²	600 mg in 500 mL	<ul style="list-style-type: none"> • Start at 40 mL per hour • Increase by 40 mL per hour every 30 minutes • Maximum: 200 mL per hour • Duration: 3.5 hours or longer

Nursing instruction: Because of possible need to vary infusion rates depending on tolerance of the infusion, the total infusion time may exceed the time stated.

Nursing instruction: After completion of the infusion, the IV cannula should remain in situ for at least 1 hour to allow for administration of drugs intravenously, if necessary, in the event of a delayed reaction. If no adverse events occur during this period of time, the IV cannula may be removed and the patient may be discharged.