New DRUGS

PART 1 2011

4.0 ANCC CONTACT HOURS

4.0 PHARMACOLOGY CREDITS

IN THIS ARTICLE, you'll learn about 13 recently approved drugs, including:

> pitavastatin calcium, a new statin indicated for adults with primary hyperlipidemia or mixed dyslipidemia.

> liraglutide, a subcutaneously administered antidiabetic drug that may be used as monotherapy or in conjunction with one or more oral antidiabetic drugs.

> denosumab, a human monoclonal antibody indicated for postmenopausal women with osteoporosis at high risk for fracture.

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

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SELECTED REFERENCES

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Nursing2011 Drug Handbook. Ambler, PA: Lippincott Williams & Wilkins; 2011.

Physicians' Desk Reference, 65th ed. Montvale, NJ: Medical Economics; 2011.

*Common adverse reactions are italicized throughout this article.

The author has disclosed that he has no significant relationship with or financial interest in any commercial companies that pertain to this educational activity.

ANTIARTHRITIC DRUG

Tocilizumab

Biologic agent for rheumatoid arthritis

A chronic, debilitating autoimmune disorder, rheumatoid arthritis is characterized by inflammation and joint damage. Traditional treatment includes the use of nonsteroidal antiinflammatory drugs and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate. The addition of biologic agents to treat rheumatoid arthritis is an important treatment advance. Biologic agents include tumor necrosis factor (TNF) antagonists such as etanercept, infliximab, and adalimumab.

Tocilizumab (*Actemra*, Genentech) is another biologic agent classified as an interleukin-6 (IL-6) receptor inhibitor. A recombinant humanized monoclonal antibody, tocilizumab binds to IL-6, a proinflammatory cytokine that contributes to local inflammation. Administered I.V., it's indicated as monotherapy or in combination with other DMARDs for adults with moderately-to-severely active rheumatoid arthritis who've had an inadequate response to one or more TNF antagonists.

Like TNF antagonists, tocilizumab is an immunosuppressant that carries the risk of serious infection, including tuberculosis (TB). The labeling for tocilizumab contains a black box warning about this risk.

Tocilizumab should be used in pregnancy only if the expected benefit justifies the risk to the fetus. Pregnant women taking the drug should be enrolled in the pregnancy registry by calling 1-877-311-8972. The safety and effectiveness of tocilizumab in patients under age 18 haven't been established.

Precautions: (1) Avoid using concurrently with another biologic agent because their similar risks increase the possibility of serious complications. (2) Don't administer live vaccines to patients taking tocilizumab. (3) Tocilizumab may increase the risk of malignancies, demyelinating disorders, or gastrointestinal perforation (usually as a complication of diverticulitis). (4) Don't initiate tocilizumab therapy in patients with a clinically significant infection, including a local infection. (5) Don't initiate therapy if the patient's absolute neutrophil count is below 2,000/mm^3, platelet count below 100,000/mm^3, or alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values above 1.5 times the upper limit of normal. Consult the product labeling for information about adjusting the dosage or discontinuing therapy if the patient develops these lab abnormalities during treatment. (6) Not recommended for use in patients with hepatic impairment or active hepatic disease.

Adverse reactions: *upper respiratory tract infections*, *nasopharyngitis*, *headache*, *hypertension*, *elevated ALT*, and infusion reactions, such as serious hypersensitivity reactions

Supplied as: a sterile solution in a concentration of 20 mg/mL in single-use vials containing 4 mL (80 mg), 10 mL (200 mg), and 20 mL (400 mg) of solution

Dosage: 4 mg/kg administered as an I.V. infusion over 60 minutes once every 4 weeks; may be increased to 8 mg/kg once every 4 weeks based on patient response. Dosages over 800 mg aren't recommended. The volume of solution needed to provide the appropriate dose should be diluted to 100 mL in 0.9% sodium chloride injection.

Nursing considerations: (1) Recommended vaccines should be administered before therapy starts. Tell patients not to get vaccines during therapy unless approved by the healthcare provider. (2) Make sure patients are screened for TB before starting therapy. Patients with active or latent TB should be treated before therapy starts. The healthcare provider may also consider treating patients who test negative for TB if they have risk factors for the disease. (3) Teach patients to recognize and report signs and symptoms of infection during therapy. (4) Monitor the patient for hypersensitivity reactions during treatment. Although rare, serious reactions are most likely to occur during the second to fourth infusion. (5) Monitor patients for signs and symptoms of demyelinating disorders such as multiple sclerosis. (6) Store vials in a refrigerator and protect them from light. (7) Fully diluted solutions for infusion may be stored in the refrigerator or at room temperature for up to 24 hours. Discard any unused drug remaining in vials.

LIPID-REGULATING DRUG

Pitavastatin calcium

One more statin hits the market

Pitavastatin calcium (*Livalo*; Kowa, Lilly) is the seventh lipid-lowering statin currently on the market in the United States, joining atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Like the others, pitavastatin is indicated for adults with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides; and to increase high-density lipoproteins. Indications for pitavastatin are more limited than those for other statins, which have been approved for a larger number of dyslipidemias than the new drug.

Contraindications, warnings, and precautions for pitavastatin are similar to those for other statins. All are in Pregnancy Category X.

Precautions: (1) Contraindicated in pregnant and nursing women. (2) Contraindicated in patients with active liver disease. (3) Contraindicated for use concurrently with cyclosporine, which significantly increases serum pitavastatin concentrations. (4) Use caution in patients with a history of liver disease and in those who consume large quantities of alcohol. (5) Perform liver enzyme testing before therapy, 12 weeks after therapy starts, and semiannually thereafter, or as indicated. Reduce the dosage or suspend therapy if AST or ALT values of more than three times the upper limit of normal persist. (6) Use pitavastatin concurrently with a fibrate (fenofibrate, gemfibrozil) only if benefits outweigh the added risk of myalgia, myopathy, and rhabdomyolysis, a rare but potentially fatal complication of statins. Combining statins and fibrates increases the risk of these skeletal muscle disorders. (7) Suspend treatment in patients who develop an acute, serious condition suggesting myopathy or raising the risk of renal failure secondary to rhabdomyolysis, such as sepsis, hypotension, dehydration, electrolyte imbalances, or major surgery. (8) Avoid concurrent use with lopinavir/ritonavir, erythromycin, and rifampin. (9) In patients taking warfarin, monitor

prothrombin time and international normalized ratio (INR) after adding pitavastatin to the regimen. Consult the product labeling for specific precautions and recommendations related to potential drug interactions. (10) Reduce the dosage in patients with moderate renal impairment and in those with end-stage renal disease receiving hemodialysis.

Adverse reactions: *back pain*, *constipation*, *diarrhea*, *myalgia, pain in extremity,* myopathy, rhabdomyolysis

Supplied as: tablets providing the equivalent of 1 mg, 2 mg, and 4 mg of pitavastatin

Dosage: 2 mg/day P.O.; may be increased if indicated after 4 weeks. Maximum recommended dosage: 4 mg/day.

Nursing considerations: (1) Ensure that baseline liver function tests and blood lipid concentrations are obtained before therapy and at subsequent intervals during therapy, as recommended. (2) Tell the patient that the drug can be taken without regard to food. (3) Instruct the patient to immediately report unexplained muscle pain, tenderness, or weakness, especially if accompanied by malaise or a fever.

ANTIDIABETIC DRUG

Liraglutide

This drug may also aid weight loss.

Administered subcutaneously, liraglutide (*Victoza,* Novo Nordisk) has properties similar to exenatide, which is also administered subcutaneously. Both drugs reduce blood glucose concentrations via several mechanisms that include increased insulin release in the presence of elevated glucose concentrations, decreased glucagon secretion, and delayed gastric emptying. Liraglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, and may be used as monotherapy or in combination with one or more oral antidiabetic drugs, such as metformin, glimepiride, or a thiazolidinedione. It's not recommended as a first-line treatment for patients whose blood glucose is inadequately controlled by diet and exercise.

Like exenatide, liraglutide is associated with weight loss (about 3 kg on average), an added benefit for patients who are overweight. In contrast, glimepiride and other sulfonylureas are often associated with weight gain.

Precautions: (1) Contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2, because the drug has been associated with malignant thyroid tumors in rodents. This is the subject of a boxed warning in the drug labeling. (2) Use caution in patients with a history of pancreatitis, particularly when treatment is initiated and following dosage increases. Discontinue treatment if the patient develops signs and symptoms of pancreatitis, such as persistent severe abdominal pain that may radiate to the back and vomiting. If pancreatitis is confirmed, treatment should not be resumed. (3) Although liraglutide is unlikely to cause hypoglycemia, serious hypoglycemia may develop when it's used concurrently with a sulfonylurea. The sulfonylurea dosage should be reduced to minimize this risk. (4) Closely monitor patients taking any oral drugs concurrently. Because liraglutide delays gastric emptying, it may affect the absorption and activity of oral drugs. (5) Use liraglutide with caution in patients with impaired hepatic or renal function.

Adverse reactions: *nausea, diarrhea*, vomiting, constipation, upper respiratory tract infection, headache

Dosage: 0.6 mg/day subcutaneously in the abdomen, upper arm, or thigh. After 1 week, dosage is increased to 1.2 mg/day. Dosage may be raised to 1.8 mg/day if necessary to achieve glycemic control.

Supplied as: prefilled multidose pens that deliver doses of 0.6 mg, 1.2 mg, or 1.8 mg

Nursing considerations: (1) The initial dosage (0.6 mg) isn't enough to achieve glycemic control, but starting with a low dose helps mitigate gastrointestinal adverse reactions. (2) Tell patients they should administer the drug at the same time each day. (3) Observe and assess patients' injection technique and teach them to rotate injection sites. (4) Tell patients to store the drug pens in the refrigerator before use. Following initial use, a pen may be stored for 30 days at controlled room temperature or in a refrigerator. (5) Instruct patients to discontinue the drug and contact their healthcare provider immediately if they experience signs and symptoms of pancreatitis. (6) Tell nursing mothers to discuss risks with the healthcare provider. Whether the drug is excreted in breast milk isn't known, and patients should either discontinue nursing or not use the drug.

DRUG FOR MULTIPLE SCLEROSIS

Dalfampridine

Helping patient walk

Approximately 400,000 Americans have been diagnosed with multiple sclerosis (MS), a chronic autoimmune disease of the central nervous system.[1] Signs and symptoms often include fatigue, vision problems, numbness in the limbs, loss of balance/coordination, and difficulty walking.

Dalfampridine (*Ampyra*, Acorda), also known as fampridine, is a potassium channel blocker that, in animal studies, has been shown to increase conduction of action potentials in demyelinated axons. Administered orally, it's approved to improve walking ability in patients with MS. In clinical trials, it was shown to increase walking speed. Compared with patients taking placebo, a significantly higher percentage of patients taking the drug showed a faster walking speed. However, more than half of patients taking the drug experienced no benefit.

The most important concern associated with dalfampridine is the risk of seizures, which is dose-related. The drug is available only through a limited network of specialty pharmacies and Kaiser Permanente.

Precautions: (1) Contraindicated in patients with a history of seizures; the drug should be discontinued in patients who experience a seizure during treatment. (2) Contraindicated in patients

with moderate-to-severe renal impairment (creatinine clearance of 50 mL/minute or less). (3) Use caution in patients with mild renal impairment (creatinine clearance of 51 to 80 mL/minute). Impaired drug clearance may increase the risk of seizures. (4) Don't exceed the recommended dosage: 10 mg twice a day. (5) Take precautions to ensure that patients don't take more than one product containing dalfampridine (also known as 4-aminopyridine).

Adverse reactions: *urinary tract infections*, *insomnia, dizziness*, *headache*, *nausea*, *asthenia*, *back pain, balance disorder*, MS relapse, paresthesias, nasopharyngitis, constipation, dyspepsia, pharyngolaryngeal pain

Supplied as: 10-mg extended-release tablets

Dosage: 10 mg twice a day, taken 12 hours apart

Nursing considerations: (1) Make sure baseline creatinine clearance has been established before therapy starts—especially for older adults, who are more likely to experience renal impairment. (2) Warn patients not to exceed the prescribed dosage. If they miss a dose, they should skip that dose, not take an extra or double dose. (3) Tell patients they can take the drug without regard to food. Emphasize that tablets should be swallowed whole and not divided, crushed, chewed, or dissolved. (4) Tell patients to keep follow-up appointments as instructed by their healthcare provider to evaluate response to treatment. In clinical trials, the treatment period was 14 days.

REFERENCE

1. National Multiple Sclerosis Society. FAQs about MS. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/faqs-about-ms/index.aspx.

DRUG FOR OSTEOPOROSIS

Denosumab

Building bone mass and strength

A human monoclonal antibody, denosumab (*Prolia*, Amgen) binds to a protein that is essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. By preventing this protein from activating its receptor, denosumab decreases bone resorption and increases bone mass and strength.

Administered subcutaneously by a healthcare professional, denosumab is indicated for postmenopausal women with osteoporosis who are at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or who have failed or are intolerant of other therapies for osteoporosis. This indication is more limited than those for other osteoporosis drugs. For example, the bisphosphonates ibandronate, alendronate, risedronate, and zoledronic acid (Reclast Injection) are also approved for preventing osteoporosis; in addition, the latter three have labeled indications for treating osteoporosis in men and treating glucocorticoid-induced osteoporosis and Paget disease in both men and women.

Denosumab is approved only for postmenopausal women, but if it's prescribed off label to pregnant women, they should be enrolled in Amgen's Pregnancy Surveillance Program.

As with the bisphosphonates, some patients treated with denosumab have experienced osteonecrosis of the jaw (ONJ). This may be related to suppression of bone remodeling.

Precautions: (1) Contraindicated in patients with hypocalcemia, which should be corrected before therapy starts. Monitor serum concentrations of calcium and minerals (including phosphorus and magnesium) in patients predisposed to hypocalcemia, such as those with severe renal impairment, hypoparathyroidism, and malabsorption syndromes. (2) Provide supplementation with calcium (1000 mg daily) and vitamin D (at least 400 IU daily) during therapy. (3) The prescriber should perform a routine oral exam before initiating therapy. Because of the risk of ONJ, patients should undergo any needed dental procedures before therapy begins. (4) Monitor patients for signs and symptoms of infection, particularly those taking immunosuppressants and those with impaired immune function. Although unusual, serious infections, including skin infections, requiring hospitalization were reported in clinical trials.

Adverse reactions: *back pain, pain in extremity*, *musculoskeletal pain*, *cystitis*, *hypercholesterolemia*, dermatologic reactions (dermatitis, eczema, rash)

Supplied as: single-use prefilled syringes and single-use vials containing the drug in a concentration of 60 mg/mL

Dosage: 60 mg once every 6 months, administered subcutaneously by a healthcare professional in the upper arm, upper thigh, or abdomen

Nursing considerations: (1) Tell patients to get a dental checkup before starting therapy and to inform their dentist that they're taking denosumab. (2) Tell patients to immediately report signs and symptoms of a serious infection or dermatologic adverse reactions to the healthcare provider. (3) Tell patients to immediately report possible signs and symptoms of ONJ, such as pain, swelling, loosening of teeth, or drainage. (4) Reinforce the importance of taking calcium and vitamin D supplements as prescribed and encourage good oral hygiene. (5) Store drug vials in the refrigerator. Once removed from the refrigerator, they should be used within 14 days. (6) Before administering the drug, allow the vial to warm to room temperature by standing it in its original container for 15 to 30 minutes. Don't heat the drug in any other manner. (7) Don't handle the gray needle cap if you're sensitive to latex because it contains dry natural rubber. (8) In late 2010, denosumab (marketed as Xgeva) was approved for an additional indication: the prevention of skeletal-related events in patients with bone metastases from solid tumors. For this indication, the drug is used in a higher dosage, and the single-use vials contain a higher drug potency.

SCLEROSING AGENT

Polidocanol

Treatment to occlude small varicose veins

Most common in the lower extremities, varicose veins include spider veins (which involve the capillaries and look like a spider web or tree branch) and reticular veins (flat blue dilated veins typically

seen behind the knees). Sclerosing agents already available for the treatment of varicose veins include sodium tetradecyl sulfate and morrhuate sodium. Injected into a vein, these agents cause local endothelial damage, platelet aggregation, and fibrosis. As the treated vein occludes, it fades away and is replaced with fibrous connective tissue.

Polidocanol (*Asclera*, BioForm Medical), a new sclerosing agent, is a nonionic detergent with properties similar to those of sodium tetradecyl sulfate. It's indicated to sclerose uncomplicated spider veins (varicose veins 1 mm or less in diameter) and uncomplicated reticular veins (1 to 3 mm in diameter) in the lower extremities. In a clinical trial comparing it with sodium tetradecyl sulfate and placebo, it was found to be as effective as sodium tetradecyl sulfate. About 85% of patients treated with the new agent said they were satisfied or very satisfied with the result, compared with 65% who received sodium tetradecyl sulfate and 15% who received placebo treatment.

Precautions: (1) Contraindicated in patients with acute thromboembolic diseases. (2) Contraindicated in patients with a known allergy to the drug. Fatal anaphylactic reactions to the drug have been reported. Practitioners should administer the smallest effective dose to minimize the risk of a severe reaction; volumes greater than 3 mL increase the risk. (3) Practitioners must take care to avoid inadvertent intra-arterial injection, which may cause severe ischemia, necrosis, and gangrene, or inadvertent perivascular injection, which may cause severe pain.

Adverse reactions: *mild injection-site reactions: hematoma, irritation, discoloration, pain, pruritus, warmth*

Supplied as: 0.5% and 1% solution in 2 mL glass ampules

Dosage: 0.1 to 0.3 mL for each injection; no more than 10 mL should be injected per session. Repeat sessions, if needed, should be separated by 1 to 2 weeks. The 0.5% solution should be used to treat spider veins and the 1% solution to treat reticular veins.

Nursing considerations: (1) The drug should be administered slowly, using a fine needle (typically 26- or 30-gauge). (2) Following treatment, cover the injection site and apply a compression stocking or bandage. Encourage the patient to walk for 15 to 20 minutes. (3) To reduce the potential for deep vein thrombosis, compression should be maintained for 2 to 3 days following treatment of spider veins and for 5 to 7 days following treatment of reticular veins. For extensive varicosities, longer treatment with compression bandages or a graduated compression stocking of a higher compression class is recommended. (4) Because of the potential for a severe allergic reaction, make sure emergency drugs and equipment are at hand. Monitor the patient for at least 20 minutes after treatment. (5) Severe pain from inadvertent perivascular injection may be treated with a local anesthetic (without epinephrine).

CONTRACEPTIVE

Dienogest

Used in combination to minimize breakthrough bleeding

Dienogest is a new progestin used with estradiol valerate in a combination oral contraceptive formulation marketed as *Natazia* (Bayer). Most other combination oral contraceptive products include ethinyl estradiol as the estrogen component. It's the first contraceptive product with a four-phase dosage regimen in which the estrogen dosage is decreased and the progestin dosage increased during the 28-day cycle. This is intended to prevent breakthrough bleeding. Tablet color varies according to the tablet's hormonal dosage. The two white tablets are inert.

Dienogest/estradiol valerate prevents pregnancy primarily by suppressing ovulation, although other mechanisms (such as cervical mucus changes) also contribute. In tests, it was highly effective at preventing pregnancy, but no data are available to determine whether it's more or less effective than similar products. Risks and contraindications for dienogest/estradiol valerate are similar to those for other combination oral contraceptives.

Dienogest/estradiol valerate is indicated to prevent pregnancy, but its effectiveness in women with a body mass index greater than 30 hasn't been evaluated.

Precautions: (1) Classified in pregnancy category X, dienogest/estradiol valerate is contraindicated in pregnant women. Oral contraceptive use should be discontinued if pregnancy is confirmed. (2) Contraindicated in patients at high risk for arterial or venous thrombotic events. This includes patients with past or current deep vein thrombosis or pulmonary embolism, cerebrovascular or coronary artery disease, thrombogenic cardiac disorders such as atrial fibrillation and valvular heart disease, hypercoagulopathies, uncontrolled hypertension, diabetes with vascular disease, headaches with focal neurologic symptoms, and migraine headaches in women over age 35. If major surgery or other procedures that increase the risk of thromboembolism are planned, discontinuing oral contraceptives for at least 4 weeks before and 2 weeks after the procedure is recommended. (3) Contraindicated in women over age 35 who smoke because of the risk of serious cardiovascular events. This is the subject of a boxed warning in the labeling. (4) Contraindicated in patients with undiagnosed abnormal genital bleeding, past or current breast cancer or other estrogen- or progestin-sensitive cancer, and liver tumors or liver disease. (5) Discontinue use if the patient develops jaundice. Steroid hormones may be poorly metabolized in patients with hepatic dysfunction. (6) Immediate discontinuation should be considered in women who experience an increase in frequency or severity of migraine headaches. (7) Concurrent use of drugs or herbal products that cause enzyme induction may reduce the effectiveness of oral contraception and increase breakthrough bleeding. Women using strong CYP3A4 inducers such as carbamazepine, phenytoin, rifampin, or St. John's wort shouldn't use dienogest/estradiol valerate as their contraceptive while using these inducers and for at least 28 days after discontinuing the inducer. Women using moderate or weak enzyme inducers, such as barbiturates or topiramate, should use an alternative or backup contraceptive method. (8) Women taking thyroid hormone replacement therapy or the antiepileptic drug lamotrigine may require increased dosages of these drugs. Consult the product labeling for complete warnings and possible drug interactions.

Adverse reactions: *headache, metorrhagia*

and *irregular menstruation, breast tenderness*, *nausea or vomiting*, acne, weight gain

Supplied as: 28 tablets in a blister pack

Dosage: one tablet per day in the sequence directed on the packaging

Nursing considerations: (1) Teach patients to take one tablet at the same time each day in the sequence directed on the packaging. Tablets shouldn't be skipped or delayed by more than 12 hours. (2) Advise patients to use a nonhormonal contraceptive for the first 9 days after starting therapy. (3) Inform patients that breakthrough bleeding and spotting may occur, especially during the first 3 months of use. (4) If amenorrhea occurs in two or more consecutive cycles, pregnancy should be ruled out. (5) Advise nursing mothers to use another form of contraception until the child is weaned, because estrogens can reduce milk production. (6) Monitor BP in patients with well-controlled hypertension. (7) Monitor women with diabetes and prediabetes. (8) Inform patients that vomiting or diarrhea may impair drug absorption, so they should use additional contraceptive measures to prevent pregnancy. If vomiting or diarrhea occurs within 4 hours of taking a colored tablet, this should be considered a missed tablet. Consult the product labeling for instructions to follow if one or more doses are missed, or if a woman is switching from another hormonal contraceptive to the new drug. (9) Some women taking oral contraceptives develop chloasma, a pattern of facial hyperpigmentation also known as melasma or mask of pregnancy. Tell patients with a predisposition to this response to avoid exposure to the sun or UV radiation while taking dienogest/estradiol valerate.

ANTINEOPLASTIC DRUGS

Sipuleucel-T

I.V. treatment for prostate cancer derived from a patient's own cells

Prostate cancer is the second most common type of cancer in men in the United States. Factors that inacrease a man's risk are older age, family history of prostate cancer, and being African American.[1]

Sipuleucel-T (*Provenge,* Dendreon) is an I.V. drug created from a patient's own (autologous) blood cells. It's designed to induce an immune response against prostatic acid phosphatase, an antigen expressed in most prostate cancers. It's indicated to treat asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. This autologous cellular immunotherapy is also designated as a therapeutic vaccine.

About 3 days before a scheduled treatment, the patient's immune cells are collected using a leukapheresis procedure. The cells are activated with a recombinant human protein suspended in lactated Ringer's injection. The drug is supplied in an infusion bag in a special insulated polyurethane container and shipped to the provider who will administer it. The drug should remain in the insulated container until the time of administration.

In clinical trials, sipuleucel-T didn't alter disease progression but it extended survival time compared with placebo (25.8 months versus 21.7 months in the largest study). The drug costs approximately $93,000 for the three-dose course of treatment. This fuels the debate about the cost-effectiveness of this expensive treatment for a brief survival benefit. [2,3]

Precautions: (1) Sipuleucel-T may cause acute infusion reactions (fever, chills, dyspnea, nausea, fatigue, hypertension, headache). Patients should be premedicated with oral acetaminophen and an antihistamine such as diphenhydramine about 30 minutes before the infusion to reduce the risk. (2) The concomitant use of the new drug with an immunosuppressant drug (such as a systemic corticosteroid) or chemotherapy may reduce the new drug's effectiveness. The provider may discontinue or reduce the dosage of immunosuppressant drugs before starting treatment with sipuleucel-T.

Adverse reactions: *chills, fatigue, fever, back pain, nausea, arthralgia, headache*

Supplied as: a suspension in an infusion bag containing a volume of 250 mL

Dosage: administer via I.V. infusion over about 60 minutes until the entire volume has been infused. Don't use a cell filter. The recommended course of treatment is three doses administered at approximately 2-week intervals.

Nursing considerations: (1) Because sipuleucel-T isn't routinely screened for infectious diseases, follow standard precautions when handling the drug. (2) The drug is for autologous use only. Confirm the patient's identity and match it with patient identifiers on the infusion bag and the form provided with the drug. (3) Premedicate the patient as prescribed. Closely monitor the patient for an infusion reaction during treatment and for at least 30 minutes after each infusion. If the patient develops an acute infusion reaction during treatment, the provider may slow or stop the infusion, depending on the reaction's severity.

REFERENCES

1. Centers for Disease Control and Prevention. Cancer and Men. http://www.cdc.gov/Features/CancerAndMen.

2. Longo DL. New therapies for castration-resistant prostate cancer. *N Engl J Med.* 2010; 363:479-481.

3. New treatments for metastatic prostate cancer. *The Medical Letter.* 2010; 52(1346): 70.

Romidepsin

I.V. treatment for cutaneous T-cell lymphoma

From 16,000 to 20,000 Americans have been diagnosed with cutaneous T-cell lymphoma (CTCL), a group of non-Hodgkin lymphomas in which malignant T cells typically manifest initially in the skin.[1] Skin lesions may be intensely pruritic and painful. Patients with later-stage CTCL are susceptible to infection because their skin barrier is compromised. Over time, the malignancy can become systemic, involving lymph nodes, spleen, liver, and other viscera.

Romidepsin (*Istodax*, Gloucester) works by inhibiting the activity of histone deacetylases (HDACs), enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins. It's the second HDAC inhibitor to be approved to treat CTCL, joining the oral drug vorinostat. Administered I.V., romidepsin is indicated to treat CTCL in patients who've received at least one prior systemic therapy.

Precautions: (1) Romidepsin may cause ECG changes. Initiate appropriate cardiovascular monitoring precautions (such as monitoring serum potassium and magnesium concentrations), particularly in

patients with congenital long QT syndrome, those with significant cardiovascular disease, and those taking antiarrhythmic drugs or other drugs that may cause significant QT prolongation. (2) Monitor hematologic parameters. Development of thrombocytopenia, neutropenia, lymphopenia, or anemia may require a dosage reduction or interruption of therapy. (3) Use caution in patients with moderate or severe hepatic impairment or end-stage renal disease. (4) Although romidepsin's potential to interact with other drugs hasn't been specifically studied, it may prolong prothrombin time and increase the INR in patients taking warfarin. Monitor these patients closely. (5) Romidepsin may reduce the effectiveness of hormonal contraceptives containing estrogen. (6) Avoid using romidepsin concurrently with potent CYP3A4 inducers (such as carbamazepine, rifampin, St. John's wort) or CYP3A4 inhibitors (such as clarithromycin).

Adverse reactions: *infections* (including sepsis), pyrexia, *nausea*, *vomiting*, *anorexia, fatigue*, *thrombocytopenia*, *neutropenia*, leukopenia, *lymphopenia, anemia,* edema, ventricular or supraventricular dysrhythmias, *T-wave changes on ECG*

Supplied as: a kit including a single-use vial containing a lyophilized powder with 10 mg of the drug and 20 mg of the bulking agent, povidone; and a 2-mL vial of diluent. The medication must be reconstituted with the diluent and diluted in 500 mL of 0.9% sodium chloride injection.

Dosage: 14 mg/m^2 via I.V. infusion over 4 hours on days 1, 8, and 15 of a 28-day cycle. Cycles should be repeated every 28 days if patient benefits from and tolerates the treatment.

Nursing considerations: (1) Consult the product labeling for treatment and dosage recommendations if the patient experiences hematologic or nonhematologic toxicities. (2) The reconstituted drug is stable for at least 8 hours at room temperature. The diluted solution is stable for at least 24 hours, but should be administered as soon as possible after dilution. (3) Advise women of childbearing potential that romidepsin may reduce the effectiveness of estrogen-containing contraceptives. Tell them to use an alternate form of contraception. (4) Closely monitor patients taking warfarin concurrently for increased INR and prolonged prothrombin time.

REFERENCE

1. CTCL-MF fast facts. Cutaneous Lymphoma Foundation. http://www.clfoundation.org/about_cutaneous_lymphoma/CL_fast_facts.htm.

DRUG FOR DUPUYTREN CONTRACTURE

Collagenase clostridium histolyticum

Treatment derived from bacteria to treat a debilitating hand disorder

In Dupuytren contracture, a connective tissue disease, collagen builds up in the palm of the hand. Thick, ropelike cords of tissue extend to the base of the fingers and reduce the ability to straighten the fingers normally.[1,2] Collagenase clostridium histolyticum (*Xiaflex*, Auxilium) consists of two microbial collagenases (enzymes that break down collagen) obtained from the fermentation of *Clostridium histolyticum* bacteria. These enzymes, which consist of about 1,000 amino acids each, are thought to act synergistically in hydrolyzing collagen, with a resultant lysis of collagen deposits. Administered by injection, the new drug is indicated for intralesional use to treat adults with Dupuytren contracture with a palpable cord.

Surgical treatment of Dupuytren contracture is associated with a long recovery and the need for physical therapy. The availability of collagenase clostridium histolyticum as an effective alternative is a significant treatment advance.

The most important concern with this drug is the risk of tendon rupture or other serious injury to the injected extremity. The drug should be administered only by a healthcare provider who's experienced in injection procedures of the hand and in the treatment of patients with Dupuytren contracture.

Precautions: (1) The drug should be injected only into a palpable collagen cord with a metacarpophalangeal (MP) joint or proximal interphalangeal (PIP) joint contracture. Injecting the drug into tendons, nerves, blood vessels, or other collagen-containing structures may cause permanent injury. (2) Beware of the potential for a serious allergic reaction (although none occurred in clinical trials). (3) Take care in patients being treated with anticoagulant medications such as warfarin, clopidogrel, or prasugrel. The safety of using these medications concurrently with the new drug hasn't been studied.

Adverse reactions: *contusion/ecchymosis*, *injection-site hemorrhage*, mild allergic reactions (pruritus), *edema of the injected hand*, *injection-site reaction (erythema, irritation, pain)*

Supplied as: lyophilized powder in single-use vials containing 0.9 mg of the drug

Dosage: 0.58 mg per injection into a palpable cord (0.25 mL of reconstituted solution in cords affecting MP joints and 0.2 mL for cords affecting PIP joints)

Nursing considerations: (1) Reconstitute the drug with the diluent provided. Consult product labeling for detailed guidelines for reconstitution, preparation before injection, and the injection procedure. (2) Store vials in the refrigerator. (3) After treatment, instruct the patient to keep the injected hand elevated until bedtime and return to the healthcare provider's office the following day. (4) If a contracture remains when the patient is evaluated the following day, a passive finger extension procedure should be performed to facilitate cord disruption. (5) If the first finger extension procedure doesn't disrupt the cord, a second and third attempt can be performed at 5- to 10-minute intervals. If the contracted cord persists at the subsequent visit, an additional injection with finger extension procedures may be performed. (6) Following finger extension procedures, the patient will be fitted with a splint to use at bedtime for up to 4 months. Teach the patient how to use the splint and to follow instructions for finger extension and flexion exercises several times a day for several months, as prescribed.

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DRUG FOR HYPERAMMONEMIA

Carglumic acid

Treating a dangerous genetic enzyme deficiency

A rare genetic disorder causes a deficiency of N-acetylglutamate synthase (NAGS), a hepatic enzyme. The deficiency can lead to a rapid increase in serum ammonia concentrations (hyperammonemia). Without prompt treatment, the ammonia build-up can cause severe brain damage and death.

Carglumic acid (*Carbaglu*, Orphan Europe) is a synthetic analogue of N-acetylglutamate, normally a product of NAGS that helps convert ammonia to urea. This oral drug is approved for adult and pediatric patients as adjunctive therapy for acute hyperammonemia and for maintenance therapy in patients with chronic hyperammonemia caused by NAGS deficiency. In patients with acute hyperammonemia, the drug is used with other ammonia-lowering drugs (such as sodium phenylbutyrate and sodium benzoate/sodium phenylacetate) and hemodialysis. Dietary protein restriction and hypercaloric intake are also recommended to block ammonia-generating catabolic pathways. During maintenance treatment, use of other ammonia-lowering therapies may be discontinued based on plasma ammonia concentrations. When these concentrations have normalized, protein intake can usually be increased; the goal is to permit unrestricted protein intake.

Precaution: Regularly monitor plasma ammonia concentrations and titrate the dosage based on response to treatment.

Adverse reactions: *vomiting, abdominal pain*, *pyrexia, tonsillitis*, *anemia, ear infection*, *nasopharyngitis, headache, diarrhea*

Supplied as: 200-mg scored tablets

Dosage: *For acute hyperammonemia*—100 mg/kg/day to 250 mg/kg/day. Divide total daily dosage into 2 to 4 doses that, in the treatment of adults, should be rounded to the nearest 100 mg (half tablet). *Maintenance dosage*—titrated to response; usually less than 100 mg/kg/day.

Nursing considerations: (1) Tablets shouldn't be swallowed whole or crushed. (2) For adults, disperse each tablet in at least 2.5 mL of water and administer immediately. Because the tablets don't dissolve completely and particles may remain in the container, add additional water to the container and have the patient swallow immediately to deliver the complete dose. (3) Don't mix the drug with anything besides water. (4) For pediatric patients, mix each tablet with 2.5 mL of water to provide a concentration of 80 mg/mL. Draw up the prescribed volume in an oral syringe and administer immediately. Discard the unused portion. Refill the oral syringe with 1 to 2 mL water and administer immediately. (5) Carglumic acid may be given via nasogastric tube in both adults and children.

DRUG FOR HEREDITARY ANGIOEDEMA

Ecallantide

Produced by yeast cells via recombinant DNA technology

A rare genetic disorder, hereditary angioedema (HAE) afflicts about 1 in 10,000 to 1 in 50,000 people.[1,2] It's characterized by severe and often painful edema that most often occurs in the extremities, face, gastrointestinal tract, or larynx. Laryngeal edema may lead to death from asphyxiation. HAE attacks are recurrent and usually unpredictable. The frequency of attacks varies widely; some patients experience weekly episodes, others may not have an attack for a year or more.[1]

Indicated for patients age 16 and older, ecallantide (*Kalbitor*, Dyax) is the second drug approved to treat acute HAE attacks, joining C1 esterase inhibitor. Administered subcutaneously, ecallantide is a selective, reversible inhibitor of plasma kallikrein. Unregulated activity of plasma kallikrein results in excessive production of bradykinin, a vasodilator thought to be responsible for signs and symptoms of HAE.

The most important risk associated with ecallantide is hypersensitivity reactions, including anaphylaxis, the subject of a boxed warning in the labeling.

Precaution: Signs and symptoms of an HAE attack are similar to those of a hypersensitivity reaction, which may occur in the first hour following drug administration. Closely monitor patients for chest discomfort, flushing, pharyngeal edema, pruritus, and other signs and symptoms of a hypersensitivity reaction. Ecallantide is contraindicated in patients who've previously experienced a hypersensitivity reaction to the drug.

Adverse reactions: *headache, nausea*, fatigue, *diarrhea*, upper respiratory tract infection, *injection site reactions*, *nasopharyngitis*, vomiting, pruritus, abdominal pain, *pyrexia*

Supplied as: vials containing 10 mg of the drug in 1 mL of solution

Dosage: 30 mg administered in three subcutaneous injections containing 10 mg each

Nursing considerations: (1) Store vials in the refrigerator and protect from light. (2) Administer injections in the abdomen, thigh, or upper arm. The site for each of the three injections may be in the same or a different anatomic location. (3) Injection sites should be separated by at least 5 cm (2 in) and administered away from the anatomical site of the HAE attack. (4) Use a large-bore needle to withdraw a 10 mg dose from the vial. Then change the needle to a size suitable for subcutaneous injection (27 gauge). Repeat this procedure for each of the 3 doses. (5) If the HAE attack persists following the initial 30 mg dose, an additional 30 mg dose may be given within 24 hours.

REFERENCES

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DRUG FOR GAUCHER DISEASE

Velaglucerase alfa

Long-term enzyme replacement therapy for adults and children

Gaucher disease is a rare autosomal recessive lysosome storage disorder caused by mutations in the glucosidase beta acid

gene. The disorder causes a deficiency of beta-glucocerebrosidase, resulting in accumulation of glucocerebroside in the bone marrow, liver, spleen, and other organs. Complications of type 1 Gaucher disease, the most common type, include anemia, thrombocytopenia, and organomegaly. An estimated 1 in 50,000 to 1 in 100,000 Americans have Gaucher disease, but it's more common among Jewish people of eastern and central European (Ashkenazi) descent.[1]

Velaglucerase alfa (*Vpriv*, Shire) is an I.V. drug indicated for long-term enzyme replacement therapy for adults and children age 4 and older with type 1 Gaucher disease. Imiglucerase has been the standard of treatment for type 1 Gaucher disease since its approval in 1994, but a recent shortage of this drug has spurred development of alternative treatments. Data comparing the two drugs are limited, but the cost of imiglucerase treatment is approximately $200,000 year. The manufacturer of velaglucerase alfa has announced it will price the new drug at about 15% less.[2,3]

Precautions: (1) Use caution in patients who've had hypersensitivity reactions to this drug or other enzyme replacement therapies. (2) Premedication with an antihistamine or corticosteroid may be indicated for patients who experience infusion-related reactions.

Adverse reactions: *infusion-related reactions (headache, dizziness, pyrexia, asthenia/fatigue, nausea, hypotension, hypertension); upper respiratory tract infection; abdominal, back, or joint pain; prolonged activated partial thromboplastin time (aPTT)*

Supplied as: a lyophilized powder in single-use vials containing 200 and 400 units per vial

Dosage: 60 units/kg every other week via 60-minute I.V. infusion

Nursing considerations: (1) Store vials in the refrigerator. (2) Reconstitute the drug with Sterile Water for Injection and dilute in 100 mL of 0.9% sodium chloride solution (see the product labeling for complete instructions). (3) In both the reconstitution and dilution steps, mix contents gently—don't shake. (4) Administer the drug immediately after preparation, if possible. If not, it can be stored in the refrigerator for up to 24 hours. (5) Give the diluted solution over 60 minutes. Don't administer it with other drugs or fluids in the same infusion tubing. (6) Administer the drug using an in-line low protein-binding 0.2 um filter. (7) Closely monitor the patient for adverse reactions, including hypersensitivity and infusion reactions. Upper respiratory tract infections, rash, pyrexia, and prolonged aPTT were more common in pediatric patients than adults. ■

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