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New Drugs 2019 PART 4

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Abstract: This article reviews nine drugs recently approved by the FDA, including indications, precautions, adverse reactions, and nursing considerations.

Keywords: andexanet alfa, avatrombopag maleate, coagulation factor Xa (recombinant) inactivated-zhzo, eravacycline dihydrochloride, fostamatinib disodium hexahydrate, inotersen sodium, lusutrombopag, moxidectin, patisiran, plazomicin

THIS ARTICLE reviews nine recently marketed drugs, including:

- three new drugs to treat thrombocytopenia in select patients.
- the first drug that rapidly reverses the anticoagulant action of the factor Xa inhibitors rivaroxaban and apixaban.
- two antibacterial drugs indicated for certain complicated infections.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the prescribing information, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions for all these drugs.

SELECTED REFERENCES

Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, Inc.; 2019.

Nursing2020 Drug Handbook. Philadelphia, PA: Wolters Kluwer; 2019.

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EPIC CREATIONS / SHUTTERSTOCK

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Thromobocytopenia, or low platelet count, can be a complication of many disorders. In 2018, three new drugs were marketed to treat thrombocytopenia related to specific causes. Fostamatinib disodium hexahydrate is indicated for patients with chronic immune thrombocytopenia (ITP; formerly known as immune or idiopathic thrombocytopenic purpura), which is characterized by dysfunction of the immune system that destroys platelets. Avatrombopag maleate and lusutrombopag were approved to treat thrombocytopenia in patients with chronic liver disease (CLD). In June 2019, the indication for avatrombopag was expanded to include patients with chronic ITP who have not responded adequately to prior therapy. The three drugs are described separately in the following discussions.

Fostamatinib disodium hexahydrate

First drug with activity against spleen tyrosine kinase

Patients with chronic ITP are at increased risk for serious bleeding and resultant complications. Corticosteroids, I.V. immunoglobulin, and splenectomy are often initial treatments for ITP. In patients who have an insufficient response to these treatments, a thrombopoietin (TPO) receptor agonist (eltrombopag or romiplostim) may be prescribed to increase platelet production. Other treatment options include the anti-CD20 monoclonal antibody rituximab, the pituitary gonadotropin inhibitor danazol, and immunosuppressants such as azathioprine.

Spleen tyrosine kinase (SYK) has an important role in the underlying autoimmune cause of ITP. Fostamatinib disodium hexahydrate (*Tavalisse*, Rigel) is a phosphate prodrug that, following oral administration, is converted in the gastrointestinal (GI) tract to its active metabolite, R406. Classified as a tyrosine kinase inhibitor, it is the first drug with activity against SYK. By inhibiting SYK, it reduces antibody-mediated destruction of platelets. Fostamatinib is specifically indicated for treatment of thrombocytopenia in adult patients with chronic ITP who have not responded adequately to a previous treatment.[1]

The effectiveness of fostamatinib was demonstrated in two placebo-controlled studies in patients who had an insufficient response to at least one prior treatment (most often with corticosteroids, immunoglobulins, or TPO receptor agonists), and who were receiving stable concurrent ITP therapy. A stable platelet response was achieved in 17% of the patients treated with fostamatinib and 2% of those receiving placebo. Almost 50% of the patients treated with fostamatinib had been previously treated with a TPO receptor agonist and, of these patients, eight achieved a stable response with fostamatinib. Rescue treatment with corticosteroids, immunoglobulins, or platelet transfusions was required by 30% and 45% of the patients receiving fostamatinib and placebo, respectively. The incidence of bleeding was 29% in patients treated with the new drug and 37% in those receiving placebo.

Precautions: (1) Monitor BP every 2 weeks until stable, then monthly. Patients with preexisting hypertension may be more susceptible to elevations in BP. About 1% of patients in clinical trials experienced hypertensive crisis (systolic over 180 mm Hg and/or diastolic over 120 mm Hg). (2) Monitor liver function tests monthly during treatment. Elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been commonly reported. If ALT or AST increases to more than three times the upper limit of normal, the dosage of fostamatinib should be reduced or treatment should be interrupted or discontinued. (3) Monitor absolute neutrophil counts monthly. A few patients treated with fostamatinib have experienced neutropenia, including febrile neutropenia. (4) Tell women of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose. Women should also be advised to not breastfeed during treatment and for at least 1 month after the last dose. (5) The effectiveness and safety of fostamatinib in pediatric patients have not been established. It is not recommended for patients under age 18 because adverse events on actively growing bones were observed in nonclinical studies. (6) Exposure to R406 is increased by the concurrent use of a strong CYP3A4 inhibitor such as ketoconazole. Monitor patients taking a CYP3A4 inhibitor for increased frequency and severity of adverse reactions, which may require a reduction of the fostamatinib dosage. (7) Concurrent use of a strong CYP3A4 inducer such as rifampin reduces exposure to R406, and concurrent use is not recommended. Consult the prescribing information for warnings and recommendations about other potential drug interactions.

Adverse reactions: diarrhea, hypertension, nausea, dizziness, increased ALT, increased AST, respiratory infection, rash, abdominal pain, fatigue, chest pain, neutropenia

Supplied as: 100 mg and 150 mg tablets

Dosage: Initially, 100 mg twice a day. If the platelet count has not increased to at least 50 x 10^9/L after a month of treatment, the dosage should be increased to 150 mg twice a day. If a patient on this maximum recommended dosage experiences an adverse reaction, the dosage should be reduced to 100 mg twice a day initially. Consult the prescribing information for specific dosage modification recommendations for patients experiencing adverse reactions.

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Nursing considerations: (1) Fostamatinib may be taken without regard to food. (2) If the patient experiences diarrhea, the initiation of supportive measures (dietary changes, hydration, and/or antidiarrheal medications) soon after the onset of symptoms is usually effective. If diarrhea becomes severe, however, treatment should be interrupted, reduced, or discontinued. (3) Tell patients to store the medication at room temperature. The bottle contains two desiccant canisters that should not be removed.

REFERENCE

1. Tavalisse (fostamatinib disodium hexahydrate) tablets, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/209299lbl.pdf.

Avatrombopag maleate

Reducing bleeding risks in patients with CLD undergoing procedures

In patients with CLD, thrombocytopenia may be associated with multiple factors, including decreased production of TPO, the primary regulator of platelet production. TPO is produced in the liver and stimulates the production of platelets in the bone marrow. Liver damage experienced by most patients with CLD reduces TPO production and decreases platelet production, resulting in thrombocytopenia.

Most patients with CLD require one to three invasive diagnostic and therapeutic procedures per year, and thrombocytopenia increases their risk of severe bleeding.[1] Patients with significant thrombocytopenia have typically received platelet transfusions immediately before such procedures to increase platelet counts. However, transfusions are associated with a risk of infections and other potentially serious adverse reactions.

Classified as a TPO receptor agonist, avatrombopag maleate (*Doptelet*, Dova) is indicated to treat thrombocytopenia in adults with CLD who are scheduled to undergo a procedure and to treat thrombocytopenia in adults with chronic ITP who have had an insufficient response to a previous treatment.[2] FDA approval of avatrombopag was based on two placebo-controlled trials. Patients in the low baseline platelet count cohort (< 40 x 10^9/L) were treated with 60 mg once a day for 5 days. Patients in the high baseline platelet count cohort (40 to < 50 x 10^9/L) were treated with 40 mg once a day for 5 days. Patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk. The major efficacy outcome was the proportion of patients (responders) who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

At both dosage levels, a higher proportion of patients were responders with avatrombopag treatment compared with those receiving placebo. For patients in the low baseline platelet count cohort, 66% and 69% of those receiving the medication were responders in the two studies, compared with 23% and 35% of those receiving placebo. For patients in the high baseline platelet count cohort, 88% of those treated with avatrombopag were responders in each of the two studies, compared with 38% and 33% of those receiving placebo.

The safety and tolerability of avatrombopag for patients with ITP was supported by safety data on 128 patients with ITP and data from multiple clinical trials involving more than 1,000 patients treated in the avatrombopag clinical development program.[3]

For patients with CLD scheduled for a procedure, avatrombopag therapy should be initiated 10 to 13 days before the procedure, and patients should undergo their procedure within 5 to 8 days after the last dose of the 5-day course of treatment. Platelet counts should be determined before administration of avatrombopag and on the day of the procedure to ensure an adequate increase in platelet count.

Precautions: (1) TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic ITP or CLD, and one patient in the clinical studies experienced treatment-emergent portal vein thrombosis. Monitor platelet counts and be aware of the risk of thromboembolic events. (2) Avatrombopag may cause fetal harm if used in pregnant women and breastfeeding is not recommended during treatment and for 2 weeks after the last dose. (3) Dose adjustments are recommended for patients with chronic ITP taking moderate or strong dual CYP2C9 and CYP3A4 inducers or inhibitors.

Adverse reactions: *In patients with CLD:* pyrexia, abdominal pain, nausea, headache, fatigue, peripheral edema. *In patients with chronic ITP:* headache, fatigue, contusion, epistaxis, upper respiratory tract infection, arthralgia, gingival bleeding, petechiae, nasopharyngitis

Supplied as: 20 mg tablets

Dosage: *In patients with CLD scheduled for a procedure with a platelet count of less than 40 x 10^9/L:* 60 mg (3 tablets) with food once a day for 5 days. *In patients scheduled for a procedure with a platelet count of 40 to < 50 x 10^9/L:* 40 mg (2 tablets) with food once a day for 5 days. *In patients with chronic ITP:* 20 mg (one tablet) once daily; the dose or frequency of dosing may be adjusted based on patient response.

Nursing considerations: (1) Monitor platelet counts and assess patients for thromboembolic events. (2) Educate women of reproductive potential about the risk to a fetus and tell them to inform the healthcare provider of a known or suspected pregnancy. (3) Advise lactating women to interrupt breastfeeding and pump and discard

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breast milk during treatment and for at least 2 weeks after the last dose of avatrombopag to minimize exposure to a breastfed child. (4) Instruct patients to take each dose with food as prescribed.

REFERENCES

1. Dova Pharmaceuticals. Dova Pharmaceuticals announces US FDA approval of supplemental new drug application for Droptelet (avatrombopag) for treatment of immune thrombocytopenia (ITP). News release. June 27, 2019.

2. Doptelet (avatrombopag) tablets, for oral use. Prescribing information. https://dova.com/wp-content/uploads/2019/06/doptelet-prescribing-information.pdf.

3. FDA expands use of avatrombopag for adults with chronic immune thrombocytopenia. *Pharmacy Times*. June 27, 2019.

Lusutrombopag

Another option for patients with CLD

Also a TPO receptor agonist, lusutrombopag (*Mulpleta,* Shionogi) is currently indicated only to treat thrombocytopenia in adults with CLD who are scheduled to undergo a procedure.[1] Its effectiveness was evaluated in two placebo-controlled trials in patients with CLD who were undergoing an invasive procedure and who had a platelet count less than 50 x 10^9/L. Patients were treated with 3 mg once a day for up to 7 days. In the first study, the major efficacy outcome was the proportion of patients who required no platelet transfusion before the primary invasive procedure. In the second study, the major efficacy outcome was the proportion of patients who required no platelet transfusion before the primary invasive procedure and who required no rescue therapy for bleeding (such as platelet preparations or other blood preparations) from randomization through 7 days after the primary invasive procedure. Responders in both studies were defined as patients who had a platelet count of at least 50 x 10^9/L with an increase of at least 20 x 10^9/L from baseline. In both studies, a higher proportion of patients treated with lusutrombopag did not require a platelet transfusion and were responders compared with those receiving placebo.

Treatment with lusutrombopag should be initiated 8 to 14 days before a scheduled procedure and patients should undergo their procedure 2 to 8 days after the last dose. Platelet counts should be determined before administration of lusutrombopag and not more than 2 days before the procedure.

Precautions: (1) TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with CLD. In clinical studies, two patients treated with lusutrombopag and two patients receiving placebo experienced portal vein thrombosis. Monitor platelet counts and be aware of the risk of thromboembolic events. (2) Based on animal studies, lusutrombopag may cause fetal harm if used in pregnant women. (3) Because lusutrombopag is likely to be expressed in breast milk, breastfeeding is not recommended during treatment and for 28 days after the last dose.

Adverse reaction: headache

Supplied as: 3 mg tablets

Dosage: 3 mg once a day for 7 days

Nursing considerations: (1) Monitor platelet counts and assess patients for thromboembolic events. (2) A lactating woman should interrupt breastfeeding and pump and discard breast milk during treatment and for 28 days after the last dose. (3) Tell women of reproductive potential to inform the healthcare provider of known or suspected pregnancy. (4) Lusutrombopag may be taken without regard to food.

REFERENCE

1. Mulpleta (lusutrombopag tablets) for oral use. Prescribing information. www.shionogi.com/pdf/pi/wp-content/themes/pdfs/mulpleta.pdf.

DRUGS FOR AMYLOIDOSIS

Transthyretin (TTR), a protein primarily produced in the liver, transports vitamin A and thyroxine in the body. Hereditary transthyretin-mediated amyloidosis (hATTR), also called familial TTR amyloidosis, is a rare, debilitating, and often fatal genetic disease that affects about 50,000 people worldwide.[1,2] Patients with this disease have a mutation in the gene for TTR that results in the formation of defective and unstable proteins that can degrade to form smaller, "misfolded" proteins. Over time, these can form amyloid deposits, or plaques, in the organs and tissues. The abnormal amyloid protein deposits most often occur in the peripheral nervous system, which can result in a loss of sensation, pain, or mobility in the upper and lower extremities. Amyloid deposits can also affect the heart, kidneys, eyes, and GI tract. The disease often worsens rapidly and can result in premature death. Treatment options have primarily focused on symptom management.[2,3]

RNA carries instructions from DNA for controlling the synthesis of proteins. RNA interference (RNAi) is a process that occurs naturally within cells to block how certain genes are expressed. Dysfunction resulting from gene mutations is an important factor in the occurrence of disease. The development of oligonucleotides that work inside the cell at the RNA level has provided the ability to target specific RNA messages and the potential to design therapies for a wide range of diseases. Two new drugs indicated to treat the polyneuropathy of hATTR in adults are discussed separately in the following pages.

REFERENCES

1. US Food and Drug Administration. New class of drugs fulfills promise of RNA-based medicine. Spotlight on CDER Science. August 14, 2018.

2. US Food and Drug Administration. FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease. News release. August 10, 2018.

3. Ionis. Akcea and Ionis receive FDA approval of Tegsedi (inotersen) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. News release. October 5, 2018.

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Patisiran

First treatment for polyneuropathy caused by hATTR

Patisiran (*Onpattro*, Alnylam) is a double-stranded small interfering ribonucleic acid (siRNA) designed to interfere with RNA production of an abnormal form of TTR. It causes degradation, or "silencing," of mutant and wild-type TTR messenger RNA (mRNA) through RNAi, which reduces serum TTR protein and TTR protein deposits in tissues. Patisiran is formulated in a lipid nanoparticle complex that is administered by I.V. infusion for delivery to hepatocytes. It is the first siRNA therapy to be approved and the first treatment to be approved for patients with polyneuropathy caused by hATTR.[1]

The effectiveness of patisiran was evaluated in a placebo-controlled trial involving 225 patients. Those who received the new drug had better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes, and autonomic signs and symptoms (BP, heart rate, and digestion) compared with those receiving placebo infusions. Patients treated with patisiran also had better assessments of walking, nutritional status, and the ability to perform activities of daily living.

The lipid nanoparticle carrier molecule in which patisiran is formulated can trigger an infusion-related reaction (IRR) that includes flushing, dyspnea, nausea, and abdominal pain. All patients in the clinical trials were premedicated with a corticosteroid, acetaminophen, and both H1 and H2 histamine blockers. The frequency of IRRs decreased with continued treatment, but infusion interruption was necessary for 5% of patients. Treatment was permanently discontinued in less than 1% of patients. One patient in the expanded access program had a severe adverse reaction of hypotension and syncope during an infusion.

Adverse reactions: upper respiratory tract infections, IRRs

Precautions: (1) Because patisiran reduces serum concentrations of vitamin A, patients may experience vision changes including dry eyes, blurred vision, and floaters. Patients should receive supplementation at the recommended daily allowance of vitamin A, but higher dosages are not recommended to achieve normal serum vitamin A concentrations because serum concentrations do not reflect total body stores of vitamin A. Patients who experience ocular symptoms suggesting vitamin A deficiency such as night blindness should be referred to an ophthalmologist. (2) At least 60 minutes before starting the patisiran infusion, patients should be premedicated with an I.V. corticosteroid such as dexamethasone, oral acetaminophen, an I.V. H1 blocker such as diphenhydramine, and an I.V. H2 blocker such as ranitidine.

Supplied as: an opalescent, homogeneous solution provided in single-dose vials containing 10 mg of the drug in 5 mL

Dosage: *For patients weighing less than 100 kg:* 0.3 mg/kg once every 3 weeks via I.V. infusion. *For patients weighing 100 kg or more:* 30 mg once every 3 weeks via I.V. infusion.

Nursing considerations: (1) Store vials in a refrigerator. (2) The calculated dose of patisiran injection must be filtered and then diluted into an infusion bag containing 0.9% Sodium Chloride Injection for a total volume of 200 mL. The diluted solution should be infused I.V. via an ambulatory infusion pump over approximately 80 minutes. Consult the prescribing information for details on recommended procedures and infusion rates. (3) Closely monitor patients during and after the infusion for adverse reactions. (4) Teach patients to recognize signs and symptoms of IRR, such as flushing, dyspnea, chest pain, rash, tachycardia, and facial edema, and tell them to contact the healthcare provider immediately (or seek emergency treatment if appropriate) if they experience these signs and symptoms. (5) Inform patients about the risk of ocular adverse reactions related to vitamin A deficiency.

REFERENCE

1. Onpattro (patisiran) lipid complex injection, for intravenous use. Prescribing information. www.alnylam.com/wp-content/uploads/2018/08/ONPATTRO-Prescribing-Information.pdf.

Inotersen sodium

Second drug approved to treat the polyneuropathy of hATTR

Inotersen sodium (*Tegsedi*, Akcea; Ionis) is an antisense oligonucleotide inhibitor of TTR protein synthesis. By binding to TTR mRNA, it causes degradation of mutant and wild-type TTR mRNA, reducing serum TTR protein and TTR protein deposits in tissues. Following the approval of patisiran, it was the second drug to become available to treat the polyneuropathy of hATTR in adults.[1]

The effectiveness of inotersen was evaluated in a placebo-controlled trial involving 173 patients, 113 of whom were randomly assigned to receive a subcutaneous injection of the drug once per week for 65 weeks (three doses were administered during the first week of treatment). Inotersen demonstrated significant benefit compared with placebo in measures of neuropathy and quality of life and produced up to a 79% mean decrease from baseline in serum TTR protein.

Because of the risks associated with thrombocytopenia and glomerulonephritis (discussed below), inotersen is available only through a restricted FDA program.

Precautions: (1) Contraindicated in patients with a platelet count less than 100 x 10^9/L. Inotersen causes reductions in platelet counts that can lead to sudden, unpredictable,

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and potentially life-threatening hemorrhage. This risk is identified in a boxed warning in the labeling. In the clinical trial, one patient died from intracranial hemorrhage. Monitor platelet counts weekly if values are 75 x 10^9/L or greater, and more frequently if values are less than 75 x 10^9/L. (2) The risk of bleeding may be increased by the concurrent use of an antiplatelet or anticoagulant drug. (3) In the clinical trial, 23% of the patients treated with inotersen had at least one uninterpretable platelet count caused by platelet clumping. One of the possible explanations for platelet clumping is that it is caused by a reaction between antiplatelet antibodies and ethylenediaminetetraacetic acid (EDTA). If EDTA-mediated platelet clumping is suspected, a repeat platelet count should be performed using a different anticoagulant (such as sodium citrate or heparin) in the blood collection tube. (4) Contraindicated in patients with a history of a hypersensitivity reaction or acute glomerulonephritis caused by the drug. The latter, which may require immunosuppressive treatment and result in dialysis-dependent renal failure, is also the subject of a boxed warning in the labeling. Cases of glomerulonephritis were accompanied by nephrotic syndrome, which is characterized by edema, hypercoagulability with venous or arterial thrombosis, and increased susceptibility to infection. Before treatment starts, serum creatinine, estimated glomerular filtration rate (eGFR), and urine protein to creatinine ratio (UPCR) should be determined, and a urinalysis should be performed. Treatment should generally not be initiated in patients with a UPCR of 1,000 mg/g or higher. During treatment, serum creatinine, eGFR, urinalysis, and UPCR should be monitored every 2 weeks. The drug should not be given to patients who develop a UPCR of 1,000 mg/g or higher, or an eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause. (5) Other serious adverse reactions that have been reported with inotersen include stroke and cervicocephalic arterial dissection, other neurologic adverse events, and inflammatory and immune adverse events. Four percent of patients treated with the new drug in clinical studies discontinued treatment because of a hypersensitivity reaction that generally occurred within 2 hours of administration and was associated with the presence of antibodies to the drug. (6) Antisense oligonucleotides may accumulate in the liver and 8% of patients treated with inotersen had an increased ALT value of at least three times the upper limit of normal. ALT, AST, and total bilirubin should be monitored at baseline and every 4 months during treatment. (7) As with patisiran, inotersen may reduce serum vitamin A concentrations, and supplementation at the recommended daily allowance of vitamin A is advised.

Adverse reactions: injection site reactions, nausea, headache, fatigue, thrombocytopenia, fever

Supplied as: an aqueous solution for subcutaneous injection in single-dose syringes prefilled with 1.5 mL of solution containing 284 mg of inotersen

Dosage: 284 mg subcutaneously once a week on the same day every week

Nursing considerations: (1) Patients may self-administer this drug, but a healthcare professional's guidance is recommended for the first injection. Teach patients how to administer the drug correctly, based on the Instructions for Use provided in the product labeling. (2) Educate patients about possible adverse reactions that require immediate attention, including signs and symptoms of stroke or a hypersensitivity reaction. (3) Consult the prescribing information for the specific monitoring and treatment recommendations based on platelet counts, renal monitoring, and liver function tests. (4) Store syringes in the refrigerator.

REFERENCE

1. Tegsedi (inotersen) injection, for subcutaneous use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/211172lbl.pdf.

ANTHELMINTIC

Moxidectin

Preventing river blindness

Onchocerciasis, also known as river blindness, is caused by the parasitic worm *Onchocerca volvulus*.[1] It is transmitted to humans from bites of infected black flies that primarily breed in rivers. An estimated 200 million people, almost all of whom live in sub-Saharan Africa, are at risk for the disease. Adult parasites release larvae (microfilariae) that invade the skin and eyes where they can cause severe itching, disfiguring skin conditions, and visual impairment, including blindness. Ivermectin has been the standard of care in suppressing the microfilariae in the skin.

Moxidectin (Medicines Development for Global Health) is an anthelmintic drug with properties similar to those of ivermectin.[2] It is thought to bind to glutamate-gated chloride channels and is active against the microfilariae of *O. volvulus*, but does not kill the adult worms. It has a longer half-life and duration of action than ivermectin.

Moxidectin is indicated to treat onchocerciasis due to *O. volvulus* in patients age 12 and older. Its effectiveness was demonstrated in two active-controlled studies in which it was compared with ivermectin; both drugs were used as single-dose treatments. Moxidectin demonstrated statistically significant superiority in suppressing microfilariae in the skin. Twelve months following the single-dose treatment, skin microfilariae were

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undetectable in 46% of patients treated with moxidectin, compared with 5% of those treated with ivermectin.

Many of the adverse reactions experienced with moxidectin are due to allergic and inflammatory host responses to the death of microfilariae (Mazzotti reaction); these reactions appear to be more likely in patients with higher microfilarial burden. Antihistamines and/or analgesics may help relieve mild-to-moderate symptoms.

Precautions: (1) Patients may experience orthostatic hypotension, which is most likely to occur in the first 2 days following treatment and is usually transient. (2) Patients with hyperreactive onchodermatitis may be more likely to experience severe edema and worsening of onchodermatitis following administration of moxidectin. (3) Patients with onchocerciasis who are also infected with the nematode Loa loa may develop a serious or even fatal encephalopathy following treatment with moxidectin. The new agent has not been studied in patients coinfected with Loa loa. Screening for loiasis before treatment is recommended in patients who are candidates for treatment with moxidectin who have had exposure to Loa loa-endemic areas.

Adverse reactions: eosinophilia, pruritus, musculoskeletal pain, headache, lymphopenia, tachycardia, rash, abdominal pain, hypotension, pyrexia, leukocytosis, influenza-like illness, neutropenia, cough, lymph node pain, dizziness, diarrhea, hyponatremia, and peripheral edema

Supplied as: 2 mg tablets

Dosage: a single dose of 8 mg (4 tablets)

Nursing considerations: (1) Moxidectin may be taken without regard to food. (2) Tell patients that they are likely to have flulike signs and symptoms including malaise, myalgia, headache, tachycardia, hypotension, and pruritus during the first week after treatment. (3) Warn patients about the risk of orthostatic hypotension and advise them to lie down until symptoms resolve if they feel dizzy or lightheaded. (4) Educate patients about the risk of encephalopathy and instruct them to immediately report any signs and symptoms, such as tremor, seizures, or change in mental status.

REFERENCES

1. World Health Organization. Onchocerciasis (river blindness)—disease information. www.who.int/blindness/partnerships/onchocerciasis_disease_information/en.

2. Moxidectin tablets, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf.

REVERSAL DRUG

Coagulation factor Xa (recombinant), inactivated-zhzo

Rapidly reverses the anticoagulant effects of rivaroxaban and apixaban

Several orally administered anticoagulants are now widely used as alternatives to warfarin. These include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban. Bleeding, the most important risk associated with all anticoagulants, may be experienced even by some patients using an anticoagulant at the recommended dosage. Patients treated with an anticoagulant who experience accidental injuries or who require emergency surgery are at particular risk for severe bleeding that requires urgent intervention.

Vitamin K is the antidote for warfarin, and idarucizumab specifically reverses dabigatran's anticoagulant activity. Coagulation factor Xa (recombinant), inactivated-zhzo (*Andexxa*, Portola), also designated as andexanet alfa, is the first drug approved to reverse the action of anticoagulants that inhibit factor Xa. Andexanet alfa is indicated for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed to manage life-threatening or uncontrolled bleeding.[1]

As a modified form of human factor Xa, the new drug has been designed to bind to factor Xa inhibitors and rapidly reverse their anticoagulant action. When administered I.V., it acts as a decoy to which the factor Xa inhibitor anticoagulant preferentially binds, thereby preventing the anticoagulant from inhibiting factor Xa. Another observed procoagulant effect of andexanet alfa is its ability to bind to and inhibit the activity of tissue factor pathway inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor-initiated thrombin generation.

The new drug's effectiveness was evaluated in two placebo-controlled studies in healthy volunteers, in which individuals received apixaban in one study and rivaroxaban in the other. An initial I.V. bolus injection of andexanet alfa was followed by a continuous infusion for 120 minutes. The new product rapidly and significantly reversed antifactor Xa activity, with the median decrease in activity from baseline of 97% for rivaroxaban and 92% for apixaban. Thrombin generation was fully restored in almost all participants receiving the reversal agent. The antifactor Xa activity returned to placebo levels approximately 2 hours after completion of a bolus or continuous infusion.

No serious adverse reactions were reported with the use of andexanet alfa in healthy volunteers. However, patients treated with factor Xa inhibitor anticoagulants have underlying disease that predisposes them to thromboembolic events, so reversing the action of the anticoagulant exposes them to thrombotic risk. Some of the patients with bleeding events associated with the use of apixaban or rivaroxaban who were treated with andexanet alfa experienced arterial and venous thromboembolic events, myocardial infarction,

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ischemic stroke, and cardiac arrest, and more than 10% of the patients treated with the new drug died within 30 days following administration. These reactions are the subject of a boxed warning in the labeling for andexanet alfa.

Precautions: (1) Monitor patients for adverse reactions such as MI or stroke related to their underlying disease. To reduce the risk of thromboembolic adverse reactions, resume anticoagulant therapy as soon as medically appropriate following use of the reversal agent. (2) Reelevation or incomplete reversal of antifactor Xa activity may occur, leading to bleeding.

Adverse reactions: urinary tract infection, pneumonia, IRRs

Supplied as: single-use vials containing 100 mg or 200 mg of the drug

Dosage: Consult the prescribing information for two recommended dosage options that are based on the specific anticoagulant used (apixaban or rivaroxaban), the dose of the anticoagulant, and the time that has elapsed since the patient's last dose of anticoagulant.

Nursing considerations: (1) Store vials in a refrigerator. (2) Reconstitute the medication with Sterile Water for Injection. Consult the product labeling for specific recommendations for preparation and I.V. administration of the drug. (3) Closely monitor patients for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac events. Teach patients to recognize and immediately report signs and symptoms of serious adverse reactions, which may develop within 30 days of treatment.

REFERENCE

1. Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo) Lyophilized powder for solution for intravenous injection. Prescribing information. www.fda.gov/media/113279/download.

ANTIBACTERIAL DRUGS

Plazomicin

New treatment for complicated urinary tract infections

Complicated urinary tract infections (cUTI), including pyelonephritis, are usually caused by Gram-negative bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*. Although an oral fluoroquinolone such as ciprofloxacin or levofloxacin may effectively treat some of these infections, increasing bacterial resistance to the fluoroquinolones has been observed. Hospitalized patients with cUTI may be treated parenterally with a cephalosporin such as cefepime, a carbapenem such as meropenem, a fluoroquinolone, or a combination product such as piperacillin/tazobactam. However, the emergence of carbapenem-resistant Enterobacteriaceae and other resistant strains of these bacteria has created additional treatment challenges.

Plazomicin sulfate (*Zemdri,* Achaogen) is a semisynthetic aminoglycoside antibacterial drug with properties similar to those of gentamicin, tobramycin, and amikacin. Like these other aminoglycosides, it inhibits protein synthesis by binding to bacterial 30S ribosomal subunits and exhibits a bactericidal action. However, its action is not inhibited by most of the aminoglycoside-modifying enzymes that may result in resistance to other aminoglycosides, and cross-resistance is unlikely. Activity of plazomicin has also been demonstrated *in vitro* against extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and carbapenem-resistant Enterobacteriaceae.

Administered I.V., plazomicin is primarily active against Gram-negative aerobic bacteria. It is indicated in adults age 18 or older for treatment of cUTI, including pyelonephritis, caused by susceptible *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *Enterobacter cloacae*.

In a study of 609 hospitalized adults with cUTI, plazomicin administered I.V. once a day was compared with meropenem administered I.V. every 8 hours. At Day 5 of treatment, the rates of resolution or improvement of symptoms and microbiological eradication for plazomicin and meropenem were 88% and 91%, respectively. A test of cure (resolution of symptoms and microbiological eradication) visit was scheduled for at least 2 weeks following the first dose of treatment. These results for plazomicin and meropenem were 82% and 70%, respectively. Some of the patients who were effectively treated with plazomicin had cUTI that were caused by isolates of bacteria that were resistant to gentamicin and tobramycin.

Because plazomicin and the other aminoglycosides are more likely than beta-lactam and most other antibiotics to cause serious adverse reactions such as nephrotoxicity and ototoxicity, they are not considered a primary treatment for cUTI, and their use should be reserved for patients who have limited treatment options. However, the new drug may be of great value in patients who are allergic to the beta-lactams and/or have infections caused by bacteria that are resistant to the primary treatments.

Precautions: (1) Contraindicated in patients with known hypersensitivity to any of the drugs in this class because cross-sensitivity among the aminoglycosides is possible. (2) Like other aminoglycosides used for systemic infections, plazomicin may cause nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm, and these risks are outlined in a boxed warning. (3) The risk of nephrotoxicity is greater in patients with impaired renal function, older adults, and in those receiving concomitant nephrotoxic medications. (4) Signs and symptoms of ototoxicity such as

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tinnitus, hearing loss, and vertigo may be irreversible and may not become evident until after completion of therapy. (5) The risk of neuromuscular blockade is increased in patients with underlying neuromuscular disorders such as myasthenia gravis and in those who are concomitantly receiving neuromuscular blocking agents. (6) Creatinine clearance should be assessed in all patients before therapy starts and daily during therapy. The initial dosage and subsequent doses should be based on the assessment of renal function and/or therapeutic drug monitoring.

Adverse reactions: decreased renal function, diarrhea, hypertension, headache, nausea, vomiting, hypotension

Supplied as: single-dose vials in an amount equivalent to 500 mg/10 mL plazomicin base

Dosage: individualized based on renal function and/or therapeutic drug monitoring. Consult the prescribing information for details.

Nursing considerations: (1) As prescribed, dilute the appropriate drug volume in 0.9% Sodium Chloride Injection or Lactated Ringer Injection to achieve a final volume of 50 mL for I.V. infusion. Following dilution, the solution is stable for 24 hours at room temperature. (2) Administer plazomicin I.V. over 30 minutes. Most patients receive a dose once every 24 hours. (3) To guide dosage adjustments, estimate creatinine clearance with the Cockcroft-Gault formula using total body weight (TBW). For patients with TBW greater than ideal body weight (IBW) by 25% or more, IBW should be used to determine adjusted body weight. (4) In patients with an estimated creatinine clearance of at least 15 to less than 90 mL/min, therapeutic drug monitoring is recommended to maintain plasma trough concentrations below 3 mcg/mL. The plasma trough concentration should be measured within approximately 30 minutes before administration of the second dose of plazomicin. (5) For patients with plasma trough concentrations equal to or greater than 3 mcg/mL, the dosing interval should be extended by 1.5-fold (for example, from every 24 hours to every 36 hours). (6) Monitor patients for signs and symptoms of *Clostridium difficile*-associated diarrhea, which has been reported with almost all systemic antibacterial agents. Inform patients that this may even occur several months after treatment has been completed. (7) Teach patients to recognize signs and symptoms of other potentially serious adverse reactions (nephrotoxicity, ototoxicity, neuromuscular blockade, hypersensitivity reactions), and instruct them to report these to the healthcare provider immediately. (8) Store drug vials in the refrigerator. The solution may become yellow in color; this does not indicate a decrease in potency.

REFERENCE

1. Zemdri (plazomicin) injection, for intravenous use. Prescribing information. https://zemdri.com/assets/pdf/Prescribing-Information.pdf.

Eravacycline dihydrochloride

A novel tetracycline for complicated intra-abdominal infections

Intra-abdominal infections occur within the peritoneal cavity and retroperitoneal space. Complicated intra-abdominal infections (cIAI) extend beyond local visceral structures and may include appendicitis, cholecystitis, diverticulitis, peritonitis, intra-abdominal abscess, gastric/duodenal perforation, and intestinal perforation. Infections are usually polymicrobial and caused by Gram-negative, Gram-positive, and/or anaerobic bacteria, and are associated with systemic signs and symptoms of infection. Treatment goals include correction of the intra-abdominal disease process, abscess drainage, and resolution of the infection. Empiric treatment with a broad-spectrum antibacterial regimen is often initiated before culture results are available. Beta-lactam antibiotics (carbapenems, cephalosporins, penicillins) would often be included in these regimens, but some patients have a history of hypersensitivity to these drugs. In addition, some patients experience cIAI caused by bacteria that produce beta-lactamase, in which case the use of a beta-lactam antibiotic with a beta-lactamase inhibitor or another antibacterial regimen would be used.

Eravacycline dihydrochloride (*Xerava,* Tetraphase) is a synthetic tetracycline-class antibacterial agent that is also designated as a fluorocycline. It includes two structural substitutions, including a fluorine substituent, that are not present in other tetracyclines and which impart *in vitro* activity against strains of Gram-positive and Gram-negative bacteria that express certain tetracycline-specific resistance mechanisms. Activity of eravacycline has also been demonstrated *in vitro* against Enterobacteriaceae in the presence of certain beta-lactamases, including ESBLs. The new drug disrupts bacterial protein synthesis by binding to the 30S ribosomal subunit and is generally bacteriostatic.

Administered I.V., eravacycline is indicated in adults age 18 and older to treat cIAI caused by susceptible microorganisms identified in the prescribing information.[1] Although other tetracyclines have been approved to treat many other types of infections, cIAI is currently the only labeled indication for eravacycline.

The effectiveness of eravacycline was demonstrated in two noninferiority clinical trials enrolling approximately 1,400 patients, in which it was compared with ertapenem or meropenem. Clinical cure was

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defined as complete resolution or significant improvement of signs or symptoms of the infection at the test of cure visit almost 1 month after randomization. This response was achieved in approximately 87% of patients with both of the treatment regimens in the trial comparing eravacycline to ertapenem, and 91% of patients with both of the treatment regimens comparing eravacycline to meropenem.

Eravacycline was well tolerated in the clinical trials. The most common reason for discontinuation of therapy was GI upset.

Precautions: (1) Contraindicated in patients with known hypersensitivity to any of the tetracyclines. (2) As with other tetracyclines, the labeling for eravacycline includes warnings regarding tooth discoloration and enamel hypoplasia as well as inhibition of bone growth. These risks are related to the use of these agents in infancy and childhood, and during the last half of pregnancy. Although the labeled indication for eravacycline is limited to adults, the use of any of the tetracyclines in infants and children younger than 8 years, nursing mothers, or women in the second or third trimester of pregnancy is not recommended. (3) Eravacycline has the potential for causing other adverse events associated with tetracyclines, such as photosensitivity and antianabolic effects. (4) Dosages should be adjusted in patients with severe hepatic impairment. (5) Strong CYP3A inducers such as rifampin decrease the exposure of eravacycline, so the dosage of the new drug should be increased in patients receiving such drugs concurrently. (6) Because tetracyclines may decrease plasma prothrombin activity, the concomitant use of eravacycline with an anticoagulant may require downward adjustment of the anticoagulant dosage.

Adverse reactions: infusion site reactions, nausea, vomiting

Supplied as: a lyophilized powder in single-dose vials in an amount equivalent to 50 mg of eravacycline

Dosage: 1 mg/kg via I.V. infusion every 12 hours for 4 to 14 days. The duration of treatment is guided by the severity and location of the infection and the patient's clinical response.

Nursing considerations: (1) Store vials in a refrigerator. (2) When the specific dosage of eravacycline is calculated and the number of vials needed to supply the dose determined, the contents of each vial should be reconstituted with 5 mL of Sterile Water for Injection to deliver 50 mg (10 mg/mL) of the drug. Gently swirl (do not shake) the vial until the powder has entirely dissolved. Then dilute the reconstituted solution to a target concentration of 0.3 mg/mL (within a range of 0.2 to 0.6 mg/mL) in a 0.9% Sodium Chloride Injection infusion bag. (3) Administer the diluted solution I.V. over approximately 60 minutes. It must be infused within 6 hours if stored at room temperature or within 24 hours if refrigerated. (4) Monitor patients for signs and symptoms of *C. difficile*-associated diarrhea, which has been reported with almost all systemic antibacterial drugs. (5) Monitor patients for signs and symptoms of hypersensitivity reactions.

REFERENCE

1. Xerava (eravacycline) for injection, for intravenous use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf.

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