In This Issue

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March/April Issue **2017 Volume 5, Issue 2**

Ustekinumab for Crohn's Disease

By: Christine Hwang, Pharm.D.

Background: Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) system and can cause a wide spectrum of GI-related symptoms and complications.[1,2] The main goals of treatment are to suppress inflammatory processes and induce remission. Medical management for moderate-to-severe CD usually involves treatment with tumor necrosis factor (TNF) blockers (e.g., infliximab) and anti-integrin agents (e.g., vedolizumab). However, up to 40% of patients do not respond to TNF blockers; of those who fail TNF therapy, 47% do not respond to velodizumab.[1,2] The high rate of non-response to the biologic therapies warrants the need to evaluate newer agents.

A Novel Indication: Ustekinumab, known by the brand name Stelara® (Janssen Biotech, Inc.), is a human immunoglobulin G1K monoclonal antibody with high binding capacity to shared p40 protein subunit on interleukin-12 (IL-12) and interleukin-23 (IL-23).[1,3] It blocks the actions of IL-12/23 cytokines including natural killer cell activation and CD4+ T-cell differentiation and activation, which contribute to the chronic inflammation of CD. Ustekinumab was first approved by the Food and Drug Administration (FDA) in 2009 to treat adult patients with moderate-to-severe plaque psoriasis or psoriatic arthritis. In 2016, it gained FDA approval for moderately to severely active CD in adult patients who failed or were intolerant to treatment with corticosteroids or immunomodulators, but never failed a TNF blocker, or those who failed or were intolerant to one or more TNF blockers.

Key Clinical Trial: Ustekinumab's FDA approval for CD was based on three phase 3 randomized, placebo-controlled studies.[4] Two of the studies, UNITI-1 and UNITI-2, investigated the

Reslizumab for Eosinophilic Phenotype, Severe Asthma

By: Jacyln Hawn, Pharm.D.

Background: Eosinophilic asthma is characterized by high eosinophil levels in the blood and bronchial fluid, which can lead to severe asthma that is poorly controlled by inhaled corticosteroids and bronchodilators.[1] This asthma phenotype is most prevalent in adults and is estimated to be present in less than 5% of cases with adult–onset asthma.[2,3] Elevated eosinophil levels in the serum and sputum are independent risk factors for future exacerbations.[1] Reslizumab (Cinqair®; Teva Respriatory) is an anti-asthmatic monoclonal antibody that received Food and Drug Administration (FDA) approval on March 23, 2016 for add-on maintenance treatment for patients with an eosinophilic phenotype, severe asthma who are 18 years and older.[4]

Mechanism of Action: Reslizumab is an interleukin-5 (IL-5) antagonist.[4] Interleukin-5 is the key cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Eosinophils are one of the

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use of intravenous (IV) ustekinumab for induction therapy in either patients who had primary or secondary non-response or intolerable side effects to TNF blockers (UNITI-1) or conventional therapy with immunomodulators (UNITI-2). Patients were randomized to receive either 130 mg or ~6 mg/kg of IV ustekinumab or placebo. The primary endpoint for these induction studies was a clinical response at week 6, which was defined as at least a 100 point decrease from baseline in the Crohn's Disease Activity Index (CDAI) score. In both studies, a significantly higher percentage of patients who received IV ustekinumab experienced a clinical response compared to placebo (P=0.002 [130 mg vs. placebo] and P=0.003 [6 mg/kg vs. placebo] in UNITI-1; P<0.001 for both comparisons in UNITI-2). Patients who completed the induction trials were enrolled in the 44-week IM-UNITI maintenance trial, which randomized patients to receive 90 mg subcutaneous ustekinumab either every 8 weeks or every 12 weeks or placebo. The primary endpoint was clinical remission at week 44, which occurred in a significantly higher percentage of patients who received ustekinumab for maintenance compared to placebo (P=0.005 [every 8 weeks vs. placebo] and P=0.04 [every 12 weeks vs. placebo]). This study also showed that every 8 week administration of the maintenance dose was more effective in maintaining remission compared to every 12 weeks. The most common side effects were CD events, arthralgia, pyrexia, headache, and nasopharyngitis. From these results, the authors concluded that ustekinumab administered initially as an IV infusion followed every 8 weeks by subcutaneous therapy induces response and remission in patients with moderate-to-severe CD that is refractory to either TNF blockers or conventional therapy.

Availability and Cost: The IV formulation of ustekinumab is available as a 130 mg/26 mL single-dose glass vial and has a suggested wholesale price (SWP) of $1920 per vial.[5] The subcutaneous formulation is available as a 90 mg/mL preservative-free, prefilled single-dose syringe and has a SWP of $21,216 per syringe. The glass vial for the IV formulation is latex-free, but the prefilled syringe contains latex.

Dosing and Administration: The IV induction dose of ustekinumab is weight-based, but utilizes entire vials (no need to dose round) and is as follows:[3]

- 260 mg (2 vials) for patients weighing ≤ 55 kg
- 390 mg (3 vials) for patients weighing >55 to 85 kg
- 520 mg (4 vials) for patients weighing > 85 kg

For the induction dose, the contents of the single-dose vials should be diluted in 250 mL of 0.9% sodium chloride and infused intravenously through a 0.2 micrometer filter over at least 1 hour. For the maintenance dose, the 90 mg prefilled syringe is administered subcutaneously 8 weeks after the induction dose and then every 8 weeks thereafter. The single-dose vial and prefilled syringe must be stored at refrigerated temperatures (2° to 8°C [36° to 46°F]). The diluted IV infusion can be stored at room temperature (up to 25°C [77°F]) for up to 4 hours.

Formulary Status: Intravenous ustekinumab was recently added to the CCHS Adult Formulary restricted to the Department of Gastroenterology for outpatient use only. The intravenous formulation of ustekinumab was also added to the CCHS Pediatric Formulary restricted to the Department of Pediatric Gastroenterology for outpatient use only for patients ≥ 18 years old with moderate to severe Crohn's disease that have failed therapy with at least one TNF blocker. The subcutaneous syringe formulation was not added to either formulary, since patients can self-administer maintenance doses at home.

References:

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many types of mediators involved in the inflammatory process.[4,5] Reslizumab reduces the production and survival of eosinophils by antagonizing the IL-5 pathway and therefore, reduces inflammation associated with asthma. The exact mechanism of action of reslizumab in asthma has not been definitively established.[4]

Efficacy: Three hundred and fifteen patients with inadequately controlled eosinophilic phenotype, severe asthma were included in a randomized, double-blind, placebo-controlled trial.[6] The primary outcome was to compare the change in Forced Expiratory Volume (FEV_1) from baseline to 16 weeks among treatment groups, reslizumab 0.3 mg/kg (n=104), reslizumab 3 mg/kg (n=106), or placebo (n=105). The primary outcome resulted in a statistically significant difference in FEV_1 after 16 weeks of treatment in both the reslizumab 0.3 mg/kg group (P=0.0237) and the reslizumab 3 mg/kg group (P=0.0018) compared to placebo. However, the reslizumab 3 mg/kg group demonstrated significant improvement as early as 4 weeks and this was maintained throughout the study. Secondary outcomes in the 3 mg/kg reslizumab group also showed significant improvement in forced vital capacity (FVC) (P=0.0174), forced expiratory flow (FEF) at 25% to 75% of FVC ($FEF_{25\%-75\%}$) (P=0.0552), and a reduction in short-acting beta agonist use (P=0.0151) compared to placebo. The FVC and $FEF_{25\%-75\%}$ for the 0.3 mg/kg group were not significantly different from placebo. The authors concluded that IV reslizumab 3 mg/kg provided greater improvement than reslizumab 0.3 mg/kg in lung function, asthma symptoms, and quality of life for patients with uncontrolled eosinophilic asthma. Additional randomized, double-blind, placebo-controlled trials have demonstrated similar results in reslizumab's ability to improve pulmonary function and clinical outcomes.[1,6-8] Statistically significant results included reduction in blood eosinophils from baseline, decreased frequency of clinical asthma exacerbations, improved Asthma Control Questionnaire-7 results, and improved FEV_1 among patients with eosinophilic phenotype, severe asthma.

Safety: Reslizumab carries a black box warning for anaphylaxis, which can occur as early as the second dose and within 20 minutes after completion of the infusion.[4] The most common adverse events in clinical trials were increased creatinine phosphokinase (20%), antibody development (5%), and oropharyngeal pain (2.6%).

Dosing and Administration: Reslizumab is available as a 100 mg/mL 10 mL vial and has a suggested wholesale price of $1000 per vial.[9] The recommended dose of reslizumab is 3 mg/kg which is mixed in 50 mL of 0.9% sodium chloride and infused over 20 to 50 minutes every 4 weeks. There is no dosage adjustment for reduced renal or hepatic function. There have been no studies to determine compatibility with other IV drugs, and thus, reslizumab should be administered separately. After receiving a dose of reslizumab, patients should be monitored by a healthcare professional for an appropriate period of time for signs and symptoms of anaphylaxis.

Role in Therapy: Reslizumab is indicated as add-on maintenance treatment for patients with an eosinophilic phenotype, severe asthma who are 18 years and older.[4] It is not indicated for other eosinophilic conditions or for the treatment of acute bronchospasms or status asthmaticus. Mepolizumab (Nucala®), a monoclonal antibody which is FDA-approved for patients 12 years and older for similar indications as reslizumab, is on the CCHS Adult Formulary restricted to Allergy and Clinical Immunology and Pulmonary Medicine for outpatient use.[10] Reslizumab offers another treatment option for patients who could benefit from an anti-asthmatic monoclonal antibody.

Formulary Status: Reslizumab was recently added to the CCHS Adult Formulary restricted to the Departments of Allergy and Clinical Immunology and Pulmonary Medicine for outpatient use only.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Dornase Alfa (Pulmozyme®)	Mucolytic Agent	Management of CF Intrapleural use in combination with alteplase to treat pleural infections	Restricted to the Department of Pulmonary and Critical Care Medicine for management of CF Restricted to the Department of Pulmonary and Critical Care Medicine and Cardiothoracic Surgery for intrapleural use in combination with alteplase to treat pleural infections
Filgrastim-sndz (Zarxio®)	Colony Stimulating Factor	Mobilization of peripheral blood hematopoietic stem cells in bone marrow transplant patients	Restricted to the Department of Bone Marrow Transplant as continuation of home therapy for mobilization of peripheral blood hematopoietic stem cells in patients whose insurance mandates the use of Zarxio® as an outpatient
Levonorgestrel-releasing intrauterine system (Kyleena®)	Contraceptive	Contraception	Restricted to outpatient use only
Pancreatic Enzymes (Pertzye®) (Zenpep®)	Enzyme	Pancreatic insufficiency due to CF	Restricted to the Department of Pulmonary and Critical Care Medicine for the management of CF **Note:** The therapeutic interchange for enteric-coated pancreatic enzymes to Creon® and non-enteric coated pancreatic enzymes to Viokace® still applies to all non-CF patients.
Reslizumab (Cinqair®)	Monoclonal Antibody	Asthma	Restricted to the Departments of Allergy and Clinical Immunology and Pulmonary Medicine for outpatient use only

CF=Cystic fibrosis

Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Tenofovir alafenamide fumarate (Vemlidy®)	Antihepadnaviral Reverse Transcriptase Inhibitor	Chronic hepatitis B	Restricted to Hepatology, Transplant, and Infectious Diseases for initiation of therapy No restrictions for continuation of home therapy
Ulipristal (ella®)	Contraceptive	Emergency contraception	Ulipristal will be available to sexual assault nurse examiner coordinators and outpatient clinics
Ustekinumab (Stelara®)	Monoclonal Antibody	Moderate-to-severe Crohn's disease	Restricted to the Department of Gastroenterology for outpatient use only **Note:** Only the ustekinumab **IV infusion** will be on formulary. The subcutaneous syringes for home use will be non-formulary.

IV=Intravenous

Change to Restrictions of Medication on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Change in Restriction**
Ketamine (Ketalar®)	General Anesthetic	Severe agitation Analgesia	Restricted to Emergency Medicine Staff Physicians per guidelines/protocol for severe agitation Restricted to Emergency Medicine Staff Physicians per guidelines/protocol for sub-dissociative dosing for analgesia

Removals from the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/ Comments**
Evomela® (Melphalan)	Antineoplastic Agent	Multiple myeloma	Reason for removal: Evomela®, the CASI Pharmaceutical brand of melphalan, will be removed from formulary and will be replaced by standard melphalan which is: • Equally cost effective • May be used in pediatrics and for intraocular indications (unlike Evomela®)
Rho (d) immune globulin liquid (WinRho® SDF)	Immune Globulin	ITP	Reason for removal: Rhophylac® which is currently on formulary for Rho(d) negative pregnant patients and incompatible transfusions will also be used for ITP thus allowing for a single Rho(d) immune globulin product to be on formulary. **Note:** WinRho® is still available for Pediatrics.
Risperidone long-acting injection (Risperdal Consta®)	Atypical Antipsychotic	Bipolar Disorder Schizophrenia	Reason for removal: More cost effective alternatives are available.

ITP=Immune thrombocytopenic purpura

Therapeutic Interchanges on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Therapeutic Interchange**
Calcium and/or Vitamin D products	Dietary Supplements	Mineral replacement Dietary Supplement	Pharmacy will carry: 1) Calcium oral 500 mg tablet 2) Calcium chewable 500 mg tablet 3) Calcium plus Vitamin D (500 mg-200 units) tablet 4) Calcium Oral 500 mg/5 mL suspension 5) Calcium citrate 950 mg tablet 6) Vitamin D3 tablet (400-, 1000- , 5000-unit) 7) Vitamin D3 400 units/mL oral drops 8) Vitamin D2 8000 units/mL oral liquid 9) Vitamin D2 50,000 unit capsule Pharmacists will be allowed to automatically interchange patients' home calcium and vitamin D supplements with the closest formulation stocked on the formulary. Reason for Interchange: Standardization of calcium and vitamin D supplements/cost effectiveness **Note:** Calcium gluconate, calcium lactate, and calcium glubionate will not be stocked in inpatient pharmacies due to low usage. If patients have their own medication from home, they may continue to use it per policy.
Dicyclomine Injection (Bentyl®)	Anticholinergic Agent	Gastrointestinal motility disorders/ Irritable bowel	Dicyclomine injection will be automatically converted to: Hyoscyamine sublingual (Levsin®SL); Dicyclomine 10 mg IM converted to: Hyoscyamine 0.125 mg SL Dicyclomine 20 mg IM converted to: Hyoscyamine 0.25 mg SL Reason for interchange: Cost saving initiative

IM=Intramuscular SL=Sublingual

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Dornase Alfa (Pulmozyme®)	Mucolytic Agent	Management of CF	Restricted to the Department of Pediatric Pulmonology for the management of CF
Nusinersen (Spinraza®)	Antisense Oligonucleotide	Treatment of spinal muscular atrophy	Restricted to the Department of Pediatric Neurology Staff Physicians in patients with genetically confirmed spinal muscular atrophy for outpatient use only **Note:** Insurance coverage must be confirmed.
Olaratumab (Lartruvo™)	Monoclonal Antibody	Soft tissue sarcoma	Restricted to the Department of Pediatric Hematology/ Oncology for outpatient use only in patients ≥ 18 years old
Pancreatic Enzymes (Pertzye®) (Zenpep®)	Enzyme	Pancreatic insufficiency due to CF	Restricted for CF patients for continuation of therapy from home **Note:** The therapeutic interchange for enteric-coated pancreatic enzymes to Creon® and non-enteric coated pancreatic enzymes to Viokace® still applies to all non-CF patients.
Ustekinumab (Stelara®)	Monoclonal Antibody	Moderate-to-severe Crohn's disease	Restricted to the Department of Pediatric Gastroenterology for outpatient use only in patients age ≥ 18 years old with moderate to severe Crohn's disease that have failed therapy with at least one TNF blocker **Note:** Only the ustekinumab **IV infusion** will be on formulary. The subcutaneous syringes for home use will be non-formulary.

CF=Cystic fibrosis IV=Intravenous TNF=Tumor necrosis factor

Therapeutic Interchanges and Change of Formulary Product on Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Calcium and/or Vitamin D products	Dietary Supplements	Mineral replacement Dietary Supplement	Pharmacy will carry: 1) Calcium oral 500 mg tablet 2) Calcium chewable 500 mg tablet 3) Calcium plus Vitamin D (500 mg-200 units) tablet 4) Calcium Oral 500 mg/5 mL suspension 5) Calcium citrate 950 mg tablet 6) Vitamin D3 tablet (400-, 1000- , 5000-unit) 7) Vitamin D3 400 units/mL oral drops 8) Vitamin D2 8000 units/mL oral liquid 9) Vitamin D2 50,000 unit capsule Pharmacists will be allowed to automatically interchange patients' home calcium and vitamin D supplements with the closest formulation stocked on the CCHS Formulary. Reason for Interchange: Standardization of calcium and vitamin D supplements/cost effectiveness **Note:** Calcium gluconate, calcium lactate, and calcium glubionate will not be stocked in inpatient pharmacies due to low usage. If patients have their own medication from home, they may continue to use it per policy.
Dicyclomine Injection (Bentyl®)	Anticholinergic Agent	Gastrointestinal motility disorders/ Irritable bowel	Dicyclomine injection will be automatically converted to: Hyoscyamine sublingual (Levsin®SL); Dicyclomine 10 mg IM converted to: Hyoscyamine 0.125 mg SL Dicyclomine 20 mg IM converted to: Hyoscyamine 0.25 mg SL Reason for interchange: Cost saving initiative
Kinrix® (DTaP/IPV)	Vaccine	Immunization against Diphtheria/Tetanus/ Pertussis/Polio	Quadracel® will be the formulary product instead of Kinrix®. Reason: Cost savings initiative

DTaP/IPV=Diphtheria/tetanus/acellular pertussis/inactivated polio vaccine IM=Intramuscular SL=Sublingual