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New Drugs 2018:

PART 2

BY DANIEL A. HUSSAR, PhD
REMINGTON PROFESSOR OF PHARMACY
PHILADELPHIA COLLEGE OF PHARMACY
UNIVERSITY OF THE SCIENCES
PHILADELPHIA, PA.

THIS ARTICLE REVIEWS nine drugs recently approved by the FDA, including:

> two new drugs for treatment of atopic dermatitis.

> two new drugs for treatment of moderate-to-severe plaque psoriasis.

> an important treatment advance for patients with primary progressive multiple sclerosis.

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.; 2018.

Nursing2018 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2018.

Physician's Desk Reference. 71st ed. Montvale, NJ: Medical Economics; 2018.

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The term *eczema* has been used to identify many dermatologic conditions associated with inflammation. Atopic dermatitis, the most common type of eczema, is a chronic inflammatory skin disease that typically begins in childhood and can last through adulthood. It's caused by a combination of genetic, immune, and environmental factors, and may be characterized by red, scaly lesions, pruritus, inflammation, cracking, exudation, and, eventually, coarsening and thickening of the skin.[1] An estimated 18 million Americans have atopic dermatitis.[2]

Two new drugs approved for patients with atopic dermatitis are described in the following discussions.

REFERENCES

1. FDA approves Eucrisa for eczema. U.S. Food & Drug Administration. News release. December 14, 2016.

2. National Eczema Foundation. Atopic dermatitis. https://nationaleczema.org.

Crisaborole

Soothing ointment for mild-to-moderate disease in adults and children

Classified as a phosphodiesterase 4 (PDE-4) inhibitor, crisaborole (*Eucrisa*, Pfizer) acts by increasing intracellular cyclic adenosine monophosphate levels, which may suppress the production of proinflammatory cytokines. Applied topically, it's indicated to treat mild-to-moderate atopic dermatitis in patients ages 2 years and older.[1]

The effectiveness of crisaborole was evaluated in two vehicle-controlled studies.[2,3] Investigator's Static Global Assessment (ISGA) scores, based on erythema, induration/papulation, and oozing/crusting on a severity scale of 0 to 4, were determined at baseline and the day following completion of the 28-day course of twice-daily treatment. Success was defined as an ISGA grade of Clear (score of 0) or Almost Clear (score of 1) with a 2-grade or greater improvement from baseline. Patients treated with crisaborole achieved a greater response with successful results experienced by 33% and 31% of the patients in the two studies, compared with 25% and 18% of patients treated with the vehicle.

Precaution: In trials, a few hypersensitivity reactions were reported. Discontinue treatment in patients who experience such events.

Adverse reaction: application-site pain such as stinging and burning

Supplied as: ointment containing the medication in a 2% concentration

Dosage: apply a thin layer twice a day to affected skin

Nursing considerations: (1) Teach patients to wash their hands following application of the ointment (unless the hands are being treated). (2) Tell patients to discontinue the drug and report signs and symptoms to the healthcare provider if they experience severe pruritus, edema, and/or erythema at the application site or at a distant site. (3) Warn patients that the ointment is for external use only, and not for ophthalmic, oral, or intravaginal use. (4) Tell them to store the ointment at room temperature with the cap closed tightly.

REFERENCES

1. FDA approves Eucrisa for eczema. U.S. Food & Drug Administration. News release. December 14, 2016.

2. U.S. Department of Health and Human Services. Statistical Review and Evaluation (Eucrisa). www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM538659.pdf.

3. Eurcrisa—crisaborole ointment, 2%, for topical use. Prescribing Information. http://labeling.pfizer.com/ShowLabeling.aspx?id=5331.

Dupilumab

Administered via subcutaneous injection

Dupilumab (*Dupixent*, Regeneron; Sanofi) is a human monoclonal antibody that acts as an interleukin-4 (IL-4) receptor alpha inhibitor.[1] It inhibits IL-4 and interleukin-13 (IL-13) cytokine-induced responses, including the release of proinflammatory cytokines.

Administered subcutaneously, dupilumab is indicated to treat adults with moderate to severe atopic dermatitis whose disease can't be adequately controlled with topical prescription therapies. It may be used with or without a topical corticosteroid such as triamcinolone. Topical calcineurin inhibitors (tacrolimus or pimecrolimus) may also be used in the treatment regimen, but they should be reserved for problem areas only, such as the face, neck, intertriginous, and genital areas.

The effectiveness of dupilumab was established in three placebo-controlled clinical trials that included more than 2,100 patients with moderate-to-severe atopic dermatitis that wasn't adequately controlled with topical medications.[2] The rate of success was generally greater in the study in which dupilumab and topical corticosteroids were used concomitantly.

Dupilumab is being evaluated in patients with asthma, chronic sinusitis, and eosinophilic disorders, but these aren't labeled indications at present. The effectiveness and safety of dupilumab in patients under age

18 with atopic dermatitis is also being evaluated. Because atopic dermatitis is often first experienced during childhood, indications for the drug may soon be expanded to include these pediatric patients.

Precautions: (1) Discontinue treatment if clinically significant hypersensitivity occurs. Hypersensitivity reactions were experienced by less than 1% of the patients in the clinical studies. (2) Instruct patients with atopic dermatitis who also have asthma not to adjust or stop their asthma treatment without consulting their healthcare provider. (3) Dupilumab may cause a change in eosinophil concentrations. Because eosinophils may be involved in the immunologic response to helminth infections, patients with helminth infections were excluded from participation in clinical studies. It isn't known whether dupilumab will influence the immune response against helminth infections. (4) Patients being treated with dupilumab should avoid receiving live vaccines.

Adverse reactions: injection-site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, dry eye. In trials, most patients who experienced conjunctivitis or keratitis recovered or were recovering during the treatment period.

Supplied as: single-dose prefilled syringes with a needle shield that contain the drug in a concentration of 300 mg/2 mL.

Dosage: Initially, 600 mg administered subcutaneously as two 300 mg injections at different injection sites. Following the initial dose, the recommended dosage is 300 mg every other week.

Nursing considerations: (1) Educate patients about proper subcutaneous injection technique. (2) Teach patients to prepare the drug as directed in the Prescribing Information and to administer the drug subcutaneously into the thigh or abdomen (except for the 2 inches around the umbilicus). If a caregiver administers the injection, it can be administered into the upper arm. (3) If they miss a dose, tell patients to administer the injection within 7 days of the missed dose and then resume the original schedule. If the missed dose isn't administered within 7 days, the patient should wait until the next dose on the schedule. (4) Advise patients to discontinue the drug and seek immediate medical attention if they experience signs and symptoms of a systemic hypersensitivity reaction such as generalized urticaria and serum sickness. (5) Tell patients to inform their healthcare provider if they develop new onset or worsening eye symptoms. (6) Warn patients with asthma not to adjust or stop their asthma treatment without talking to their healthcare provider. (7) Instruct the patient to store syringes in a refrigerator and to discard any unused portions because the drug contains no preservative. Teach patients recommended disposal procedures, including safe sharps disposal.

REFERENCES

1. FDA approves new eczema drug Dupixent. U.S. Food & Drug Administration. News release. March 28, 2017.

2. Dupixent (dupilumab) injection, for subcutaneous use. Prescribing Information. www.regeneron.com/sites/default/files/Dupixent_FPI.pdf.

DRUG FOR TARDIVE DYSKINESIA

Valbenazine tosylate

First drug approved for this disabling movement disorder

A neurologic disorder, tardive dyskinesia is characterized by repetitive involuntary movements, usually of the mouth, lips, and tongue and, occasionally, rapid movement of the arms and legs. Some patients experience difficulty speaking, swallowing, and breathing. The disorder can be disabling and further stigmatizing for patients with mental illness.[1]

Tardive dyskinesia occurs most often in patients treated for long periods with older antipsychotic medications (for example, phenothiazines or haloperidol), and may develop during the period of treatment or even after treatment is discontinued. The long-term use of metoclopramide for gastrointestinal conditions is among other drugs associated with the occurrence of tardive dyskinesia.[2]

Treatment has generally been limited to discontinuing or reducing the dosage of the causative medication or using different medications. However, signs and symptoms usually persist even when the medication is discontinued. In addition, stopping the use of an antipsychotic medication can have serious consequences for patients being treated for diseases such as schizophrenia.

Valbenazine tosylate (*Ingrezza*, Neurocrine) was the first drug to be approved to treat adults with tardive dyskinesia and represents an important advance in the treatment of this disorder.[3] Subsequent to this approval, the indications for deutetrabenazine (discussed below) were expanded to include tardive dyskinesia.

Valbenazine's specific mechanism of action is unknown, but its therapeutic effect is thought to be mediated through the reversible inhibition of vesicular monoamine transporter 2 (VMAT2), a transporter that regulates monoamine (for example, dopamine) uptake from the cytoplasm to the synaptic vesicle for storage and release. Its actions are most similar to those of tetrabenazine, which was the first drug approved for the treatment of chorea associated with Huntington disease. Both valbenazine and tetrabenazine are converted to the active metabolite, alpha-dihydrotetrabenazine.

The effectiveness of valbenazine was demonstrated in a placebo-controlled

clinical trial of 234 patients with moderate-to-severe tardive dyskinesia who had underlying schizophrenia/schizoaffective disorder or mood disorder. Approximately 85% were being treated with antipsychotic agents. The Abnormal Involuntary Movement Scale (AIMS) was used for the assessment of tardive dyskinesia severity, and the primary efficacy endpoint was the mean change from baseline in the AIMS dyskinesia total score at the end of Week 6.

The patients treated with valbenazine experienced improvement in the severity of abnormal involuntary movements compared with those who received placebo. At the end of Week 6, patients initially assigned to placebo were rerandomized to receive valbenazine and follow-up was continued through Week 48, followed by a 4-week period off of the drug. When valbenazine treatment was discontinued, the mean AIMS dyskinesia total score appeared to return toward baseline, suggesting a need for ongoing treatment.

Precautions: (1) Avoid use of valbenazine in patients with congenital long QT syndrome or with dysrhythmias associated with a long QT interval. Valbenazine may prolong the QT interval, although the degree of QT prolongation isn't clinically significant at the recommended dosage. However, in patients who are CYP2D6 poor metabolizers or who are taking a strong CYP2D6 or CYP3A4 inhibitor, drug concentrations may be higher and QT prolongation clinically significant; a dosage reduction is usually indicated. (2) Closely monitor patients for depression and suicidality, which are the subject of a boxed warning in the labeling for the related drug tetrabenazine along with several contraindications. Although these risks aren't emphasized in the labeling for valbenazine, the similarities of the two drugs and limited experience with the new drug warrant close monitoring of its use. (3) Valbenazine isn't recommended for use in patients with severe renal impairment (creatinine clearance less than 30 mL/min). A dosage reduction is recommended for patients with moderate or severe hepatic impairment. (4) Valbenazine shouldn't be used concurrently with a monoamine oxidase inhibitor (such as isocarboxazid, phenelzine, or selegiline) because the resultant increased concentration of monoamines in synapses may increase the risk of adverse reactions such as serotonin syndrome or reduce valbenazine's therapeutic effect. (5) The concentrations, actions, and risks of valbenazine and its active metabolite are increased by the concurrent use of a strong CYP3A4 inhibitor (such as clarithromycin or itraconazole), or a strong CYP2D6 inhibitor (such as paroxetine, fluoxetine, or quinidine), and a reduction in dosage of the new drug is often necessary. (6) Valbenazine isn't recommended for concurrent use with strong CYP3A4 inducers (such as carbamazepine or St. John's wort) because they reduce valbenazine's concentration and action. (7) In patients taking digoxin concurrently, valbenazine may inhibit intestinal P-glycoprotein and increase digoxin concentrations. A reduction of the digoxin dosage may be necessary.

Adverse reaction: somnolence

Supplied as: 40 mg and 80 mg capsules

Dosage: Initially, 40 mg once a day. After 1 week, increase the dosage to the recommended maintenance dosage of 80 mg once a day. See the Prescribing Information for dosage adjustments recommended for patients with moderate or severe hepatic impairment, patients treated concurrently with a strong CYP3A4 inhibitor, patients who are known to be CYP2D6 poor metabolizers, and patients treated concurrently with a strong CYP2D6 inhibitor.

Nursing considerations: (1) Because valbenazine may cause somnolence, advise patients not to perform activities requiring mental alertness such as driving or operating hazardous machinery until they know how the drug affects them. (2) Tell patients that the drug may be taken without regard to food.

REFERENCES

1. FDA approves first drug to treat tardive dyskinesia. U.S. Food & Drug Administration. News release. April 11, 2017.
2. Reglan ODT (metoclopramide) orally disintegrating tablets. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2010/021793s008lbl.pdf.
3. Ingrezza (valbenazine) capsules, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209241lbl.pdf.

DRUG FOR CHOREA IN HUNTINGTON DISEASE

Deutetrabenazine

Now indicated for both Huntington disease and tardive dyskinesia

Huntington disease is an inherited neurologic disorder that causes the progressive breakdown of nerve cells in the brain. It's caused by an inherited defect in a single gene and each child of a parent with the disease has a 50% chance of inheriting the mutation. Approximately 30,000 people in the United States have Huntington disease, symptoms of which usually appear in adulthood between ages 30 and 50. The signs and symptoms include a wide spectrum of movement (chorea), cognitive, and psychiatric manifestations. Chorea is primarily characterized by involuntary jerking or writhing movements and is experienced by 90% of patients with Huntington disease.[1]

In 2008, tetrabenazine became the first drug approved to treat chorea associated with Huntington disease. Deutetrabenazine (*Austedo*, Teva) was approved to treat chorea associated with Huntington disease in April 2017. In August, its indications were expanded to include tardive dyskinesia in adults as well.[2]

Deutetrabenazine is the deuterated form of tetrabenazine, and is

metabolized at a slower rate than tetrabenazine and can be administered less frequently. As with tetrabenazine, deutetrabenazine is thought to act as a reversible VMAT2 inhibitor. The two drugs haven't been directly compared in clinical studies, but separate studies of the two drugs suggest that they're similar in effectiveness.

Both deutetrabenazine and tetrabenazine may increase the risk of depression and suicidality and cause other serious adverse events. A boxed warning regarding depression and suicidality is included in their labeling. Data from separate clinical studies of the two drugs suggest that deutetrabenazine is less likely to cause adverse events.

Precautions: (1) Contraindicated in patients who are suicidal and in patients with untreated or inadequately treated depression. (2) Contraindicated in patients with hepatic impairment and in patients treated with a monoamine oxidase inhibitor (MAOI) or reserpine. At least 20 days should elapse following the discontinuation of reserpine, and 14 days following the discontinuation of an MAOI, before initiating treatment with deutetrabenazine. (3) Contraindicated in patients currently taking tetrabenazine, but deutetrabenazine may be initiated the day following discontinuation of tetrabenazine. (4) Somnolence is the most common dose-limiting adverse reaction. Concurrent use of alcohol and/or other sedating drugs increases the risk of central nervous system depressant effects. (5) Deutetrabenazine may prolong the QT interval. Avoid concurrent use with other drugs that are known to prolong the QT interval, such as certain antipsychotic agents (for example, chlorpromazine, haloperidol, thioridazine, and ziprasidone), certain antimicrobial agents (such as moxifloxacin), or Class IA (such as quinidine or procainamide) or Class III (such as amiodarone or sotalol) antiarrhythmic medications. (6) The concurrent use of a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, quinidine, or bupropion) has been shown to increase the systemic exposure to the active metabolites of deutetrabenazine by approximately threefold, and a reduced dosage of the new drug is recommended.

Adverse reactions: *In patients treated for Huntington disease:* somnolence, diarrhea, dry mouth, fatigue. *In patients treated for tardive dyskinesia*: nasopharyngitis, insomnia.

Supplied as: 6 mg, 9 mg, and 12 mg tablets

Dosage: initially, 6 mg twice a day with food. Titrate the dosage upward at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea or tardive dyskinesia, up to a maximum recommended daily dosage of 48 mg (24 mg twice a day). Total daily dosages of 12 mg or above should be administered in two divided doses. Consult the Prescribing Information for dosage adjustments for patients being treated concurrently with a strong CYP2D6 inhibitor and patients being switched from tetrabenazine to deutetrabenazine.

Nursing considerations: (1) Tell patients to take the tablets with food and to swallow them whole; warn them not to chew, crush, or break the tablets. (2) Because sedation is the most common dose-limiting adverse reaction, caution patients about driving or engaging in other activities requiring mental alertness until they know how the drug affects them. (3) Warn patients that consuming alcoholic beverages or taking other sedating drugs or substances increases the risk of central nervous system depressant effects.

REFERENCES

1. Huntington's Disease Society of America. What is HD? http://hdsa.org/what-is-HD.

2. Austedo (deutetrabenazine) tablets, for oral use. Prescribing Information. www.austedo.com/hcp/renderpdf.aspx?file=PrescribingInformation.pdf.

DRUGS FOR PSORIASIS

Brodalumab

A risk for suicidal ideation calls for caution

Because certain naturally occurring interleukins (ILs) have been identified as having a role in the occurrence and worsening of psoriasis, the development of IL receptor inhibitors has been a focus of recent research efforts. Brodalumab (*Siliq*, Valeant) is the third monoclonal antibody that acts as an IL-17 receptor A (IL-17RA) antagonist. Administered subcutaneously, it's indicated to treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and who've failed to respond or have lost response to other systemic therapies. The effectiveness of brodalumab was demonstrated in three placebo-controlled studies that included more than 4,000 participants.[1]

The greatest concern with brodalumab is the risk of suicidal ideation and behavior. Although a causal association hasn't been established, four patients treated with brodalumab in the clinical studies committed suicide compared with none of those receiving placebo. This is the subject of a boxed warning in the labeling and the basis for limiting the availability of the drug through a restricted program designated as the SILIQ REMS Program, in which prescribers and pharmacies must be certified in the program and patients must sign an agreement form.

Precautions: (1) Contraindicated in patients with Crohn disease. Although patients with active Crohn disease were excluded from the clinical trials, one patient developed Crohn disease and the drug was discontinued. In other studies, exacerbation of Crohn disease was observed in patients treated with brodalumab. (2) In patients with a history of depression and/or suicidality,

brodalumab should be used only if the anticipated benefit justifies the risk. (3) As with other medications that suppress immune function, brodalumab increases the risk of infection. If a serious infection occurs during treatment or an infection isn't responding to standard therapy, brodalumab should be discontinued until the infection resolves, and the patient should be closely monitored. (4) Patients should avoid the use of live vaccines during treatment. (5) Patients should be evaluated for tuberculosis infection before initiating treatment with brodalumab. In patients with a history of latent or active tuberculosis in whom an adequate course of antitubercular treatment can't be confirmed, such treatment should be considered before initiating treatment with the new drug.

Adverse reactions: arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection-site reactions, influenza, neutropenia, tinea infections

Supplied as: single-dose prefilled syringes containing 210 mg of the drug in 1.5 mL of solution

Dosage: 210 mg subcutaneously at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks. If the patient doesn't achieve an adequate response after 16 weeks of treatment, discontinuing the drug should be considered.

Nursing considerations: (1) Teach patients about possible adverse reactions including Crohn disease, infection, and suicidal ideation. (2) Tell patients to notify their healthcare provider immediately if they experience new or worsening depression or other disturbing changes in mood or behavior. In a crisis, patients should call 911 or the National Suicide Prevention Lifeline at 1-800-273-8255. (3) Review the Instructions for Use with patients and teach them how to inject the drug properly and safely dispose of syringes. (4) Instruct patients to store syringes in a refrigerator in the original carton. Before administering the drug, they should wait for it to reach room temperature (about 30 minutes after removing the syringe from the refrigerator). If necessary, however, the syringes can be stored at room temperature in the original carton for a maximum single period of 14 days with protection from light and heat sources. (5) Patients receive a Siliq Patient Wallet Card listing possible signs and symptoms as part of the treatment program; tell them to carry it with them at all times and show it to all healthcare providers.

REFERENCE

1. Siliq (brodalumab) injection, for subcutaneous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf.

Guselkumab

Subcutaneous treatment for moderate-to-severe plaque psoriasis

A human monoclonal antibody, guselkumab (*Tremfya*, Janssen) selectively binds to the p19 subunit of interleukin-23 (IL-23), a cytokine involved in normal inflammatory and immune responses. This action inhibits the interaction of IL-23 with the IL-23 receptor and inhibits the release of proinflammatory cytokines and chemokines. Administered subcutaneously, guselkumab is indicated to treat adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

Like other medications that suppress immune function, guselkumab increases the risk of infection. Patients should be evaluated for tuberculosis infection before treatment with guselkumab begins. In patients with a history of latent or active tuberculosis in whom an adequate course of antitubercular treatment can't be confirmed, such treatment should be considered before initiating treatment with the new drug.

Precautions: (1) Treatment shouldn't be initiated in patients with a clinically important active infection until the infection resolves or is adequately treated. If a serious infection occurs during treatment or an infection isn't responding to standard therapy, guselkumab should be discontinued until the infection resolves and the patient should be closely monitored. (2) Patients should avoid use of live vaccines during treatment.

Adverse reactions: upper respiratory infections, headache, injection-site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, herpes simplex infections

Supplied as: single-dose prefilled syringes containing 100 mg of the drug (in 1 mL)

Dosage: 100 mg at Weeks 0 and 4, and every 8 weeks thereafter.

Nursing considerations: (1) Tell patients to notify the healthcare provider if they develop signs and symptoms of infection. (2) Review the Instructions for Use with patients and teach them how to administer the injection and dispose of syringes properly. (3) Instruct patients to store syringes in a refrigerator in the original carton. After removing a syringe from the refrigerator, they should give the drug time to reach room temperature (about 30 minutes) before administering it. (4) Because live vaccines are contraindicated during treatment, encourage patients to complete all appropriate immunizations according to current immunization guidelines before starting treatment.

REFERENCE

1. Tremfya (guselkumab) injection, for subcutaneous use. Prescribing Information. www.janssenmd.com/pdf/tremfya/tremfya_pi.pdf.

ANTIPARKINSON DRUG

Safinamide mesylate

Monitor patients for compulsive behavior.

Safinamide mesylate (*Xadago*, Newron) is the third monoamine oxidase type B (MAO-B) inhibitor to be marketed in the United States to treat patients with Parkinson disease, joining selegiline and rasagiline. By inhibiting MAO-B activity, these drugs reduce the catabolism of dopamine, resulting in increased dopamine concentrations and dopaminergic activity in the brain. The inhibition of MAO-B activity by safinamide is considered to be reversible, whereas selegiline and rasagiline irreversibly inhibit MAO-B activity. However, whether this distinction has clinical importance is unknown.[1]

The selective action of these three drugs in inhibiting MAO-B has been suggested to decrease the risk of adverse reactions and drug interactions associated with nonselective monoamine oxidase inhibitors such as phenelzine and tranylcypromine, which also inhibit MAO-A. However, the selectivity of the action is dose-related, and the experience of patients treated with the same dosage may vary widely. Accordingly, many of the warnings and precautions for nonselective MAO inhibitors should also be observed for selective MAO-B inhibitors including safinamide.

Safinamide is specifically indicated as adjunctive treatment to levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes (periods during treatment when Parkinson symptoms such as tremor and difficulty walking increase).[1] Its effectiveness was evaluated in two placebo-controlled studies in patients also being treated with levodopa/carbidopa, dopamine agonists, catechol-O-methyl transferase inhibitors, anticholinergics, and/or amantadine. The primary measure of effectiveness was the change from baseline in "on" time without troublesome dyskinesia. In both studies, safinamide significantly increased "on" time compared with placebo, and this was accompanied by a similar significant reduction in "off" time, as well as a reduction in the Unified Parkinson's Disease Rating Scale Part III scores that were assessed during "on" time. Safinamide hasn't been shown to be effective when used as monotherapy.

Patients treated with dopaminergic medications, including the MAO-B inhibitors, have experienced adverse reactions for which precautions must be observed with the use of safinamide. These include hallucinations, psychotic behavior, sleep attacks/sudden onset of sleep, and/or falling asleep while engaged in daily activities. Treatment with the drug is usually discontinued in patients who experience any of these reactions. If treatment is continued, however, patients should be advised to avoid driving and other potentially dangerous activities.

These medications can also cause impulse control/compulsive behaviors including intense urges to gamble, spend money, and/or binge eat, as well as increased sexual urges. Safinamide is generally not recommended for patients with a major psychotic disorder.

Precautions: (1) Contraindicated in patients with severe hepatic impairment or a history of hypersensitivity to safinamide; the dosage should be reduced in patients with moderate hepatic impairment. (2) Contraindicated for concurrent use with another MAO inhibitor, including the antibacterial agent linezolid, because of the potential for a hypertensive crisis. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with another MAO inhibitor. (3) Because of the risk of hypertension, patients should avoid food high in tyramine, including aged, fermented, cured, smoked, and pickled foods such as aged cheese. (4) Contraindicated for concurrent use with certain sympathomimetic medications, such as amphetamine, methylphenidate, and their derivatives. If safinamide is used concurrently with other prescription or nonprescription sympathomimetic medications, including oral, nasal, or ophthalmic decongestants and cold remedies, patients should be monitored for hypertension. (5) Contraindicated for concurrent use with certain serotonergic drugs including serotonin-norepinephrine reuptake inhibitors such as duloxetine and venlafaxine; tricyclic, tetracyclic, or triazolopyridine antidepressants; cyclobenzaprine; or St. John's wort, because of the risk of serotonin syndrome. Although not specifically contraindicated, concurrent use of safinamide with a selective serotonin reuptake inhibitor such as fluoxetine or sertraline is best avoided. (6) Contraindicated for concurrent use with opioids including meperidine, methadone, propoxyphene, and tramadol. At least 14 days should elapse between discontinuation of safinamide and initiation of treatment with a serotonergic drug or opioid. (7) Contraindicated for concurrent use with dextromethorphan because of reports of psychosis or bizarre behaviors in patients taking other MAO inhibitors and dextromethorphan. (8) Reducing the dosage of levodopa or other dopaminergic treatment should be considered in patients who experience dyskinesia or an exacerbation of preexisting dyskinesia. (9) Patients with a history or family history of retinal/macular disease should be monitored for vision changes because retinal degeneration and other ocular adverse reactions have been reported in animal studies.

Adverse reactions: dyskinesia, falls, nausea, insomnia

Supplied as: 50 mg and 100 mg tablets

Dosage: initially, 50 mg once a day at the same time each day. After 2

weeks, the dosage may be increased to 100 mg once a day, based on patient need and tolerability. In patients with moderate hepatic impairment, the maximum recommended dosage is 50 mg once a day. If a patient receiving treatment with this dosage experiences worsening of hepatic impairment, the drug should be discontinued.

Nursing considerations: (1) Warn patients not to discontinue treatment without the healthcare provider's guidance. A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability) has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone. The dosage should be decreased to 50 mg once a day for 1 week before stopping therapy. (2) Warn patients about the risk of hypertension if safinamide is used concurrently with other prescription or nonprescription sympathomimetic products, including oral, nasal, or ophthalmic decongestants and cold remedies. Advise them to consult the healthcare provider before taking any new prescription or over-the-counter medication. (3) Tell patients to avoid foods containing large amounts of tyramine, such as aged, fermented, cured, smoked, and pickled foods, including aged cheese. (4) Monitor all patients for hypertension or exacerbation of existing hypertension during treatment. (5) Teach patients that safinamide can be taken without regard to meals. They should take it at the same time each day. If they miss a dose, they should take the next dose at the same time the next day.

REFERENCE

1. Xadago (safinamide) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/207145lbl.pdf.

DRUG FOR MULTIPLE SCLEROSIS

Ocrelizumab

An important advance for patients with certain severe forms of MS

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune disease of the central nervous system that occurs more often in women than in men. Most patients first experience symptoms between ages 20 and 40.[1]

Relapsing-remitting MS, also called relapsing MS, is the most common form of the disease. Patients experience episodes of worsening function (relapses) that are followed by recovery periods (remissions) of varying duration. As the disease continues, remissions may be incomplete. Eventually, some patients become disabled and experience cognitive decline.[1]

According to the CDC, approximately 15% of patients with MS have primary progressive MS (PPMS), which is characterized by steadily worsening function from the onset of symptoms, sometimes without early relapses and remissions.[1] Ocrelizumab (*Ocrevus*, Genentech) is indicated to treat patients with relapsing or primary progressive forms of MS.[2] As the first drug approved by the FDA to treat PPMS, it's an important advance for patients with more severe forms of the disease.

A humanized monoclonal antibody, ocrelizumab is directed against CD20-expressing B cells. CD20 is a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab causes antibody-dependent cellular cytolysis and complement-mediated lysis. It's administered by I.V. infusion.

Infusion reactions occurred in 40% of patients in one clinical trial, with the highest incidence occurring with the first infusion. Manifestations ranged from relatively mild dermatologic events to serious reactions such as bronchospasm and hypotension. Although no fatal infusion reactions occurred in the clinical studies, 0.3% of patients experienced serious reactions and some required hospitalization.

Precautions: (1) Contraindicated in patients with a history of life-threatening infusion reactions to ocrelizumab. If such reactions occur during treatment, the infusion should be immediately and permanently stopped and appropriate supportive treatment initiated. (2) To reduce the frequency and severity of infusion reactions, a corticosteroid and antihistamine should be administered as premedications, and the addition of an antipyretic can also be considered. (3) Because the other anti-CD20 antibody, rituximab, has been associated with reactivation of hepatitis B virus (HBV) infection, ocrelizumab is contraindicated in patients with active HBV infection. (4) Vaccination with live or live-attenuated vaccines isn't recommended during treatment with ocrelizumab, or following treatment until B-cell repletion. Immunizations according to guidelines should be administered at least 6 weeks before treatment with ocrelizumab starts. (5) An increased risk of malignancy, including breast cancer, may be associated with the use of ocrelizumab. Patients should follow standard breast cancer screening guidelines. (6) The concomitant use of ocrelizumab and other immune-modulating or immunosuppressive medications, including corticosteroids, may increase the risk of immunosuppression. Use caution if these drugs are used concurrently, and also sequentially due to the long duration of action of the new drug and certain other medications.

Adverse reactions: upper respiratory tract infections, infusion reactions, skin infections, lower respiratory tract infections, herpes virus-associated infections

Supplied as: single-dose vials containing 300 mg of the drug in 10 mL

Dosage: Initially, 300 mg in 250 mL of diluted solution, followed 2 weeks

later by a second 300 mg infusion. Each of these infusions should be started at a rate of 30 mL/h; the rate may be increased by 30 mL/h every 30 minutes to a maximum of 180 mL/h, for a total infusion duration of 2.5 hours or longer. Subsequent doses are administered as a single 600 mg infusion (in 500 mL) every 6 months. Consult the Prescribing Information for details on rate titration for subsequent doses and for recommended dosage modifications for patients who experience infusion reactions.

Nursing considerations: (1) Before starting ocrelizumab treatment, patients should be screened for active HBV infection. (2) Assess patients for active infection of any type before administering each dose. If an active infection is present, the infusion of ocrelizumab should be delayed until the infection resolves. (3) As prescribed, premedicate patients with an antihistamine such as diphenhydramine 30 to 60 minutes before the infusion, and with 100 mg of methylprednisolone (or an equivalent corticosteroid) I.V. approximately 30 minutes before the infusion. The prescriber may also add an antipyretic such as acetaminophen to the premedication regimen. (4) The intended dose should be withdrawn from the vial and diluted into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL. Allow the diluted infusion solution to reach room temperature. Administer it through a dedicated line using an infusion set with a 0.2 or 0.22 micron in-line filter. (5) Closely monitor patients for infusion reactions during the infusion and for at least 1 hour after the infusion is completed. (6) Maintenance doses of the drug must be separated by an interval of at least 5 months. If a planned infusion is missed, it should be administered as soon as possible. The dosage schedule should then be adjusted so that the next scheduled dose is administered 6 months after the missed dose. (6) Advise female patients to maintain routine breast cancer screening according to current guidelines. (7) Store vials in a refrigerator. Use prepared solution immediately or store it up to 24 hours in the refrigerator or up to 8 hours at room temperature. If an infusion can't be completed the same day, discard the unused solution.

REFERENCES

1. FDA approves new drug to treat multiple sclerosis. U.S. Food & Drug Administration. News release. March 29, 2018.

2. Ocrevus (ocrelizumab) injection, for intravenous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf.

ANTIARTHRITIC DRUG

Sarilumab

Available for use as monotherapy or with other agents

Approximately 1.3 million Americans have rheumatoid arthritis, a chronic inflammatory autoimmune disease in which the immune system attacks the joints, causing inflammation, pain, and eventually joint damage and disability.[1] Interleukin-6 (IL-6) is a proinflammatory cytokine produced in various cells, including T cells, B cells, lymphocytes, and synovial and endothelial cells affected by inflammatory processes such as rheumatoid arthritis.

Sarilumab (*Kevzara*, Regeneron; Sanofi) is a humanized monoclonal antibody that binds to both soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signaling through these receptors.[2] Its properties are most similar to those of the IL-6 inhibitor tocilizumab. Administered subcutaneously, it's indicated for adults with moderately to severely active rheumatoid arthritis who've had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. In two placebo-controlled clinical trials, a greater proportion of patients who received sarilumab experienced improvement in signs and symptoms of rheumatoid arthritis compared with patients who received a placebo.[3]

The labeling for sarilumab includes a boxed warning regarding the risk of serious infections, which is highest in patients treated concurrently with other immunosuppressive drugs, such as methotrexate or corticosteroids. Sarilumab may be used as monotherapy or in combination with methotrexate or other conventional DMARDs.

Precautions: (1) Sarilumab shouldn't be used in patients with an active infection, including localized infections. If a serious infection develops during treatment with sarilumab, therapy should be interrupted until the infection is controlled. (2) Sarilumab shouldn't be used concurrently with another biologic therapy because of the increased risk of infection. (3) Before treatment with sarilumab, patients should be screened for tuberculosis (TB). Patients with active or latent TB should be treated before initiating sarilumab therapy. Antitubercular treatment should also be considered for patients who test negative for latent TB but have risk factors for TB infection. (4) Patients are also at greater risk of invasive fungal infections and other infections caused by opportunistic pathogens. Reactivation of viral infections, such as herpes zoster, has been reported with immunosuppressive biologic therapies, and reactivation of HBV may also be a risk. (5) Patients shouldn't receive live vaccines while being treated with sarilumab. They should receive any recommended vaccinations before therapy starts. (6) Like other immunosuppressant drugs, sarilumab may increase the risk of malignancies. (7) Gastrointestinal perforations were reported in the clinical studies of sarilumab, primarily as a complication of diverticulitis. This risk is also increased by the concomitant use of nonsteroidal anti-inflammatory drugs or corticosteroids. (8) Multiple lab abnormalities are associated with sarilumab. Treatment shouldn't be

initiated in patients with an absolute neutrophil count less than 2,000/mm^3 or a platelet count less than 150,000/mm^3, or in those who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values above 1.5 times the upper limit of normal. (9) Treatment with sarilumab isn't recommended in patients with active hepatic disease or hepatic impairment. (10) Elevated IL-6 concentrations can influence the expression and activity of certain cytochrome P450 (CYP) enzymes, and this effect may be clinically relevant with the use of CYP substrates with a narrow therapeutic index, such as warfarin. Because sarilumab may reverse this effect of IL-6 and restore CYP activity, a dosage adjustment of the CYP substrate may be indicated. Sarilumab's effect on enzyme activity may persist for several weeks after stopping therapy. Consult the Prescribing Information for more details about potential drug interactions.

Adverse reactions: neutropenia, increased ALT, injection-site erythema, upper respiratory infections, urinary tract infections

Supplied as: single-dose prefilled syringes containing the drug in concentrations of 150 mg/1.14 mL and 200 mg/1.14 mL

Dosage: 200 mg once every 2 weeks via subcutaneous injection. The dosage may be reduced to 150 mg once every 2 weeks to manage neutropenia, thrombocytopenia, and elevated liver enzymes. Consult the Prescribing Information for other dosage adjustment recommendations.

Nursing considerations: (1) Make sure patients undergo recommended lab tests before initiating treatment, and tell them they must continue lab testing throughout therapy as directed by the healthcare provider. Neutrophil count, platelet count, ALT, and AST should be determined before treatment starts and monitored 4 to 8 weeks after the start of therapy and every 3 months thereafter. Blood lipid concentrations should be assessed 4 to 8 weeks after starting treatment and then at approximately 6-month intervals. (2) Review Instructions for Use with patients and teach them proper technique for administering a subcutaneous injection. (3) Warn patients about the infection risk associated with this drug and tell them to notify the healthcare provider immediately if they develop any signs and symptoms of an infection. (4) Tell patients to store syringes in a refrigerator in the original carton to protect from light. Before use, they should let the syringe warm to room temperature for approximately 30 minutes. A syringe should be used within 14 days after being taken out of the refrigerator. (5) Tell patients not to reuse syringes, and teach them how to create and use a sharps disposal container. ■

REFERENCES

1. Sanofi and Regeneron announce FDA approval of Kevzara (sarilumab) for the treatment of moderately to severely active rheumatoid arthritis is adult patients. Sanofi US. News release. May 22, 2017.

2. Kevzara (sarilumab) injection, for subcutaneous use. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf.

3. U.S. Food and Drug Administration. Drug trials snapshots: Kevzara. www.fda.gov/Drugs/InformationOnDrugs/ucm562381.htm.

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