In This Issue

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From the Department of Pharmacy

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Tofacitinib (Xeljanz®) for Moderate to Severe Ulcerative Colitis

By: Kristen Neuhaus, Pharm.D.

Background: Ulcerative colitis (UC) is a chronic disease characterized by inflammation of the mucosal lining of the colon causing an increased frequency of bowel movements and bloody diarrhea.[1,2] It affects approximately 500,000 individuals in the United States with an incidence of 8-12 per 100,000 population per year.[2] Current therapy for UC includes mesalamine, glucocorticoids, thiopurines, tumor necrosis factor (TNF) blockers (e.g., infliximab) and an alpha 4 beta 7 integrin antagonist (e.g., vedolizumab).[3] Since some patients may become refractory to these therapies, alternatives effective against UC were needed. Consequently, tofacitinib (Xeljanz®; Pfizer Pharmaceutical), a medication with a unique mechanism of action, was approved by the Food and Drug Administration (FDA) for use in the treatment of moderate to severe active UC in adult patients in May 2018.[3-5]

Mechanism of Action: Janus kinases (JAKs) are enzymes that activate the signal transducers and activators of transcription (STATs), which are intracellular transcription proteins that modulate immune function.[5,6] The JAK-STATs pathway contributes to the pathogenesis of UC through stimulation of pro-inflammatory cytokine production. Tofacitinib, a JAK inhibitor, interferes with JAK-STAT pathway thus modulating this inflammatory process.

Key Clinical Trials: Two phase 3 induction trials (OCTAVE Induction 1 and 2) and one phase 3 maintenance trial (OCTAVE Sustain) led to tofacitinib's FDA approval for UC.[3,4] These trials were multicenter, randomized, double-blind, and placebo-controlled. Patients included in this these trials were ≥ 18 years of age and had moderate to severe UC. They could receive oral mesalamine or oral prednisone at a

(Continued on page 2)

Mometasone Furoate (Sinuva™) Implant for Refractory Nasal Polyps

By: Joshua Eudy, Pharm.D.

Background: Chronic rhinosinusitis (CRS), an inflammatory sinus condition, can be classified into two subtypes, CRS with nasal polyps (CRSwNP) and without nasal polyps.[1] The American Academy of Otolarynology-Head and Neck Surgery recommends treating CRSwNP with daily inhaled corticosteroids and saline nasal irrigation.[2] The efficacy of intranasal corticosteroids may be limited due to patient noncompliance and inadequate drug delivery to the sinus cavity. Failure of corticosteroid therapy can lead to costly surgical procedures. In the United States over 250,000 endoscopic surgeries are performed on patients with CRS annually with 20% requiring additional surgeries within 5 years.[3] Mometasone furoate sinus implant (Sinuva™; Intersect ENT, Inc.) may help avert those repeat surgical procedures associated with treatment failure by providing long-term, corticosteroid delivery directly into the sinuses. In December 2017, the Food and Drug Administration (FDA) approved the mometasone furoate sinus

(Continued on page 3)

(Continued from page 1)

stable dose of ≤ 30 mg per day. A total of 598 patients in OCTAVE Induction 1 and 541 patients in OCTAVE Induction 2 were randomized in a 4:1 ratio to receive induction therapy with tofacitinib 10 mg twice daily or placebo for 8 weeks, patients who achieved a clinical response to induction therapy in the OCTAVE Induction 1 and 2 trials were included in the OCTAVE Sustain trial. Patients in the OCTAVE Sustain trial were randomly assigned in a 1:1:1 ratio to receive maintenance therapy with tofacitinib 5 mg twice daily, 10 mg twice daily, or placebo for 52 weeks. The primary efficacy endpoint in OCTAVE Induction 1 and 2 trials was remission at 8 weeks and the key secondary endpoint was mucosal healing at 8 weeks. In the OCTAVE Sustain trial the primary endpoint was remission at 52 weeks and a key secondary endpoint included sustained and glucocorticoid-free remission among patients who were in remission at maintenance trial entry. In the OCTAVE Induction 1 trial, 18.5% of patients achieved remission in the 10 mg tofacitinib group vs. 8.2% in the placebo group (p=0.007). In the OCTAVE Induction 2 trial, 16.6% achieved remission in the 10 mg tofacitinib group vs. 3.6% in the placebo group (p<0.001). The secondary endpoint of mucosal healing at 8 weeks in OCTAVE Induction 1 and OCTAVE Induction 2 trials occurred in significantly more patients in the 10 mg tofacitinib group than the placebo group (p<0.001 for both comparisons). In the OCTAVE Sustain trial, 34.3% in the 5 mg tofacitinib group and 40.6% in the 10 mg tofacitinib group achieved remission at 52 weeks vs. 11.1% in the placebo group (p<0.001 for both comparisons with placebo); glucocorticoid-free remission was maintained in 35.4% in the 5 mg tofacitinib, 47.3% in the 10 mg tofacitinib group, vs. 5.1% in the placebo group (p<0.001 for both comparisons with placebo). The authors concluded that among patients with moderate to severe active UC, tofacitinib 10 mg twice daily was more effective than placebo for induction of remission and mucosal healing and that maintenance therapy at a dose of 5 mg or 10 mg twice daily was more effective than placebo in sustaining remission.

Safety: Nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster were the most common side effects occurring in ≥5% of patients treated with tofacitinib.[5] Serious infections, malignancies and lymphoproliferative disorders, gastrointestinal perforations, and laboratory abnormalities have also been reported. It is recommended to monitor lymphocyte, neutrophil/ platelet counts, liver function test, lipids, heart rate and blood pressure while receiving tofacitinib.[7]

Dosing and Administration: The recommended dosage of tofacitinib in adult patients with UC is 10 mg by mouth twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response.[5] Treatment should be discontinued after 16 weeks of treatment with 10 mg twice daily if an adequate clinical response is not achieved. For patients who develop moderate or severe renal impairment or moderate hepatic impairment while taking 10 mg twice daily, the dose should be reduced to 5 mg twice daily and if taking 5 mg twice daily, the dose should be reduced to 5 mg daily. Dosing recommendations for patients on concomitant cytochrome P450 (CYP) 3A4 inhibitors or CYP 2C19 inhibitors are available in the package insert. Also included are specific recommendations for dosage adjustments based on lymphocyte/ neutrophil counts and hemoglobin levels.

Availability and Cost: Tofacitinib is available as a 5 mg tablet (NDC 63539-012-12) and 10 mg tablet (NDC 63539-016-02).[5] The suggested wholesale price (SWP) is $89.61 per tablet.[8] The estimated cost of 1 month of therapy is about $5018.

Formulary Status: Tofacitinib was added to the CCHS Formulary restricted to the Department of Gastroenterology for initiation of therapy. Any prescriber may order tofacitinib for continuation of therapy.

References:

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(Continued from page 1)
implant for the treatment of CRSwNP in patients ≥ 18 years of age who have had ethmoid sinus surgery (ESS).[4]

Mechanism of Action: Mometasone furoate sinus implant is a drug-eluting, bioabsorbable, self-expanding implant designed to deliver a sustained concentration of corticosteroids to the sinus cavity for up to 90 days.[4] Mometasone furoate is a corticosteroid that has anti-inflammatory effects. Although their mechanism of action is not entirely understood, corticosteroids have demonstrated a wide range of effects on multiple cell lines involved in inflammatory process.

Key Clinical Trial: A prospective, phase 3, randomized, sham-controlled, double-blind trial (RESOLVE II) evaluated mometasone furoate sinus implant for the treatment of CRSwNP.[1] Patients (N=300) included in the study were ≥ 18 years old, had confirmed CRSwNP, a history of ESS, and were candidates for repeat ESS. The intervention group (n=201) received bilateral placement of mometasone furoate implants (1350 mcg per implant), while the control group (n=99) received a sham procedure. Both groups received concomitant intranasal inhaled mometasone furoate 200 mcg daily throughout the study duration. On day 60, the intervention group had the implant removed and the control group had a simulated removal to allow for blinded evaluation at day 90. The co-primary outcomes measured subjective improvement in nasal obstruction/congestion score at day 30 and baseline change in bilateral polyp grade at day 90. Nasal obstruction/congestion was measured subjectively through patient symptom scaling 0 (no symptoms) to 3 (severe symptoms). Polyp grade change was assessed by an independent blinded panel using a 0 (no polyps) to 4 (polyps with complete obstruction) scale which was combined for bilateral assessment (0-8). A select secondary endpoint was the need for repeat ESS at day 90. Results in mean change in nasal obstruction/congestion from baseline between the treatment and control group was a difference of -0.23 (95% CI, -0.39 to -0.06; p=0.0074) favoring the intervention group. For bilateral polyp grade, there was a baseline mean change of -0.35 (95% CI, -0.6 to -0.09; p=0.0073) favoring the intervention group. For the secondary outcome of need for ESS at day 90 there was a reduction of 61% in the intervention group compared to 37% in the control patients (OR 2.69;95% CI, 1.63-4.44; p=0.0004). The authors concluded that the use of bilateral mometasone furoate sinus implants provided superior outcomes to the current standard of care and may play a significant role in reducing the need for repeat ESS procedures.

Safety: The most common side effects of mometasone furoate implants were chronic sinusitis 11%, upper respiratory infections 8%, and hypersensitivity 4%.[4] Mometasone furoate concentrations have been shown to be significantly increased with concomitant use of cytochrome P450 (CYP) 3A4 inhibitors and in hepatic failure. Monitoring for systemic corticosteroid side effects (e.g., hyperglycemia, osteoporosis, and adrenal suppression) may be warranted.

Dosing and Administration: Each mometasone furoate implant contains 1350 mcg of mometasone furoate which is slowly released for up to 90 days.[4] Implants have been studied and are typically placed bilaterally, totaling 2700 mcg mometasone furoate for two implants. Insertion and removal after 90 days of these implants must be done by an otolaryngologist as an in-office procedure. There is no evidence evaluating the recurrent use of implants after initial treatment.

Cost and Availability: Mometasone furoate sinus implant is available as a single-use, self-expanding bioabsorable polymer implant coated in 1350 mcg of mometasone furoate.[4] The product is supplied in a single foil packaged kit which contains a single implant, crimper, and delivery system (NDC 10599-003-01). The average wholesale price for a single 1350 mcg Sinuva™ implant is $1530.[5]

Formulary Status: Mometasone furoate sinus implant was added to the CCHS Formulary restricted to the Department of Otolaryngology for outpatient use only.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Atenolol (Tenormin®)	Beta-Blocker	Angina pectoris Atrial fibrillation Hypertension MI Supraventricular tachycardia	The cost of atenolol has significantly declined; therefore, it was added back to the CCHS Formulary
Fluocinolone Acetonide Intravitreal Implant (Yutiq®)	Corticosteroid	Chronic Non-infectious Uveitis	Restricted to Ophthalmology for outpatient use only
Mometasone Furoate Sinus Implant (Sinuva™)	Corticosteroid	Treatment of CRSwNP in patients ≥ 18 years of age who have had ESS	Restricted to ENT (Otolaryngology) for outpatient use only
Ravulizumab-cwvz (Ultomiris®)	Monoclonal Antibody	PNH	Restricted to the Department of Hematology/Oncology for PNH for outpatient use only
Tofacitinib (Xeljanz®)	Janus Kinase Inhibitor	Moderate to Severe UC	Restricted to Gastroenterology for initiation of therapy for inpatients May be ordered by any prescriber for continuation of therapy

MI=Myocardial infarction CRSwNP=Chronic rhinosinusitis with nasal polyps ESS=Ethmoid sinus surgery
ENT=Ears, nose, and throat PNH=Paroxysmal nocturnal hemoglobinuria UC=Ulcerative colitis

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction/ Comments**
Eculizumab (Soliris®)	Monoclonal Antibody	aHUS TMA gMG PNH	Modified restrictions to allow inpatient ordering by REMS-certified prescribers from Nephrology and Hematology/Oncology for the treatmen of aHUS and complement-mediated TMA when certain criteria are met.
Fulvestrant (Faslodex®)	Antineoplastic Agent	Breast Cancer	Modified restriction to state: Restricted to the Department of Hematology/Oncology for outpatient use only
Zoledronic acid (Zometa®)	Bisphosphonate	Hypercalcemia of Malignancy Bone Metastases	Removed outpatient use only as a restriction/The cost of generic zoledronic acid has declined

aHUS= Atypical hemolytic uremic syndrome TMA= Thrombotic microangiopathy
gMG=Generalized myasthenia gravis PNH= Paroxysmal nocturnal hemoglobinuria REMS=Risk evaluation mitigation strategy

New Therapeutic Interchange			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Topical Corticosteroids (creams, ointments, and lotions)	Corticosteroid	Dermatitis	Topical steroid therapeutic interchange:*† Very high potency cream/ ointment = Clobetasol 0.5% cream/ointment High potency cream/ointment= Fluocinonide 0.05% cream/ ointment Intermediate potency cream/ ointment= Triamcinolone 0.1% cream/ ointment Low potency cream/ointment= Hydrocortisone 2.5% cream/ ointment Low-to-intermediate potency lotion= Hydrocortisone 2.5% lotion

*Rectal preparations, scalp solutions, gels, and combination topical corticosteroids are excluded from this interchange.
†A small inventory of propylene glycol-free products will be stocked to accommodate patients allergic to propylene glycol (this was requested by Dermatology).

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Antihemophilic factor (recombinant) Fc fusion protein (Eloctate®)	Blood Factor	Hemophilia A	Restricted to Pediatric Hematology/ Oncology for continuation of home therapy only
Atenolol (Tenormin®)	Beta-Blocker	Arrhythmias Hypertension Hemangioma Infantile Thyrotoxicosis	The cost of atenolol has significantly declined; therefore, it was added back to the CCHS Formulary
Cholecalciferol 50,000 unit capsules	Vitamin	Graft versus Host Disease	Restricted to Pediatric BMT
Emapalumab-lzsg (Gamifant®)	Monoclonal Antibody	HLH	Restricted to Pediatric Hematology/ Oncology and BMT
Epoetin alfa-epbx (Retacrit®)	CSF	Anemia	Restricted to outpatients whose insurance mandates the use of Retacrit®
Laronidase (Aldurazyme®)	Enzyme	Hurler Syndrome	Restricted to outpatient use only
Pegfilgrastim-jmbd (Fulphila™)	CSF	Prevention of Chemotherapy-Induced Neutropenia	Restricted to Hematology/Oncology for outpatients whose insurance mandates the use of Fulphila™
Ulipristal (ella®)	Contraceptive	Emergency Contraception	Will be available to SANE coordinators at the CCHS EDs including free-standing EDs only

BMT=Bone marrow transplant HLH=Primary hemophagocytic lymphohistiocytosis CSF=Colony stimulating factor
SANE=Sexual assault nurse examiner EDs=Emergency departments

New Automatic Processes on Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Epoetin alfa-epbx (Retacrit®) Pegfilgrastim-jmbd (Fulphila™)	CSF	Anemia Neutropenia	Pharmacists may automatically switch to insurance-approved biosimilar products for epoetin alfa and pegfilgrastim when necessary to assure reimbursement
Intravenous Acetaminophen (Ofirmev®)	Analgesic	Pain Reliever	Pharmacists may automatically round all IV acetaminophen doses as follows: 1) Patient weight 45 kg to ≤ 65 kg; automatically round to 650 mg 2) Patient weight >65 kg; automatically round to 1000 mg

CSF=Colony stimulating factor

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Eculizimab (Soliris®)	Monoclonal Antibody	aHUS	Restrictions for eculizimab were modified as follows: 1) To eliminate the outpatient requirement 2) To include aHUS as an approved indication
Fat emulsion (Smoflipid®)	Caloric Agent	Caloric/fatty acid source	Smoflipid® may be used in the Neonatal ICU without any restrictions Initiation of Smoflipid® outside of the Neonatal ICU will still be restricted to Pediatric Gastroenterology

aHUS=Atypical hemolytic uremic syndrome ICU=Intensive care unit