In This Issue

Cleveland Clinic Clinical Rx Forum

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From the Department of Pharmacy

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Ocrelizumab for Multiple Sclerosis

By: Adam Heiermann, Pharm.D.

Background: Multiple sclerosis (MS) is a neurodegenerative inflammatory disease affecting over a quarter of a million Americans.[1] There are two main subtypes of MS classified based on the progression of symptoms. The more common is relapsing-remitting MS (RRMS) accounting for 85-90% of MS patients.[2] This subtype is characterized by relapses, or acute episodes of worsening neurologic function, followed by either full or partial remission. The other 10-15% of patients experience primary progressive MS (PPMS) where there is a steady decline in neurologic function without improvement and no episodes of acute worsening. While there have been several new therapies approved by the Food and Drug Administration (FDA) in the past 2 decades for RRMS, ocrelizumab (Ocrevus®; Genentech), which was FDA-approved in March 2017, is the first treatment for both RRMS and PPMS.[3] This article will provide an overview of ocrelizumab.

Mechanism of Action: Ocrelizumab is a humanized monoclonal antibody specific for the CD20+ receptor on B-cells.[4] The binding of ocrelizumab stimulates both antibody-dependent and complement-mediated cell lysis, leading to a profound decline in pre-B and mature B lymphocytes, as both express CD20+. While ocrelizumab's precise mechanism of action is unknown, its therapeutic effect in MS is thought to be associated with the reduction in the number and function of CD20-expressing B cells.

Ocrelizumab in PPMS: Seven hundred and thirty-two patients with PPMS were randomized, in a 2:1 ratio to either 600 mg of ocrelizumab every 24 weeks or matching placebo in the ORATORIO trial.[5] The primary outcome was the percentage of patients with a confirmed increase in disability progression at 12 weeks, defined as an

(Continued on page 2)

Filgrastim for Severe Acute Alcoholic Hepatitis

By: Steven Richardson, Pharm.D.

Background: Filgrastim(Neupogen®; Amgen), a recombinant human granulocyte colony stimulating factor (G-CSF), stimulates the production of neutrophils in the bone marrow and mobilizes hematopoietic stem cells in the peripheral blood.[1,2] Filgrastim's effect on increased mobilization of bone marrow stem cells has been shown to improve liver function in patients with alcoholic hepatitis. Pentoxifylline is an anti-tumor necrosis factor (TNF) medication that, in addition to corticosteroids, has been shown to reduce mortality and the occurrence of hepatorenal syndrome in severe alcoholic hepatitis patients.[3-6] This article will assess the impact of G-CSF plus standard therapy in comparison to pentoxifylline for the treatment of severe alcoholic hepatitis.

Clinical Trials: The first study's goal was to evaluate safety and efficacy of G-CSF therapy in reducing morbidity and mortality in patients with acute-on-chronic liver failure (ACLF).[4] Patients were randomized into two groups,

(Continued on page 3)

(Continued from page 1)

increase in the Expanded Disability Status Scale (EDSS), an outcome which occurred in significantly fewer patients, 32.9% in the treatment arm (n=488) vs. 39.3% in the placebo arm (n=244) (P=0.03). Some secondary endpoints involved assessment of brain lesions and volume via magnetic resonance imaging (MRI). Based on MRI results, patients in the treatment group had significantly less brain lesions and brain volume loss. The authors concluded that treatment with ocrelizumab was associated with a lower rate of clinical and radiological progression of PPMS.

Ocrelizumab in RRMS: Two identical placebo-controlled, double-blind, double-dummy trials (OPERA I and OPERA II) were undertaken to evaluate the safety and efficacy of ocrelizumab in RRMS.[6] These trials randomized patients in a 1:1 ratio to either 600 mg of ocrelizumab (n=827 [OPERA I and II]) every 24 weeks or subcutaneous interferon beta-1a at a dose of 44 mcg three times weekly (n=829 [OPERA I and II]) for 96 weeks. The primary outcome was the annualized relapse rate at 96 weeks. This endpoint was found to be significantly lower in the treatment group versus the placebo group in both trials; 0.16 versus 0.29 favoring ocrelizumab in OPERA I (P<0.001) and 0.16 versus 0.29 in OPERA II (P<0.001). Among the secondary endpoints examined were indicators of disease activity via MRI which denoted almost no evidence of acute disease in the treatment arm. The authors concluded that ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a in patients with RRMS.

Safety: The most common adverse reactions observed in the clinical trials of ocrelizumab were upper respiratory tract infections (40-49%) and infusion reactions (34-40%).[4] Due to the high rate of infusion reactions, it is recommended that patients be premedicated with 100 mg of intravenous (IV) methylprednisolone (or equivalent) and an antihistamine (e.g., diphenhydramine). An antipyretic (e.g, acetaminophen) may also be considered as part of the premedication regimen. There is some evidence that treatment with ocrelizumab results in an increased risk of malignancy, specifically breast cancer, as was seen in the ORATORIO trial.[5] There has been one case report of progressive multifocal leukoencephalopathy (PML) with the use of ocrelizumab, however this occurred in a patient that had previously received natalizumab (Tysabri®; Biogen Inc.), which has a black-box warning for PML.[7,8] Therefore, it is unclear whether the occurrence of PML was associated with ocrelizumab or natalizumab.

Dosing and Administration: The FDA-approved dose of ocrelizumab for both PPMS and RRMS is one 600 mg IV infusion every 6 months, with the exception of the first dose which is divided into two 300 mg IV infusions 2 weeks apart.[4] Preparation for administration involves diluting ocrelizumab, which is supplied at a concentration of 30 mg/mL, to a final concentration of approximately 1.2 mg/mL in normal saline. Therefore, 300 mg and 600 mg doses of ocrelizumab should be diluted in 250 mL and 500 mL bags of normal saline, respectively. For proper administration, the infusion should be run via a dedicated line with a 0.2 or 0.22 micron in-line filter. Per the FDA labeling, it is recommended to start the first two 300 mg doses at 30 mL per hour and increase by 30 mL per hour every 30 minutes up to a maximal rate of 180 mL per hour as tolerated. The occurrence of an infusion-related reaction should prompt the initiation of supportive care and a decrease in the rate, but not the overall dose. Subsequent infusions can be started at 40 mL per hour and increased by an additional 40 mL per hour every 30 minutes up to a maximal rate of 200 mL per hour.

Availability and Cost: Ocrelizumab is available as 300 mg/10 mL vials that must be refrigerated at 2°C-8°C (36°F-46°F) and protected from light.[4] Currently, each 300 mg vial has a suggested wholesale price (SWP) of $19,500, making the cost $39,000 for each semi-annual 600 mg treatment or $78,000 annually.[9] Interferon beta-1a 44 mcg/0.5 mL (Rebif® Rebidose®; EMD Serono) which is given subcutaneously three times a week is currently $662.92 per syringe; resulting in a weekly cost of approximately $1988 and an annual cost about of $103,000. Natalizumab, which has an SWP of $7200 for each 300 mg dose, is given on a monthly basis and thus costs about $86,400 per year.

Formulary Status: Ocrelizumab was recently added to the CCHS Adult Formulary restricted to the Department of Neurology for outpatient use only.

References:

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(Continued from page 1)

Group A (n=16) received filgrastim at a dose of 5 mcg/kg subcutaneously for 12 doses over a period of a month in addition to standard therapy. Group B (n=7) received standard therapy (pentoxifylline) and a placebo. At days 2, 4, 7, and 30, G-CSF therapy produced a significant increase in total leukocytes. At days 42 and 60, leukocyte counts were no longer significantly different between groups. Group A showed a significant improvement in Child-Turcotte-Pugh (CTP), Maddrey's Discriminant Function (mDF), and Model for End-Stage Liver Disease (MELD) scores at days 7, 30, and 60. Sixteen patients (69%) in group A and seven patients (29%) in group B survived resulting in a significant between-group difference in survival rate (66% vs. 26%, respectively; P=0.001). The authors concluded that G-CSF therapy increases the survivability of patients with ACLF by reducing liver indices scores and preventing the development of sepsis, hepatorenal syndrome, and hepatic encephalopathy. Another study which evaluated G-CSF therapy analyzed liver indices and survival after 90 days in patients with severe alcoholic hepatitis.[5] Group A (n=23) received standard therapy plus G-CSF at a dose of 5 mcg/kg every 12 hours for 5 days. Group B (n=23) received standard therapy alone consisting of pentoxifylline 400 mg three times daily and normal hospital nutrition. There was a statistically significant improvement of CTP, MELD, and mDF scores favoring Group A over Group B at 1, 2, and 3 months. Overall at day 90, the survival rate was significantly greater in Group A than in Group B (78.3% vs. 30.4%, respectively; P=0.001). Therapy with G-CSF was well tolerated in patients with minor complaints composed of bone pain (16.6%) and headache (11.1%). The researchers concluded that G-CSF plus standard therapy (pentoxifylline) was safe and effective and improved liver function and survival at 90 days in patients with severe alcoholic hepatitis.

Dosing and Administration: For severe alcoholic hepatitis, filgrastim is dosed as 5 mcg/kg subcutaneously every 12 hours for 5 consecutive days along with pentoxifylline for patients with a mDF score greater than or equal to 32. Filgrastim is part of the CCHS dose rounding policy which states that for all dosing to be rounded to the nearest vial size (300- or 480-mcg).[7] For doses < 390 mcg round down (use the 300 mcg vial); for doses ≥ 390 mcg round up (use the 480 mcg vial). The dosing should be based on the patient's actual body weight.

Cost and Availability: The suggested wholesale price (SWP) per vial of filgrastim is as follows: the 300 mcg/mL vial is $367.15 and the 480 mcg/mL vial is $584.64.[1] Therefore, the following calculation can be used to determine the total cost of therapy for a 70 kg patient:

5 mcg/kg dose for 70 kg patient =
350 micrograms per dose

Five day course of every 12 hour dosing:
Use the 300 mcg vial per dose per vial rounding policy
300 mcg vial = 10 vials total per course of therapy
Total Cost = $3671.50

Formulary Status: The restriction criteria for filgrastim has been expanded as follows: Restricted to Hepatology for the treatment of severe acute alcoholic hepatitis.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Aztreonam (Cayston®)	Inhaled Antibiotic	Pulmonary infections in CF patients	Restricted to the Department of Pulmonary and Critical Care Medicine for continuation of therapy for CF patients
Bumetanide (Bumex®)	Loop Diuretic	Alternative Diuretic	Restricted to those patients with documented allergies to torsemide or furosemide (e.g., rash to torsemide/ furosemide, but oral bumetanide is tolerated)
Lipid Injectable Emulsion 20% (Smoflipid®)	Caloric Agent	Parenteral Nutrition	Restricted to the Nutrition Support Team and dieticians (regional hospitals)
Midostaurin (Rydapt®)	Antineoplastic Agent	AML Mast cell leukemia	Restricted to the Department of Hematology and Medical Oncology
Ocrelizumab (Ocrevus®)	Anti-CD20 Monoclonal Antibody	Multiple Sclerosis	Restricted to the Department of Neurology for outpatient use only
Polymyxin B	Antibiotic	Multi-Drug Resistant Gram-negative Infections	Restricted to the Department of Infectious Diseases. Note: Doses will be automatically rounded by Pharmacy to the nearest 10 mg for adult patients
Selexipag (Uptravi®)	Prostacyclin IP Receptor Agonist	Pulmonary Arterial Hypertension	For initiation of therapy in adults restricted to: 1) Providers from the Respiratory Institute (Includes Fellows and Staff Physicians only. Does not include medical residents rotating in Respiratory Institute or Nurse Practitioners). 2) Should not be first-line therapy. **There are no restrictions for continuation of therapy.**
Tirofiban (Aggrastat®)	Glycoprotein IIB/IIIa Inhibitor	Unstable Angina Non-ST Elevation Myocaridal Infarction	3.75 mg/15 mL vials and 5 mg/100 mL bags were added as a line item extensions

AML=Acute myeloid leukemia CF=Cystic Fibrosis

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Acetaminophen IV (Ofirmev®)	Analgesic	Pain Reliever	Pharmacists may round a one-time dose of acetaminophen IV of <1000 mg (e.g., 500 mg or 650 mg) to 1000 mg (1 gram) for adult patients weighing ≥ 50 kg
Chloramphenicol	Antibiotic	Multi-Drug Resistant Infections	Restricted to Department of Infectious Diseases
Diclofenac topical patch (Flector®)	Analgesic	Pain Reliever	Restricted to Pain Management for initiation of therapy, but no restrictions on continuation of therapy
Ethacrynic acid (Edecrin®)	Loop Diuretic	Loop Diuretic	Restricted to patients with a documented severe or anaphylactic allergic reaction to bumetanide, torsemide, or furosemide not currently taking one of those agents prior to admission and in all non-emergency cases, an Allergy Consult should be ordered (at available sites)
Filgrastim (Neupogen®)	G-CSF	Severe Acute Alcoholic Hepatitis	Restricted to Hepatology for treatment of severe acute alcoholic hepatitis
Filgrastim-sndz (Zarxio®)	G-CSF (biosimilar)	Neutropenia	Restricted to Hematology and Medical Oncology for outpatient use only in patients whose insurance mandates Zarxio®
Inhaled Epoprostenol (Veletri®)	Prostacyclin	Pulmonary Arterial Hypertension	Restricted to Nurse Practitioners (NP) in the CTICU after consultation with the Staff Physician to order epoprostenol from the order set
Isavuconazonium Sulfate (Cresemba®)	Antifungal Agent	Invasive Aspergillosis Invasive Mucormycosis	Restricted to the Department of Infectious Diseases
Leuprolide acetate depot (Lupron® Depot)	Gonadotropin-Releasing Hormone Agonist	Fertility Preservation	Restricted to Endocrinology, Rheumatology, and Oncology for fertility preservation
Long-Acting Reversible Contraceptives (Mirena®, Paragard®, and Nexplanon®)	Contraceptive	Contraception	Restriction criteria for Mirena®, Paragard®, and Nexplanon® modified to: Inpatient use is restricted to the immediate postpartum period

G-CSF=Granulocyte-colony stimulating factor CTICU=Cardiothoracic Intensive Care Unit IV=Intravenous

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Naloxegol (Movantik®)	Opioid Antagonist Peripherally-Acting	Opioid-induced Constipation	Modified restriction: For initiation of therapy, naloxegol is restricted to patients currently on opioid therapy who have failed two other scheduled (e.g., not PRN) laxatives administered for 48 hours. There are no restrictions for continuation of home therapy.
Posaconazole (Noxafil®) (Oral Formulations)	Antifungal Agent	Prophylaxis in patients undergoing induction regimens for AML	Modified restriction: Oral posaconazole is restricted to Infectious Diseases and Hematology and Medical Oncology (includes Bone Marrow Transplant)
Talimogene Laherparepvec (Imlygic®)	Antineoplastic Agent, Oncolytic Virus	Unresectable Melanoma	Modified restriction: Restricted to the Department of Hematology and Medical Oncology and Dermatology and Plastic Surgery for the local treatment of un-resectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery for adult outpatient use only

AML= Acute myeloid leukemia PRN=As needed

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/ Comments**
Hypotonic saline (0.225% NaCl)	Electrolyte Solution	Hypernatremia	Reason for removal: Administration of hypotonic saline has been associated with cellular edema and hemolysis leading to renal failure and death. In addition phlebitis and seizures can occur with its use. Removed due to safety concerns by Neurosciences, Critical Care, and Internal Medicine Specialty Panels.
Intranasal Antihistamines	Antihistamine	Season Allergies	Reason for removal: More cost-effective oral antihistamine alternatives should be used. However patients may use their own intranasal antihistamine supply during an inpatient admission per Medications from Home Policy or utilize the ambulatory pharmacy and bedside delivery service.
Oral cephalosporins	Antibiotic	Various Infections	Reason for removal: A therapeutic interchange has been established to standardize products and streamline inventory. The following cephalosporins have been removed: cefadroxil, cefaclor, cefprozil, cefpodoxime, cephradine, loracarbef, ceftibuten, and cefditoren

Therapeutic Interchanges on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Empagliflozin (Jardiance®)	SGLT2 Inhibitor	Type 2 Diabetes	Empagliflozin was selected as the "drug of choice" for the SGLT-2 therapeutic interchange due to positive cardiovascular morbidity and mortality outcomes. Unlike canaglifozin (Invokana®), empagliflozin does not have a boxed warning for increased risk of leg and foot amputations. All inpatients on a SGLT2 inhibitor will be automatically converted to an equivalent dose of empagliflozin. A dose conversion table will be located in the Therapeutic Interchange list on the Drug Information Center Sharepoint Site.
Ophthalmic Products	Carbonic Anhydrase Inhibitors Prostaglandin Analogs Non-selective Beta-Blockers	Various Indications	As a cost savings and product standardization initiative, the Cole Eye Institute supports a therapeutic interchange for various ophthalmic drops. A therapeutic interchange list will be located on the Drug Information Center Sharepoint Site.
Oral Cephalosporins	Antibiotics	Various Infections	As a part of the effort to standardize products and streamline inventory, the Antimicrobial P&T Committee selected the following oral cephalosporins: Cephalexin (1st Generation) Cefuroxime axetil (2nd Generation) Cefdinir and Cefixime (3rd Generation) A therapeutic interchange list for oral cephalosporins will be located on the Drug Information Center Sharepoint Site.

SGLT-2=Sodium-glucose cotransporter 2

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Darbepoetin alfa (Aranesp®)	Colony Stimulating Factor	Anemia	Restricted to Neonatal ICU
Ferric carboxymaltose (Injectafer®)	Parenteral Iron Supplement	Iron Deficiency Anemia	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation for outpatient use only for the treatment of iron deficiency anemia in patients with inflammatory bowel disease who are refractory to oral iron
Pembrolizumab (Keytruda®)	Monoclonal Antibody	Relapsed/Refactory Hodgkin's Lymphoma	Restricted to the Department of Hematology/Oncology and Bone Marrow Transplantation for outpatients with relapsed/refractory Hodgkin's lymphoma
Timolol maleate 0.5% gel-forming ophthalmic solution	Beta-blocker	Superficial Infantile Hemangioma	Restricted for the treatment of superficial infantile hemangioma. Patients must be evaluated by Dermatology and/or Cardiology prior to initiating therapy

ICU=Intensive Care Unit

Changes to Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Codeine	Opioid Analgesic	Pain Reliever	Due to the risk of serious breathing problems and death in pediatric patients, the FDA released a Drug Safety Communication restricting the use of prescription codeine pain and cough medicines and tramadol pain medications in children. Modified restriction: Codeine and codeine-containing medications should not be prescribed to treat cough or pain in children less than 12 years old. Alternative therapies must be selected for these patients.
Tramadol (Ultram®)	Opioid Analgesic	Pain Reliever	Due to the risk of serious breathing problems and death in pediatric patients, the FDA released a Drug Safety Communication restricting the use of prescription codeine pain and cough medicines and tramadol pain medications in children. Modified restriction: 1. Tramadol and tramadol-containing medications should not be prescribed for postoperative pain management in pediatric patients (i.e., less than 18 years of age) undergoing tonsillectomy and/or adenoidectomy. Alternative pain therapies must be selected for these patients. 2. Tramadol and tramadol-containing medications should not be prescribed to treat pain in children less than 12 years old. Alternative pain therapies must be selected for these patients.

FDA=Food and Drug Administration

Changes to Restrictions of Medications on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Vigabatrin (Sabril®)	Anticonvulsant	Refractory CPS	Modified Restrictions: 1. Initiation of therapy is restricted to prescribers from the Pediatric Epilepsy Service. The prescriber MUST be registered (certified) with the Vigabatrin REMS Program. 2. Continuation of therapy is restricted to prescribers from the Pediatric Epilepsy Service. The prescriber MUST be registered (certified) with the Vigabatrin REMS Program. However, the pharmacist is allowed to verify and dispense ONE dose ordered by a NON-certified prescriber for continuation of home therapy during OFF-HOURS. The primary service will need to consult with a certified inpatient prescriber from Pediatric Epilepsy Service the next day for approval of subsequent doses for continuation of therapy.

CPS=Complex partial seizures