Ocrelizumab (Ocrevus)
Considerations for Decision Making & Counseling Points

Ocrelizumab is the first FDA approved agent for use in Primary Progressive Multiple Sclerosis (PPMS). Additionally, it received approval for the treatment of Relapsing MS. Ocrelizumab's approval in PPMS has generated extensive interest from MS Veterans and their family members. The National PBM is conducting a thorough review of the evidence and safety which will be used in developing a National Criteria for Use (CFU). In the interim, the following is a summary of key drug information and counseling points.

MoA and Pharmacodynamics. Unknown; theorized to target the CD20 marker on the surface of B cells. This marker is thought to influence the abnormal immune response which results in attacks on nerve-cell myelin. Ocrelizumab triggers a CD20-directed cytolytic action and complement-mediated lysis which destroy the targeted B cells. The influence of this reduction in targeted B cells on disease progression in PPMS is unclear. (Note that ocrelizumab interferes with the CD20 assay, so assays for CD19+ B cells are used instead.) Reduction in B-cell counts with ocrelizumab is seen 14 days after infusion.

The median time to B cell repletion – defined as level at or above lower limit of normal (LLN) – is 72 weeks after last ocrelizumab dose. However, individual range may be substantially longer. 90% of patients return to baseline or LLN within 2.5 years after last infusion. This significantly lengthy time to B-cell repopulation must be considered when planning future DMT sequencing.

Clinical Trials. FDA approval was based predominantly on information from the ORATORIO trial in PPMS and the OPERA 1 and 2 trials in Relapsing forms of MS.

PPMS. **ORATORIO** compared ocrelizumab to placebo in 732 participants with PPMS. EDSS ranged from 3 to 6.5; mean age was approx. 44. Participants took either 600mg ocrelizumab or placebo infusions every 6 months for ≥120 weeks.

The primary outcome of the study was the onset of disability progression, defined as an increased EDSS which lasted 3 months. Other outcomes included increased EDSS lasting at least 6 months, 25FTW speed, brain and lesion volume.

Disability progression. Compared to placebo, participants on ocrelizumab had less disability progression. For participants whose EDSS was ≤5.5 at baseline, progression was defined as an increase in EDSS of ≥1.0 above baseline lasting for ≥12 wks. For participants whose baseline was EDSS >5.5, progression was defined as an increase in EDSS of >0.5 lasting for >12 wks. Fewer participants on ocrelizumab (32.9%) progressed vs. 39.3% of those on placebo. Progression lasting ≥6 mos. was also less in the ocrelizumab group (29.6%) vs. placebo (35.7%). Overall, participants on ocrelizumab were 24% less likely to have an increased disability compared with those on placebo.

T25FW speed. After 120 weeks of treatment, T25FW speed was 55% slower for the placebo group and 39% slower for the ocrelizumab group.

MRI measures. Participants on ocrelizumab lost less overall brain volume than did those on placebo: 0.9% to 1.09%. Measurements of lesion volume also favored ocrelizumab. Lesion volume decreased by 3.4% on ocrelizumab, whereas lesion volume increased by 7.4% on placebo.

Response in enhancing vs non-enhancing disease. Approximately 25% of study participants had enhancing lesions on MRI. However there was no significant difference in outcomes between participants with or without this active MRI disease.

Adverse events. Mild-to-moderate infusion reactions: 40%; 2 participants withdrew due to reaction. Upper respiratory tract infections: 10.9% on ocrelizumab vs 5.9% on placebo. Oral herpes: 2.3% on ocrelizumab group vs. 0.4% on placebo.

Malignancies. 2.3% of participants on ocrelizumab developed neoplasms vs 0.8% on placebo. Types of cancer occurring in more than 1 participants were breast cancer in 4 (0.8%) on ocrelizumab vs. 0 on placebo; basal-cell cancer in 3 (0.6%) on ocrelizmab vs. 1 (0.5%) on placebo.

RRMS: **OPERA I** and **OPERA II** were in participants with Relapsing forms of MS: RRMS and patients with Secondary Progressive MS who continued to experience relapses. Mean age was approx. 37; mean duration from diagnosis to randomization was approx. 4 yrs.; from symptom onset approx. 6.7 yrs. Ocrelizumab 600 mg every 24 weeks was compared for safety and efficacy against interferon beta-1a 44 mcg three times weekly. Both the OPERA I and OPERA II studies met their primary and major secondary endpoints.

Relapse rate. Treatment with ocrelizumab significantly reduced the protocol-defined annualized relapse rate at 96 weeks vs interferon beta-1a by 46% in OPERA I ($p<0.0001$) and by 47% in OPERA II ($p<0.0001$).

Sustained disability progression. In a pooled analysis of OPERA I and II, ocrelizumab treatment also significantly reduced the time to onset of both 12-week and 24-week confirmed disability progression vs interferon beta-1a by 40% for both time points ($p=0.0006$ and $p=0.0025$, respectively).

Adverse events. The most common adverse events were mild-to moderate infusion-related reactions. Herpes infections were more frequent in the ocrelizumab group (5.9% vs. 3.4%). Otherwise, overall infection rates were similar between the ocrelizumab and interferon groups.

Malignancies. Over the 96 weeks of treatment, 4 malignancies (0.5%) were reported in the ocrelizumab group(2 breast cancer, 1 renal-cell cancer, 1 melanoma), and 2 (0.2%) in the interferon group (1 mantle-cell lymphoma, 1 squamous-cell carcinoma). During the open-label extension study there were an additional 5 malignancies reported (2 breast, 2 basal-cell skin, 1 melanoma).

Dosing & Administration. Ocrelizumab is administered at the same prescribed amounts and rates in PPMS and Relapsing forms of MS.

Premedications
Methylprednisolone 100mg IV, ½ hr prior to infusion.
Diphenhydramine 50mg IV ½ hr. – 1 hr. prior to infusion
Acetaminophen 650mg p.o. prior to infusion.

Ocrelizumab Infusion

1st dose given in 2 divided infusions 14 days apart.

Day 1: 300mg in 250mL of 0.9% NaCl, IV.
Start at 30mL/hr. Increase by 30mL/hr every 30 minutes.
Max rate is 180mL/hr.
Infuse over at least 2 ½ hours.

Day 14: 300mg in 250mL of 0.9% NaCl, IV.
Start at 30mL/hr. Increase by 30mL/hr every 30 minutes.
Max rate is 180mL/hr.
Infuse over at least 2 ½ hours.

2nd & all future doses, given every 6 mos.
600mg in 500mL of 0.9% NaCl, IV every 6 mos.
Start at 40mL/hr. Increase by 40mL/hr every 30 minutes.
Max rate is 200mL/hr.
Infuse over at least 3 ½ hours.

Required 1-hour post-infusion observation period after each dose. A minimum of 5 hours total time in the infusion center should be expected.

Mild to Moderate Infusion Reactions. Reduce infusion rate to 50% of rate at start of symptoms. Continue this reduced rate for at least 30 minutes. Rate may then be increased as per standard first or subsequent ocrelizumab dose protocols, above.

Severe Infusion Reactions. Immediately stop infusion and give appropriate supportive treatment. Do not restart infusion unless all symptoms have resolved. Restart at 50% of rate at start of symptoms.

PRN Meds During Infusion. Many are standard at infusion centers and not specific to ocrelizumab:

- Acetaminophen 650mg po q 4hrs PRN pain
- Albuterol 2.5mg/3 mL nebulizer solution every 20 minutes X3 PRN for bronchospasm
- Atropine 0.4mg IV PRN for symptomatic bradycardia or vasovagal reaction
- Diphenhydramine 25 mg IV q4 hrs PRN itching
- Epinephrine 1:1000 inject 300 mcg (0.3 mg) PRN anaphylaxis
- Hydrocortisone 100mg IV PRN allergic reaction
- Ipratropium 17mcg/actuator 2 puffs every 1-2 hours PRN bronchospasm
- Ondansetron 4mg IV prn nausea
- Pantoprazole 40mg po PRN dyspepsia.

Baseline Screening

- MRI (w/in 6 mos)
- Hepatitis panel (Hep BsAg, Hep B core Ab)
    - If HBsAg neg, HBsAg neg, HB core Ab pos = low-level active infection; Hepatology/Infectious Diseases referral.
    - If HBsAg pos = active infection; Hepatology/Infectious Diseases referral.
    - See: https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf
- Zoster titer
- CBC w/diff
- Hepatic function
- Renal function
- Pregnancy
- Consider JCV Ab index

Prior to Ocrelizumab Start. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, mitoxantrone, natalizumab, or teriflunomide, consider the risk of additive immunosuppressive or immunomodulating effects.

Vaccines. There is limited information on efficacy of vaccines in patients taking ocrelizumab. A study in rituximab patients found only 50% of patients mounted an antibody response to tetanus and influenza vaccines. Per FDA, give Hepatitis B and Zoster vaccines ≥ 6 wks prior to first ocrelizumab dose if patient's screening labs do not show immunity. For other vaccines, recommendations are to give ≥ 6 wks prior to first dose of ocrelizumab if at all possible and avoid live vaccines while on drug. The influenza vaccine injection uses a killed virus and is considered safe to give ocrelizumab patients; the nasal spray uses live-attenuated virus and is not recommended.

Contraindications. Active Hepatitis B virus infection, history of life-threatening infusion reaction to ocrelizumab or rituximab.

Warnings and Precautions

Infusion reactions. Premedicate as above. Patients must be cognitively and functionally able to report symptoms of infusion reactions.

Infections. Delay administration in patients with an active infection until the infection is resolved.

PML. There have been no cases of PML in patients on ocrelizumab. There have been incidences of PML in patients on rituximab, a less-humanized monoclonal antibody otherwise very similar to ocrelizumab. Occurrence rate on rituximab is much lower rate than with natiluzumab. These rituxumab patients had other possible contributors to PML. Some MS specialists would not rule out using ocrelizumab in patients with a history of novantrone use.

Malignancies. An increased risk of malignancy, including breast cancer. Patient counseling should cover that although breast cancer most commonly occurs in women, there are rare occurrences in men as well. Per FDA, standard screening recommendations for breast and other cancers should be followed.

Overall Incidence Rate of Malignancies on Open-Label Extension (as of 6/30/2016)

Ocrelizumab	0.40 per 100 patient-yrs. (6,467 patient-yrs. exposure)
Interferon/Placebo	0.20 per 100 patient-yrs. (2,053 patient-yrs. exposure)

In observational followup, malignancy rates do not appear inconsistent with those in the general population. However, data remains insufficient for risk estimates. As smoking increases cancer risk and smoking rates are high in the Veteran population, carefully consider smoking history and risk in patients.

Adverse Reactions

Relapsing MS patients (incidence ≥10% and > Interferon beta1a subcutaneous): upper respiratory tract infections and infusion reactions

PPMS patients (incidence ≥10% and > placebo): upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections

Pregnancy. Not recommended. Insufficient data on use in pregnant women. Animal testing in simians showed increased perinatal mortality, depletion of B cells, and renal, bone marrow, and testicular toxicity. Doses were at or larger than equivalent human doses. Women of childbearing potential should use contraception during and for 6 mos. after last infusion. There is no information on perinatal effects from paternal ocrelizumab use.

Lactation. Not recommended. Insufficient data on use in lactating women. Ocrelizumab is excreted in breast milk of humans and monkeys treated with ocrelizumab. Consider benefits of breastfeeding for infant and mother, the potential adverse effects of ocrelizumab on the infant, as well as mother's clinical need for ocrelizumab.

Geriatric Use. The pivotal trials did not have sufficient numbers of patients ≥65 y.o. to show differences, if any.

Drug Interactions. Unknown.

MS DMT Sequencing. Ocrelizumab's pharmacodynamics add to the already-complex nature of DMT-switch decisions. Consider that it requires up to 2½ yrs from last ocrelizumab dose before most patient's B cells return to baseline/LLN. within 2.5 years after last infusion. This significantly lengthy time to B-cell repopulation must be considered when planning future DMT sequencing.

Availability in VA. Ocrelizumab will be available under the non-formulary request process at the facility level. This process will be implemented until the National Review is completed. Ocrelizumab procurement does not require a Specialty Pharmacy process -- it will be available through the McKesson Plasma and Biologics division. The pricing will be open market until the FSS paperwork has been implemented.

References

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