In This Issue

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From the Department of Pharmacy

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Rivaroxaban in Peripheral Artery Disease Post-Revascularization

By: Ariel Hecke, Pharm.D.

Background: Approximately 8 million individuals in the U.S. over the age of 40 have peripheral artery disease (PAD).[1] Lower extremity PAD, a narrowing of the vessels in the legs due to plaque buildup, is the third leading cause of atherosclerotic cardiovascular morbidity.[2] While PAD can be asymptomatic, upwards of 20% of people with PAD experience intermittent claudication. Serious consequences of PAD include ischemic events in the extremities leading to necrosis, gangrene, and limb loss. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial found that rivaroxaban (Xarelto®; Janssen Pharmaceutical) combined wth aspirin reduced the composite cardiovascular endpoint of stroke, myocardial infarction (MI) and death.[3] This resulted in the approval of rivaroxaban by the Food and Drug Administration in March 2017 for the indication of reducing the risk of major cardiac events in patients with chronic coronary artery disease (CAD) or PAD. A subgroup analysis of COMPASS found that rivaroxaban with aspirin lowered the incidence of major adverse limb events, including severe limb ischemia requiring intervention or amputation.[4] This led investigators to develop the Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) study, which sought to determine the benefits of rivaroxaban plus aspirin in patients with PAD undergoing revascularization surgery.[5]

Mechanism of Action: Rivaroxaban is a selective inhibitor of factor Xa (FXa) in both the intrinsic and extrinsic pathways of the coagulation cascade.[6] Inhibition of FXa prevents the formation of fibrin, ultimately preventing clot formation. By inhibiting FXa, rivaroxaban reduces the formation of thrombin

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Teprotumumab-trbw for Thyroid Eye Disease

By: Colleen Hutchinson, Pharm.D.

Background: Teprotumumab-trbw (Tepezza™; Horizon Therapeutics) is approved by the Food and Drug Administration for the treatment of thyroid eye disease (TED) in adults.[1] Thyroid eye disease is characterized by an active, inflammatory stage that develops over 1 to 2 years into an inactive, fibrotic stage.[2] It is a vision-threatening disorder most commonly associated with Graves' disease.[3] Early signs of TED include mild orbital soft tissue inflammation and ocular symptoms of foreign body sensation, excessive tearing, eye redness and swelling, blurred vision, and retro-orbital pain.[2] Enlargement of the orbital soft tissue as a result of progressive inflammation can lead to orbital and eventually optic nerve compression.[2,3] Current TED therapies include the achievement of euthyroidism (through the use of antithyroid medications or radioactive iodine), corticosteroids, and possibly thyroidectomy.[4] Mild disease may be managed symptomatically with lubricating eye drops or ophthalmic ointment.[2] Severe disease, in-

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(factor III) via positive feedback, thereby inhibiting thrombin-induced platelet activation.

Key Clinical Trial: The VOYAGER PAD study was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of rivaroxaban compared to placebo in patients with PAD that had undergone lower-limb revascularization.[5] Patients were randomized in a 1:1 fashion to receive twice-daily rivaroxaban 2.5 mg tablets (n=3286) or placebo (n=3278). Both study arms received 100 mg of aspirin taken once daily. The study included patients at least 50 years old with known symptomatic PAD that have undergone successful revascularization surgery within 10 days before randomization. Hemodynamically unstable patients taking prohibited medications such as antiplatelets (e.g., clopidogrel) were excluded. The primary efficacy endpoint was a composite of cardiovascular outcomes, including major amputation due to vascular causes, acute limb ischemia, MI, ischemic stroke, and death. The primary safety endpoint was major bleeding per the Thrombolysis in Myocardial Infarction (TIMI) classification. The primary efficacy endpoint occurred in 15.5% of patients in the rivaroxaban group compared to 17.8% in the placebo group; Kaplan-Meier estimates indicated that the incidence of this endpoint at 3 years would be 17.3% for the rivaroxaban group vs. 19.9% for the placebo group (HR: 0.85, 95% CI: 0.76 to 0.96; P=0.009). There was no difference regarding all-cause mortality between groups (HR: 1.08, 95% CI: 0.92 to 1.27; P=0.34). The primary safety endpoint of major bleed per TIMI criteria occurred in 62 patients enrolled in the rivaroxaban group compared to 44 in the placebo group (HR: 1.43; P=0.07). The authors estimated that if 10,000 patients were treated with 2.5 mg of rivaroxaban with aspirin over 1 year, this therapy would prevent the composite primary efficacy endpoint from occurring in approximately 181 patients; however, 29 patients would experience the primary safety endpoint of a major bleed. Based on the results of this study, the authors concluded that in PAD patients who had undergone revascularization, those who received rivaroxaban 2.5 mg twice daily with low-dose aspirin daily achieved a more favorable reduction in the composite primary cardiovascular endpoint without a significant increase in major bleeding compared to those who received aspirin alone.

Safety: Overall, the number of adverse events in the VOYAGER PAD trial was similar between the rivaroxaban and placebo groups.[5] No statistical difference was seen concerning the primary safety outcome of major bleed per TIMI criteria between the rivaroxaban and placebo groups, 1.9% vs. 1.35%, respectively (p=0.07). However, there was a difference noted in the secondary safety outcome of major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria 4.3% vs. 3.08% in the rivaroxaban and placebo groups, respectfully (p=0.007).

Dosing and Administration: The recommended dose of rivaroxaban for PAD is 2.5 mg twice daily in combination with once-daily 81 mg aspirin.[6] While the manufacturer does not have a recommendation for dose adjustment for end-stage renal disease, it is important to note that trials evaluating rivaroxaban for PAD excluded patients with an estimated glomerular filtration rate (eGFR) <15 mL/min. Rivaroxaban is not dialyzable and should not be used in patients requiring hemodialysis.

Availability and Cost: Rivaroxaban is available as 2.5 mg, 5 mg, 10 mg, 15 mg, and 20 mg oral tablets.[7] The average wholesale price for the 2.5 mg tablets is $9.40 per tablet.

Formulary Status: Rivaroxaban is on the CCHS Adult Formulary with no current restrictions and is on the CCHS Pediatric Formulary restricted to initiation of therapy by the Department of Pediatric Hematology/Oncology for the treatment of active venous thromboembolism after initial treatment with heparin or enoxaparin. It is also restricted to patients who can swallow solid dosage forms. Continuation of therapy for pediatric patients is not restricted.

References:

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cluding worsening orbital congestion and severe proptosis, requires rescue therapy with intravenous (IV) glucocorticoids and/or surgical orbital decompression.

Mechanism of Action: Teprotumumab binds to insulin-like growth factor-1 receptor (IGF-1R) and inhibits its activation and signaling.[1] The IGF-1R expression is increased in TED orbital fibroblasts (TED-OFs), inducing the production of interleukin-16 (IL-16) and chemokine (C-C motif) ligand 5 (CCL5).[3] Graves' Disease-immunoglobulins (GD-IgGs) displace growth factor-1 (IGF1) from its binding site on the surface of OFs. When IGF-1R function is interrupted, the GD-IgG-induced activation of TED-OFs is reduced.

Key Clinical Trials: The safety and efficacy of teprotumumab for TED treatment was evaluated in two randomized, double-blind, multicenter trials.[5-6] Smith and colleagues randomized a total of 88 patients to receive teprotumumab infusions every 3 weeks, with an initial dose of 10 mg/kg for the first infusion, then 20 mg/kg for the seven additional infusions or placebo.[5] The primary outcome was a reduction of ≥2 points in the Clinical Activity Score (CAS), a tool used to assess the activity level of TED, and a decrease of ≥2 mm in proptosis in the study eye. Key secondary outcomes included proptosis and quality of life (QOL) determinations using the Graves' Ophthalmopathy-Quality of Life (GO-QOL) assessment. Teprotumumab was found to confer a statistically significant improvement in response in the study eye at week 24 (OR 8.86, P<0.001). The decrease in proptosis from baseline was considerably greater in those receiving teprotumumab at weeks 6, 12, 18, and 24 compared to those that received placebo (P<0.001). Douglas and colleagues randomized a total of 83 patients to receive IV teprotumumab or placebo every 3 weeks.[6] The first dose of teprotumumab was 10 mg/kg, followed by 20 mg/kg for seven additional infusions. The primary outcome was proptosis response (decrease in proptosis of ≥2 mm from baseline in the study eye without an increase of ≥2 mm in the other eye). Key secondary outcomes included response to treatment, defined as a reduction of ≥2 points in CAS plus a decrease in proptosis of ≥2 mm at week 24, CAS of 0 or 1 at week 24, average change in proptosis, and change in score on GO-QOL assessment. Patients in the teprotumumab arm had a more favorable proptosis response vs. patients in the placebo arm (P<0.001). The average change from baseline in proptosis in subjects in teprotumumab group was -2.82 mm ± 0.19 vs. -0.54 mm ± 0.19 in placebo group (95% CI: -2.77 to 1.80; P<0.001). A total of 59% of patients in the teprotumumab arm had a CAS of 0 or 1 at week 24 vs. 21% of patients in the placebo arm (95% CI:17 to 55;P< 0.001). Authors of both trials concluded that among patients with active TED, teprotumumab resulted in better outcomes in reducing proptosis and improving QOL.[5-6]

Safety: Overall, teprotumumab was well-tolerated. Frequently reported adverse effects in patients receiving teprotumumab in clinical trials were muscle spasms (25%), nausea (17%), and hyperglycemia (10%).[1] The package insert lists the following warnings and precautions: infusion-related reactions, exacerbation of pre-existing inflammatory bowel disease, and hyperglycemia.

Dosing and Administration: The labeled dosage of teprotumumab is 10 mg/kg intravenously for one dose, followed by 20 mg/kg IV every 3 weeks for an additional seven doses.[1] There are no dosage adjustments recommended in geriatric patients or in patients with renal impairment. Teprotumumab has not been studied in patients with hepatic impairment or in pediatric patients.

Availability and Cost: Teprotumumab is supplied as a 500 mg single-dose vial for reconstitution.[1] The average wholesale cost of one vial is $17,880. [7]

Formulary Status: Teprotumumab is on the CCHS Adult Formulary restricted to the Departments of Endocrinology and Ophthalmology for outpatient use only.

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5. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Daily RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017;376:1748-61.
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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bempedoic acid (Nexletol®)	ACL Inhibitor	Heterozygous Familial Hypercholesterolemia LDL-C reduction in patients with established ACD	No restrictions
Burosumab-twza (Crysivta®)	Monoclonal Antibody	XLH	Restricted to Clinical Geneticists, Nephrology, and Endocrinology for outpatient use only for the treatment of XLH
Canagliflozin (Invokana®)	Antidiabetic Agent	T2DM T2DM with CV disease	Added to CCHS Formulary due to new FDA-approved indication to reduce the risk of CV death in patients with T2DM and CV disease No restrictions*
Dapagliflozin (Farxiga®)	Antidiabetic Agent	T2DM HF with reduced HFrEF	Added to CCHS Formulary due to new FDA-approved indication for reduction in CV death or worsening of HF in adults with reduced HFrEF independent of the presence of T2DM No restrictions*
Eptinezumab-jjmr (Vyepti®)	CGRP Antagonist	Prevention of Migraines	Restricted to the Department of Neurology for outpatient use only
Sacituzumab Govitecan-hziy (Trodelvy™)	Antineoplastic Agent	mTNBC	Restricted to the Department of Hematology and Oncology for outpatient use only for patients with mTNBC who have received at least two prior therapies
Stiripentol (Diacomit®)	Antiepileptic	Dravet Syndrome	Restricted to the Department of Epilepsy for initiation of adjunctive therapy in patients diagnosed with Dravet Syndrome on stable doses of clobazam or valproic acid experiencing frequent seizures or status epilepticus No restrictions for continuation of therapy
Teprotumumab-trbw (Tepezza™)	Monoclonal Antibody	TED	Restricted to the Departments of Endocrinology and Ophthalmology for outpatient use only

ACL=Adenosine triphosphate-citrate lyase LDL-C=Low density lipoprotein-cholesterol ACD=Atherosclerotic cardiovascular disease
XLH=X-linked hypophosphatemia T2DM=Type 2 diabetes mellitus CV=Cardiovascular FDA=Food and Drug Administration
HF=Heart failure HFrEF=Heart failure with reduced ejection fraction CGRP=Calcitonin gene-related peptide
mTNBC=Metastatic triple negative breast cancer TED=Thyroid eye disease

*The existing therapeutic interchange for SGLT-2 inhibitors to empagliflozin (Jardiance®) will be removed. Empagliflozin will remain on the formulary.

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
C1 esterase inhibitor (C1-INH; Cinryze®)	Blood Product Derivative	HAE ACE-inhibitor-induced Angioedema Alteplase-associated Angioedema	Modified restrictions to include the treatment of alteplase-associated angioedema
Clobazam (Onfi®)	Antiepileptic	Lennox-Gastaut Refractory Seizures	Modified restrictions to the Departments of Epilepsy and Neurology for initiation of therapy. No restrictions for continuation of therapy
Factor VIIa, Recombinant (NovoSeven®)	Blood Factor	Congenital/Acquired Hemophilia Congenital Factor VII Deficiency Intracranial Hemorrhage	Modified restrictions to remove Medical Staff from Liver Transplant Team from the CCHS Formulary restrictions for NovoSeven®
Intravenous Immunoglobulin (IVIG; Gammagard®)	Blood Derivative	Various Indications	Modified restrictions to include: Department of Dermatology for bullous pemphigoid, pemphigus vulgaris, and TEN Department of Rheumatology for polymyositis Department of Hematology and Vascular Medicine for HIT Department of Hematology for the treatment of AIHA, drug-induced thrombocytopenia, and CAS
Intravenous Levetiractam (Keppra®)	Antiepileptic	Acute Seizures Status Epilepticus	All restrictions removed

HAE=Hereditary angioedema ACE=Angiotensin-converting enzyme TEN=Toxic epidermal necrolysis
HIT=Heparin-induced thrombocytopenia AIHA=Autoimmune hemolytic anemia CAS=Catastrophic antiphospholipid syndrome

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Rituximab (Rituxan®)	Monoclonal Antibody	Various Indications	Modified restrictions to include: Department of Nephrology for the treatment of membranous nephropathy in the outpatient setting only Rituximab is NOT approved for the treatment of interstitial lung disease in the inpatient setting
Valganciclovir (Valcyte®)	Antiviral Agent	CMV Treatment and Prophylaxis	All restrictions removed

CMV=Cytomegalovirus

Product Standardization and Process Change to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Multivitamin Tablets	Vitamin	Various Indications	As part of the standardization process CCHS sites will carry Thera-M-Plus® as the standard vitamin and mineral tablet preparation
Intravenous Levetiracetam (Keppra®)	Antiepileptic Agent	Seizures	IV levetiracetam was added to the CCHS dose/vial rounding program. Loading doses of IV levetiracetam will be rounded to the nearest 100 mg Note: Maximum dose of IV levetiracetam is 4500 mg

IV=Intravenous

Denials and Removals to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale**
Icatibant (Firazyr®)	Selective Bradykinin B_2 Receptor Antagonist	Alteplase-induced Angioedema	It was recommended not to add icatibant to the CCHS Formulary since C1-INH (Cinrize®) is currently on the CCHS Formulary for treatment of alteplase-induced angioedema
Intravenous Cetirizine (Quzyttir™)	Histamine H_1 Antagonist	Acute Urticara	It was recommended not to add IV cetirizine to the CCHS Formulary since it is non-inferior in efficacy and much more costly than IV diphenhydramine
Isatuximab-irfc (Sarclisa®)	Monoclonal Antibody	Multiple Myeloma	It was recommended not to add to the CCHS Formulary due to its significant cost and lack of a clear place in therapy compared with daratumumab
Triamcinolone acetonide extended-release injectable suspension (Zilretta®)	Corticosteroid	Osteoarthritis	It is recommended not to add to the CCHS Formulary due to increased cost and lack of evidence of additional benefit compared with the immediate-release corticosteroid injections
Adefovir (Hepsera®)	Antihepanaviral	Chronic Hepatitis B	Removed from CCHS Formulary due to lack of use in the inpatient setting
Famciclovir (Famvir®)	Antiviral Agent	Herpes Simplex Herpes Zoster	Removed from CCHS Formulary due to lack of use in the inpatient setting

C1-INH=C1-esterase inhibitor IV=Intravenous

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Burosumab-twza (Crysvita®)	Monoclonal Antibody	XLH	Restricted to Clinical Geneticists, Nephrology, and Endocrinology for outpatient use only for the treatment of XLH
Rivaroxaban (Xarelto®)	Direct Factor Xa Inhibitor	Treatment of acute VTE	Restricted as follows: 1) Initiation of therapy is restricted to the Department of Pediatric Hematology/Oncology for treatment of VTE after initial treatment with heparin or enoxaparin 2) Use is restricted to patients who can swallow solid dosage forms* Continuation of therapy is not restricted
Stiripentol (Diacomit®)	Antiepileptic Agent	Dravet Syndrome	Restricted to the Departments of Pediatric Epilepsy and Pediatric Neurology for initiation of adjunctive therapy in patients diagnosed with Dravet Syndrome on stable doses of clobazam or valproic acid experiencing frequent seizures or status epilepticus. Continuation of home therapy is not restricted

XLH=X-linked hypophosphatemia VTE=Venous thromboembolism
*Note: Only rivaroxaban tablets are currently available. An oral suspension is anticipated to become commercially available.

Denial to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Intravenous Cetirizine (Quzyttir™)	Histamine H_1 Antagonist	Acute Urticara	It was recommended not to add IV cetirizine to the CCHS Formulary since it is non-inferior in efficacy and much more costly than IV diphenhydramine

IV=Intravenous

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Antithrombin III (Thrombate III®)	Blood Derivative	Congenital Antithrombin III Deficiency	Modified restrictions to include PICU Intensivists and to add requirement that an antithrombin III level must be obtained prior to administration. Levels <80% are appropriate for dosing antithrombin III
Clobazam (Onfi®)	Antiepileptic	Lennox-Gastaut Refractory Seizures	Modified restrictions to the Departments of Epilepsy and Neurology for initiation of therapy. No restrictions for continuation of therapy.
Stiripentol (Diacomit®)	Antiepileptic Agent	Dravet Syndrome	Restricted to the Departments of Pediatric Epilepsy and Pediatric Neurology for initiation of adjunctive therapy in patients diagnosed with Dravet Syndrome on stable doses of clobazam or valproic acid experiencing frequent seizures or status epilepticus. Continuation of home therapy is not restricted
Hypertonic Saline Solution 2% and 3%	Electrolyte Solution	Hyponatremia	Restricted to use in ICUs only (Emergency Departments and Operating Rooms are considered ICUs) Note: Guidelines for the use of hypertonic saline solutions in pediatrics are pending.
Intravenous Immunoglobulin (IVIG; Gammagard®)	Blood Derivative	Various Indications	Modified indications to include neonatal hyperbilirubinemia secondary to Rh/ABO hemolytic disease

PICU=Pediatric intensive care unit ICU=Intensive care unit Rh=Rheus

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Palifermin (Kepivance®)	Chemoprotective Agent	Oral Mucositis	Modified restrictions as follows: Restricted to the Department of Pediatric Hematology/ Oncology and Bone Marrow Transplant for prevention of grade 3 or 4 mucositis following chemotherapy. 1. For non-hematopoietic stem cell transplant patients, palifermin use is restricted to outpatient use only 2. For BMT patients, palifermin may be administered in both the inpatient and outpatient settings 3. A Pediatric Hematology/ Oncology Pharmacist must be involved with the approval to administer palifermin
Total Parenteral Nutrition	Parenteral Nutrition	Various Indications	Modified restrictions as follows: Initiation, continuation, and discontinuation are restricted as follows: 1. At Main Campus pediatric total parenteral nutrition must be ordered by PICU staff, NICU staff, NICU APPs, Pediatric Gastroenterology Staff, and Pediatric Gastroenterology Fellows 2. At CCCHR, Fairview, and Hillcrest pediatric total parenteral nutrition must be ordered by a hospitalist or NICU APPs 3. Refer to Inpatient Parenteral Nutrition Administration SOP on PPM

BMT=Bone marrow transplant PICU=Pediatric intensive care unit NICU=Neonatal intensive care unit
APP=Advanced practice provider CCCHR=Cleveland Clinic Children's Hospital for Rehabilitation
SOP=Standard operating procedure PPM=Policy and Procedure Manager