CE 2.9 CONTACT HOURS Rx 2.9 CONTACT HOURS

Annual Drug Update 2011 IN REVIEW

Abstract: Many new medications were approved throughout 2011. This article will cover a variety of drugs that will be useful in nurse practitioner practice.

By Jennifer M. Belavic, PharmD, BCPS, FASCP

Key words: breakthrough pain, chronic obstructive pulmonary disease hepatitis C; diabetes mellitus; kidney transplantation; seizure

▼ Infectious disease

Fidaxomicin (Dificid)

Rates of *Clostridium difficile* infection (CDI) have increased over the past decade worldwide. It has become the most common cause of infectious diarrhea in the healthcare setting. Despite appropriate treatment, recurrences of CDI are becoming a greater problem.[1]

C. difficile is an anaerobic, spore-forming, toxin-producing, Gram-positive rod.[2] The toxins that cause colitis and diarrhea are enterotoxin A and cytotoxin B. Colonization of *C. difficile* occurs via the fecal-oral route.

Recurrence rates of 25% have been shown even after treatment with metronidazole and vancomycin for first occurrences of CDI. On average, recurrences appear within 1 to 2 weeks after treatment is completed. Once a patient develops a recurrence of *C. difficile*, 45% to 65% of patients will develop repeated episodes of CDI.[1,2]

Risk factors for recurrent episodes of CDI are advanced age, hospitalizations, previous episodes of CDI, use of fluoroquinolone antibiotics, stroke, dialysis, and a history of glycopeptide use.[2]

Some researchers have noted that the increase in incidence has been associated with the emergence of the *C. difficile* strains of North American Pulsed Field type 1 (NAP1), restriction-endonuclease analysis type BI, and polymerase-chain-reaction ribotype 027 (NAP1/BI/027 strain).[3] Due to these new developments, therapy must be directed at providing antimicrobial coverage for this strain. For this reason, a new antibiotic was approved to add to *C. difficile* treatment plans.[3]

On May 27, 2011, the FDA approved fidaxomicin (Dificid) for the treatment of *C. difficile*-associated diarrhea. Dificid is distributed by Optimer Pharmaceuticals, Inc.[4]

Indication

Dificid is a macrolide antibiotic approved for use in patients age 18 or older for the treatment of *C. difficile*-associated diarrhea.

Dificid should only be used in patients that have a confirmed or strongly suggested *C. difficile* infection.[3]

Mechanism of action and pharmacokinetics

Dificid is an antibacterial agent that is active against *C. difficile* as well as the NAP1/BI/027 strains. It inhibits RNA synthesis by RNA polymerases.[3,6]

Dificid is poorly absorbed and acts locally on the gastrointestinal tract. Due to the poor absorption, Dificid stays in the gastrointestinal tract and is not distributed throughout the body. It is excreted in the feces. Dificid is metabolized by hydrolysis to form its active metabolite OP-1118.[5]

Dosing and administration

Dificid tablets are taken orally without regard to food. The recommended dose is 200 mg twice daily for 10 days.[5] No dosing adjustments are needed in patient populations with renal or hepatic impairment.

Contraindications and precautions

There are no documented contraindications to the use of Dificid. The prescribing information does warn against use in either systemic infections or in patients who are not thought to have a *C. difficile* infection.[5]

Adverse reactions

Through clinical trial data, a few adverse reactions were documented including anemia, neutropenia, nausea, vomiting and abdominal pain, flatulence, and an increase in hepatic enzymes. The most common cause for discontinuing the medication is vomiting.[5]

Clinical pearls

- Dificid is a pregnancy category B drug.
- Dificid is not metabolized by the CYP450 enzyme system. The only documented drug interaction is with cyclosporine. Dificid levels may be increased when co-administered with cyclosporine. Due to P-gp inhibition, Dificid concentrations can be decreased at the site of action. No dose adjustments are warranted.[5]
- Patients should be informed that Dificid commonly causes nausea, vomiting, and abdominal pain.
- Through clinical trial experience, Dificid has shown comparable results to vancomycin.[3]
- Dificid has a lesser recurrence rate of CDI compared to vancomycin within 25 days of completing therapy.[6]

REFERENCES

1. O'Donoghue C, Kyne L. Update on *Clostridium difficile* infection. *Curr Opin Gastroenterol*. 2010;27:38-47.
2. vanNispen tot Pannerdan CMF, Verbon A, Kuipers EJ. Recurrent *Clostridium difficile* infection: what are the treatment options? *Drugs*. 2011;71(7):853-868.
3. Louie Tj, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364(5):422-431.
4. Anon. FDA approved Dificid. www.drugs.com.
5. Dificid (fidaxomicin) Tablets Prescribing Information. Optimer Pharmaceuticals, Inc, 2011. www.dificid.com.
6. Traynor K. Pharmacy News: fidxomicin approved for *C. difficile* infections. www.ashp.org.

Diabetes

Linagliptin (Tradjenta)

Approximately 90% of all patients with diabetes have type 2 diabetes mellitus (T2DM).[1,2] The majority of patients with T2DM are not adequately controlled for many reasons including poor tolerability and a decrease in efficacy during chronic treatment.[2]

T2DM is a progressive disease that contributes to poor glycemic control. This progressive disease is mainly the result of dysfunctional pancreatic beta-cells. By the time T2DM is diagnosed, islet function is already decreased by 50%. The dysfunctional beta-cells are mainly caused by accelerated apoptosis, which contributes to the impaired islet function.[1]

According to the UK Prospective Diabetes Study, for every 1% decline in A1c there is an associated risk reduction of 14% in myocardial infarction, 21% for any diabetes-related endpoint, 21% for diabetes-related deaths, and 37% for microvascular complications.[3] It has been projected that by the year 2030, the worldwide estimates of diabetes will reach 366 million.[4]

Tradjenta is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor.

On May 2, 2011, the FDA approved linagliptin (Tradjenta) in conjunction with diet and exercise to improve blood glucose control in patients with T2DM. Tradjenta is marketed by Boehringer Ingelheim Pharmaceuticals and Eli Lilly Co.[5]

Indications

Tradjenta is approved for the management of T2DM in conjunction with diet and exercise in adult patients. Tradjenta is not to be used in patients with Type 1 diabetes or for the treatment of diabetic ketoacidosis.[6] Tradjenta is not recommended to be used in combination with insulin.

Mechanism of action and pharmacokinetics

Tradjenta is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor. This medication prevents the degradation of incretin hormones and helps control postprandial

glucose excursions.[7] The plasma DPP-4 enzyme inhibits the degradation of both glucagon-like peptide-1 and glucose-dependent insulinotropic peptide. The increase in these two hormones leads to glucose-dependent insulin release.

Tradjenta is an orally administered, selective xanthine-based DPP-4 inhibitor, which is similar to sitagliptin and saxagliptin but with a higher potency.

Tradjenta binds reversibly to DPP-4. Its absorption is determined by its 30% bioavailability.

After taking the medication, peak plasma concentrations are reached within 1.5 hours. Tradjenta has a long terminal half-life of about 100 hours. It also distributes extensively into the tissues and protein binding is concentration-dependent. The unchanged drug is eliminated via the enterohepatic system and, to a lesser extent, in the urine.

There is an increased risk of hypoglycemia when Tradjenta is used in combination with insulin secretagogues like sulfonylureas.

Dosing and administration

Tradjenta is dosed orally once daily at 5 mg and can be taken with or without food. No dosing adjustment is needed in patients with renal or hepatic impairment. Tradjenta is not to be used in combination with insulin.[6]

Contraindications and precautions

Tradjenta is contraindicated for use in patients that have a documented allergy to this medication. The allergic reaction includes signs and symptoms of urticarial, angioedema, or bronchial hyperreactivity.[6]

There is an increased risk of developing hypoglycemia when Tradjenta is used in combination with insulin secretagogues like sulfonylureas. The dose of the insulin secretagogue may need to be decreased while using Tradjenta.[6]

Adverse reactions

The most commonly reported adverse reactions associated with Tradjenta were hypertension, stuffy or runny nose, sore throat, headache, and back pain.[7] Other documented adverse effects were hypersensitivity and myalgia. Hypoglycemia is a concern when Tradjenta is given in combination with other antidiabetic medications. Patients should be monitored closely during therapy.

Clinical pearls

- Tradjenta is a pregnancy category B drug.
- Tradjenta should not be administered in combination with insulin.
- Tradjenta is only approved for use in patients with T2DM.
- Tradjenta has the potential to interact with medications that are either strong P-gp or CYP3A4 inducers.[6] This recommendation followed pharmacologic studies with rifampin.
- Nurse practitioners (NPs) should discuss the importance of monitoring for signs and symptoms of hypersensitivity reaction with patients, including rash, hives, and swelling of the face, lips, or throat.
- Tradjenta is administered once a day. If a dose is missed or forgotten, patients should be taught to take it as soon as they remember, but doses should not be doubled.
- It is important that patients taking Tradjenta also follow a diet and exercise plan.
- NPs should educate patients about the symptoms of hypoglycemia, including headache, drowsiness, weakness, dizziness, confusion, irritability, tachycardia, and increased sweating.

REFERENCES

1. Gerich J. DPP-4 inhibitors: what may be the clinical differentiators? *Diabetes Res Clin Pract.* 2010;90(2):131-140. Epub 2010 Aug 13.
2. Del Prato S, Barnett AH, Huisman H, Neubacher D, Woerle HJ, Dugi KA. Effect of linagliptin monotherapy on glycemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab.* 2011;13(3):258-267.
3. Stratton IM, Adler AI, Neil HAW, et al. Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-412.
4. Wild S, Roglic G, Green A, Sicree R, King H.. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004; 27(5):1047-1053.
5. Anon. FDA approves Tradjenta. www.drugs.com
6. Tradjenta (linagliptin) Tablets Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc, and Eli Lilly and Company, 2011. www.tradjenta.com
7. Scott LJ. Linagliptin in type 2 diabetes mellitus. *Drugs*. 2011;71(5):611-624.
8. Forst T, Uhliq-Laske B, Ring A, et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately uncontrolled type 2 diabetes. *Diabet Med.* 2010;27(12):1409-1419.

▼ Pain treatment

Fentanyl nasal spray (Lazanda)

Pain in patients with cancer can be caused by direct effects of the tumor or by complications of the treatment. Effective pain relief without adverse reactions is usually difficult to obtain. Uncontrolled pain can lead to fear of pain and depression.

Opioid analgesics are used in the treatment of moderate-to-severe pain associated with cancer.[1]

Breakthrough cancer pain is defined as an exacerbation of pain greater than moderate intensity and transitory in nature. The pain can be caused by many factors and it lasts a short period of time.[1] Typical breakthrough pain has a fast onset, with an average peak intensity of 3 minutes, and it can last between 30 minutes and 1 hour.[2-4]

The most commonly used opioids in the treatment of breakthrough pain are morphine, oxycodone, hydromorphone, buprenorphine, and methadone. The oral route of administration is the most common, but there are many other formulations available. These nonoral formulations have been shown to be more effective, and include the parenteral, rectal, sublingual, and transmucosal routes.[1] These agents have a better absorption and also avoid first-pass metabolism.[1] More recently, rapid-onset opioids, including different formulations of fentanyl, have been used such as, oral transmucosal fentanyl citrate, buccal fentanyl tablets, and intranasal fentanyl.

Intranasal fentanyl provides a short onset of action and duration of effect. Intranasal administration bypasses the oral route and shows a benefit in patients with nausea, vomiting, oral mucositis, and impaired gastrointestinal functioning.[4]

Indication

On June 30, 2011, Lazanda, a fentanyl nasal spray, was approved by the FDA to aid in the battle of breakthrough pain in cancer patients 18 years of age and older. Lazanda is marketed by Archimedes Pharma Ltd., and its subsidiary, Archimedes Pharma US Inc. Lazanda is the first fentanyl nasal spray approved in the United States. It should only be used in patients currently on an opioid regimen and who are also opioid-tolerant.[5] Lazanda is only available through the Risk Evaluation and Mitigation Strategy Program, and only healthcare providers skilled in the use of Schedule II opioids used to treat cancer pain should prescribe the drug.

Mechanism of action and pharmacokinetics

Lazanda is a pure opioid agonist that exerts its action on the mu-receptor. It has a potency that is 100 times more than that of morphine.[3] Fentanyl has been used in pain management since 1959. It is lipid-soluble and is distributed in all tissues and crosses the blood-brain barrier, producing a strong analgesic effect. It also has a short duration of analgesia of approximately 30 to 60 minutes.

Fentanyl is metabolized by the liver through the CYP3A4 enzyme system, and the drug is converted to inactive metabolites that are then excreted in the urine.[5] Lazanda provides a greater bioavailability due to the absorption from the nasal mucosa following intranasal administration.[5]

Dosing and administration

Dose titration is necessary when starting therapy with Lazanda. The starting dose of Lazanda is not determined by the daily maintenance dose of the opioid the patient was taking. In addition, because of individual patient and drug variabilities, patients cannot be switched from any other fentanyl products to Lazanda on an mcg-to-mcg basis. There is no equivalence between the Lazanda product and other fentanyl products.

Treatment is started using one 100-mcg spray in one nostril. If adequate pain control is not achieved within the first 30 minutes, then a dosing escalation is needed. See the manufacturer's complete prescribing information for the Lazanda titration steps.[5] Patients must wait 2 hours between doses before treating another episode of breakthrough pain.[5] Once an effective dose is determined, patients should use this dose for the further treatment of their breakthrough pain. No more than four doses can be used daily for pain management.

Lazanda is 100 times more potent than morphine.

Patients using Lazanda must be taught proper medication administration technique. The device must be primed before initial use by spraying four sprays into the pouch provided. The nozzle is then inserted into the nose and pointed toward the bridge of the nose. The patient then needs to press down the finger grips until a clicking sound is made. At this point, the counter advances by one.[6] Patients should refer to the Medication Guide for detailed instructions.

Contraindications and precautions

Lazanda is contraindicated in patients who are opioid naive or opioid non-tolerant. Hypoventilation can occur in this patient population. Lazanda should not be used for pain management of acute or postoperative pain, headaches, migraines, or any pain not associated with breakthrough cancer pain.[5]

Adverse reactions

The most common adverse reactions documented throughout the clinical trials included nausea,

constipation, headache, and somnolence. These adverse reactions are similar to other opioid medications. Other adverse reactions include dry eye, anemia, abdominal pain, dry mouth, insomnia, anxiety, and dizziness.[5]

Clinical pearls

- Lazanda is a pregnancy category C drug.
- Lazanda is a schedule II medication.
- Lazanda is supplied in a glass bottle, in either 100 mcg/100 mcL or 400 mcg/mcL strength, but each bottle only contains eight sprays. Each bottle is dispensed in a child-resistant container along with a pouch.

Lazanda is contraindicated in patients who are opioid naive or opioid non-tolerant.

- For disposal, all remaining liquid must be sprayed into the pouch until the number "8" appears in the counting window. Refer to the Medication Guide for further disposal instructions.
- Lazanda is metabolized by the CYP3A4 isoenzyme system, so caution should be taken when used with CYP3A4 inhibitors and CYP3A4 inducers.
- Lazanda should not be used in conjunction with vasoconstrictive nasal decongestants such as oxymetazoline.
- The use of Lazanda with an MAOI or within 14 days of stopping an MAOI is not recommended.[5]
- It is important to provide patients with the full Medication Guide for complete information.

REFERENCES

1. Prommer E, Thompson L. Intranasal fentanyl for pain control: current status with a focus on patient consideration. *Patient Pref Adherence*. 2011;5:157-164.
2. Leppert W. Role of intranasal fentanyl in breakthrough pain management in cancer patients. *Cancer Manag Res*. 2010;2:225-232.
3. Zeppetella G. An assessment of the safety, efficacy, and acceptability of intranasal fentanyl citrate in the management of cancer-related breakthrough pain: a pilot study. *J Pain Symptom Manage*. 2000;20(4):253-258.
4. Kress HG, Orońska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 mcg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Ther*. 2009;31(6):1177-1191.
5. Lazanda (fentanyl) Nasal Spray CII Prescribing Information. Archimedes Pharma UC, Inc, 2011. www.lazanda.com/common/pdfs/Lazanda_Prescribing_information.pdf.
6. Nelson R. FDA approves first fentanyl nasal spray for cancer pain. www.medscape.com.

▼ Epilepsy

Ezogabine (Potiga)

Currently, there are 50 million diagnoses of epilepsy worldwide with an annual occurrence of 20 to 70 new cases per 10,000 individuals.[1] Approximately, 65% to 70% of patients with epilepsy are successfully treated with antiepileptic medications.[2] There are numerous antiepileptic drugs available and these drugs all work by different mechanisms of action. Some of the agents target voltage-dependent sodium or calcium channels. Some agents work by enhancing gamma-aminobutyric acid (GABA) while others are antagonists of T-type calcium channels. Some reduce glutamate-induced excitation at the receptor level.[2] Despite this variety of medications with unique mechanisms of action, 30% of patients still have problems controlling their seizure activity.[1]

In response to this demand, Valeant Pharmaceuticals and GlaxoSmithKline developed and marketed the novel antiepileptic Potiga, approved by the FDA on June 10, 2011.[3,4]

Indications

Potiga was approved as an adjunctive treatment of partial onset seizures in patients age 18 and older.[5]

Mechanism of action and pharmacokinetics

The complete mechanism of action of Potiga is not fully understood. Potiga is a novel antiepileptic that works mainly to stabilize neuronal potassium-gated ion channels.[6] It is also believed that Potiga augments GABA-mediated currents.[7]

The pharmacokinetic profile of Potiga involves rapid absorption following oral administration and linear, dose-related kinetics. Potiga is metabolized by glucuronidation and acetylation.[6]

Dosing and administration

Potiga is started at 100 mg by mouth three times a day for a total dose of 300 mg. Doses can be given with or without food, and can be increased at weekly intervals by 50 mg three times a day to a maintenance dose goal of 200 to 400 mg three times a day. These doses are increased based on patient response and tolerability. Dosages greater than 400 mg three times daily (1,200 mg per day) are not recommended because there has been no demonstrated additional benefit at these doses.[5] No dosage adjustment is needed for patients with mild renal or hepatic impairment.[5] Consult the complete drug product label for recommended dosing for the elderly and those with moderate or severe renal or hepatic impairment.

Contraindications and precautions

There are no contraindications to Potiga. Caution should be taken in patients with urinary retention and neuropsychiatric symptoms, as well as patients with dizziness and somnolence. QT intervals should be monitored in patients taking medications that cause QT prolongation because concomitant use with Potiga can potentiate this adverse reaction.[5]

Adverse reactions

Through clinical trials, the most common adverse effects documented with Potiga are dizziness, fatigue, somnolence, tremor, attention disturbances, memory impairment, and blurred vision. Patients may also experience gait abnormalities aphasia, dysarthria, and balance problems, Some adverse reactions that may lead to discontinuation of Potiga therapy are dizziness, confusion, somnolence, and fatigue.[5]

Clinical pearls

- Potiga is a pregnancy category C drug. It is recommended that pregnant women taking Potiga enroll in the North American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334. Further information is available at www.aedpregnancyregistry.org.
- Potiga levels may be reduced by the use of phenytoin and carbamazepine.[5]
- Potiga may inhibit the clearance of digoxin due to its N-acetyl metabolite. Serum digoxin levels should be monitored.[5]
- When discontinuing the drug, Potiga should be withdrawn gradually to prevent the possibility of developing withdrawal seizures.
- Patients should be monitored for signs of suicidal behavior and ideation.
- Patients should be educated about the possibility of developing symptoms of suicidal thoughts and actions.
- QT intervals should be monitored in patients with known prolonged QT interval, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia, as well as those taking medications known to prolong the QT interval.[5]

REFERENCES

1. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. *Epilepsy Behav*. 2008;12(4):540-546. Epub 2008 Feb 14.
2. Czuczwar P, Wojtak A, Cioczek-Czuczwar A, Parada-Turska J, Maciejewski R, Czuczwar SJ. Retigebine: the newer potential antiepileptic drug. *Pharmacol Rep*. 2010;62(2):211-219.
3. Hitt E. FDA approves ezogabine for seizures in adults. www.medscape.com/viewarticle/744490_print.
4. Anon. FDA approves Potiga to treat seizures in adults. www.fda.gov.
5. Potiga (ezogabine) Tablets Prescribing Information. GlaxoSmithKline, 2011. www.accessdata.fda.gov/drugsatfda_docs/label/2001/0223455000lbl.pdf.
6. Owen RT. Ezogabine: a novel antiepileptic as adjunctive therapy for partial onset seizures. *Drugs Today (Barc)*. 2010;46(11):815-822.
7. Brodie MJ, Lerche H, Gil-Nagel A, et al. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology*. 2010;75(20):1817-1824. Epub 2010 Oct 13.

Hepatitis C

Boceprevir (Victrelis)

Approximately 170 to 180 million people are infected with chronic hepatitis C virus (HCV) worldwide.[1-4] Of this number, at least 130 million are chronic HCV carriers that have a greater risk of developing liver cirrhosis and liver cancer.[2] Chronic HCV is the most common indication for liver transplantation.

The current treatment for HCV is combination therapy of pegylated interferon (PEG-IFN) and ribavirin.[5] Normally this combination therapy is given for 48 weeks, which provides a sustained virologic response (SVR) in about 40% to 50% of patients, but less than 30% in patients with HCV genotype 1, advanced fibrosis, diabetes, HIV, or of African descent.[1,4] Patients who achieve SVR have the potential of long-term benefits: improvement in degree of liver fibrosis, reduction in complications of chronic liver disease, and an improvement in quality of life.[1]

HCV is an enveloped, single-stranded RNA molecule that is 9,600 nucleotides in length.[5] Viral and host peptidases cleave the reading frame into three structural proteins (core, envelope 1, envelope 2), protein (p7), and six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B).[2] It is thought that specifically targeting antiviral therapies for hepatitis C is an approach that is needed. HCV-specific protease inhibitors target the step on HCV replication by blocking the NS3/4A protease-dependent cleavage of the HCV polyprotein.[2,5]

Victrelis must be used in combination with PEG-IFN and ribavirin.

Victrelis is marketed by Schering Corporation, a subsidiary of Merck and Co, Inc., and was approved by the FDA on May 13, 2011, to be used in combination with peginterferon alfa and ribavirin.

Indications

Victrelis is a HCV NS3/4A protease inhibitor for the treatment of chronic hepatitis C genotype 1 infection.[6] Victrelis is not to be used alone. It is approved to be used in combination with

PEG-IFN and ribavirin in patients age 18 years and older who are diagnosed with compensated liver disease, who have been previously untreated or those who have failed previous interferon and ribavirin therapy.[6]

Mechanism of action and pharmacokinetics

Victrelis is a direct-acting antiviral medication that is an inhibitor of the HCV NS3/4A protease.

This protease normally works in the maturing of NS4A, NS4B, NS5A, and NS5B proteins. Victrelis reversibly binds to the NS3 protease active serine site and inhibits the activity of HCV genotype 1a and 1b NS3/4A protease enzymes.[6]

Victrelis has a half-life of around 3.4 hours and is eliminated via the feces, with a small amount in the urine.

Victrelis is a HCV NS3/4A protease inhibitor for the treatment of chronic hepatitis C genotype 1 infection.

Metabolism after oral absorption is done by aldoketoreductase-mediated pathway.[6]

Dosing and administration

Victrelis must be used in combination with PEG-IFN and ribavirin. The first 4 weeks of therapy consists of only the PEG-IFN and ribavirin. At week 5, Victrelis 800 mg is added to the regimen, and is given by mouth three times a day with food. Dosing adjustments can be made based on determinations of the patient's virus (HCV-RNA) levels at treatment weeks 8, 12, and 24.[6]

No dosing adjustments are needed in renal dysfunction. For patients who are treatment-naive, the complete therapy regimen can continue for a total of 28 weeks if HCV-RNA levels are undetectable at week 24, Victrelis can be stopped after week 36, but PEG-IFN and ribavirin continued through week 48.

For patients who had a treatment failure and have undetectable HCV-RNA levels at week 8 and 24 will complete the full regimen at week 36. For those patients with a detectable level at week 8 and undetectable at week 24, the Victrelis can be discontinued after week 36 and complete the PEG-IFN and ribavirin course through week 48.[6]

Patients who have compensated cirrhosis, their regimen begins with a 4-week course of PEG-IFN and ribavirin, followed with the addition of Victrelis for 44 weeks.[6] The regimen should be discontinued at week 12 in patients who have an HCV-RNA level of 100 IU/mL or greater, or at week 24 a confirmed detectable HCV-RNA level.[6]

Contraindications and precautions

Since Victrelis must be administered with PEG-IFN and ribavirin, the contraindications associated with their use must be applied. Victrelis combination therapy is contraindicated in pregnant women and men whose female partners are pregnant. Also, this combination of medications should not be given concomitantly with potent CYP3A4/5 inducers and medications that rely on CYP3A4/5 for clearance.[6]

Adverse reactions

Through clinical trials, the combination treatment has the potential for causing the most common adverse reactions of fatigue, anemia, neutropenia, nausea, and headache. Other adverse reactions include vomiting, diarrhea, dry mouth, chills, arthralgia, insomnia, and dry skin.[6]

Clinical pearls

- Victrelis in combination with PEG-IFN and ribavirin is a pregnancy category X drug. Combination treatment should not be started in women who are pregnant or in men whose female partners are pregnant.
- Victrelis must be used in combination with PEG-IFN and ribavirin.
- Victrelis must be refrigerated at 36° F to 46.4° F (2° C to 8° C) until dispensed.
- Anemia and neutropenia are common adverse reactions. A complete blood cell count should be drawn prior to starting therapy and throughout the course of treatment.
- There is an extensive list of potential drug interactions associated with Victrelis. Refer to the package insert for a complete list.[6]
- Patients should be offered education about missed doses. If a dose is missed and it is less than 2 hours before the next dose is due, the missed dose must be skipped. However, if the missed dose is more than 2 hours before the next dose, the patient should take the dose and resume the original schedule.[6]
- Patients should be educated about the appropriate prevention of HCV transmission.

REFERENCES

1. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicenter phase 2 trial. *Lancet*. 2010;376(9742):705-716. Epub 2010 Aug 6.
2. Susser S, Welsch C, Wang Y, et al. Characterization of resistance to the protease inhibitor boceprevir in hepatitis C virus-infected patients. *Hepatology*. 2009;50(6):1709-1718.
3. Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1207-1217.
4. Berman K, Kwo PY. Boceprevir, an NS3 protease inhibitor of HCV. *Clin Liver Dis*. 2009;13(3):429-439.

5. Anon. FDA approves Victrelis. www.drugs.com.
6. Victrelis (bocepravir) Capsule Prescribing Information. Merck & Co., 2011. www.victrelis.com/bocepravir/victrelis/hcp/index.jsp#.

▼ Immunosuppressive therapy

Belatacept (Nulojix)

Long-term survival in kidney transplant recipients has not improved despite a significant improvement in acute rejection rates.[1] The major reasons for allograft loss at a later point after transplantation include chronic allograft nephropathy and death with a functioning graft.[2] The introduction and use of calcineurin inhibitors (CNIs) has played a major role in reducing the incidence of acute rejection events.[3]

CNIs and corticosteroids have been employed in the maintenance immunosuppression in kidney transplant patients. These medications are associated with adverse reactions that may contribute to the increased risk in morbidity and mortality.

Recent protocol development has been focused on minimizing or avoiding CNI use. The complete removal of CNIs from treatment increases the risk of late acute rejection.[3] The option of costimulation blockade is providing an alternative in the immunosuppression therapy in patients who undergo kidney transplantation.

On June 15, 2011, the FDA approved Nulojix for the prevention of acute rejection in patients who have undergone a kidney transplant.[5] Nulojix is marketed by Bristol-Myers Squibb Company.

Nulojix is designed to avoid the renal and nonrenal toxicities that are associated with CNIs.[6]

Indication

Nulojix, a selective T cell costimulation blocker, is indicated for use in the prevention of acute organ rejection in patients receiving a kidney transplant. Nulojix is recommended to be used in combination with basiliximab, mycophenolate mofetil, and corticosteroids.[7] Nulojix is only approved for use in kidney transplant recipients. Use in other organ transplant populations is not recommended.

Mechanism of action and pharmacokinetics

Nulojix, a selective T cell costimulation blocker, works by binding to the CD80 and CD86 on antigen-presenting cells. This then leads to the blocking of CD28 mediated costimulation of T lymphocytes.

The pharmacokinetics described in the package insert were based on the following doses: a single 10mg/kg intravenous infusion in healthy volunteers, a 10mg/kg intravenous infusion at week 12 following a kidney transplant and 5mg/kg intravenous infusion every 4 weeks at month 12 post-transplant. The half-life was consistent amongst the groups at 9.8days, a volume of distribution averaging 0.11L/kg, and a systemic clearance averaging 0.46mL/h/kg.[7]

Dosing and administration

Nulojix is administered via intravenous infusion. Dosing of Nulojix is based on actual body weight at the time of kidney transplantation. This weight is to be used throughout therapy unless the change in weight is greater than 10%. When calculating the dose of Nulojix, the prescribed dose must be divisible by 12.5 mg. This ensures that the reconstituted solution is prepared accurately.[7] It is important to remember that Nulojix is reconstituted using only the silicone-free disposable syringe that comes with each vial. The infusion of Nulojix should be administered over 30 minutes.[7]

Contraindications and precautions

Nulojix is contraindicated in patients who are Epstein-Barr virus (EBV) seronegative, as well as patients who have an unknown EBV status. Being negative for EBV increases the patient's risk of developing posttransplant lymphoproliferative disorder (PTLD).[7]

> ***When calculating the dose of Nulojix, the prescribed dose must be divisible by 12.5 mg.***

Be aware of the potential to develop other malignancies while using Nulojix, as seen with other immunosuppressants. It is important to avoid prolonged exposure to the sun and UV light. Patients using Nulojix also have an increased risk of developing progressive multifocal leukoencephalopathy as well as other serious infections.[7]

Adverse reactions

Through clinical trials, a number of adverse effects were documented. The most common that patients may experience are anemia, diarrhea, vomiting, constipation, urinary tract infections, headache, hypertension, and graft dysfunction. Other adverse effects include abdominal pain, influenza, pyrexia, and electrolyte disorders.[7]

Clinical pearls

- Nulojix is a pregnancy category C drug.
- Nulojix is approved only to be used in patients who have received a kidney transplant.

- Do not use live vaccines while on Nulojix.
- Do not use doses higher than what is recommended in the package insert since there is an increased risk of developing serious infections and malignancy.
- Premedication is not required prior to intravenous administration.
- Educate patients to monitor for changes in mood or behavior, confusion, memory loss, changes in walking or talking, changes in vision, or weakness. These signs and symptoms can indicate the development of progressive multifocal leukoencephalopathy or PTLD.

REFERENCES

1. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant.* 2004;4(3):378.
2. Webber A, Hirose R, Vincenti F. Novel strategies in immunosuppression: issues in perspective. *Transplantation.* 2011;91(10):1057-1064.
3. Snanoudj R, Zuber J, Legendre C. Co-stimulation blockade as a new strategy in kidney transplantation: benefits and limits. *Drugs.* 2010;70(16):2121-2131.
4. Ferguson R, Grinyó J, Vincenti F. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant.* 2011;11(1):66-76. Epub 2010 Nov 29.
5. Anon. FDA approves Nulojix. www.drugs.com.
6. Larsen CP, Grinyó J, Medina-Pestana J.,et al. Belatacept-based regimens versus a cyclosporine A-based regimen in kidney transplant recipients: 2-year results from the BENEFIT and BENEFIT-EXT studies. *Transplantation.* 2010 Dec 27;90(12):1528-35.
7. Nulojix (belatacept) Prescribing Information. Bristol-Myers Squibb, 2011. www.drugs.com.

▼ COPD

Indacaterol inhalation powder (Arcapta Neohaler)

The guidelines in place for chronic obstructive pulmonary disease (COPD) are from the Global Initiative for Chronic Obstructive Lung Disease (GOLD). These guidelines recommend the inhaled bronchodilators of beta$_2$-agonists and anticholinergics for treatment of COPD symptoms.[1,2] The long-acting bronchodilators are more effective than the short-acting bronchodilators in patients with COPD. The only long-acting anticholinergic available on the market is tiotropium and provides a duration of action of 24 hours.[2] The long-acting beta$_2$-agonists salmeterol or formoterol provide coverage of about 12 hours.[3] Adherence to a treatment plan may be an issue when treating patients with COPD. With that in mind, a new long-acting beta$_2$-agonist that requires once daily dosing was developed.

Arcapta Neohaler is contraindicated in patients with asthma.

On July 1, 2011, the FDA approved Arcapta Neohaler for the long term, once daily maintenance bronchodilator treatment of COPD. Arcapta Neohaler is a long-acting beta$_2$-agonist.[4] Arcapta Neohaler is manufactured and distributed by Novartis Pharmaceuticals Corporation.

Indication

Arcapta Neohaler is approved for use as a long term, once daily maintenance treatment of COPD including patients with chronic bronchitis and emphysema.[5] Arcapta Neohaler should not be used to treat acute exacerbations of COPD or in patients with asthma.

Mechanism of action and pharmacokinetics

Arcapta Neohaler is a long-acting beta$_2$ adrenergic agonist. Arcapta Neohaler stimulates intracellular adenyl cyclase, an enzyme that catalyzes the conversion of adenosine triphosphate to cyclic monophosphate. This leads to an increase in cyclic adenosine monophosphate (AMP), which causes bronchial smooth muscle relaxation.[5]

Studies have shown that Arcapta Neohaler has a long duration of action and a fast onset of action.

Dosing and administration

Arcapta Neohaler should be given once daily at the same time. One 75-mcg capsule must be used via inhalation by using the Neohaler device.[5] The Arcapta capsules are not to be swallowed or taken by oral administration. The Arcapta capsules are stored in a blister pack until the time that it needs to be administered. If a dose is missed, the next dose should be taken as soon as it is remembered; but dosing should only be once daily.[5] Refer the patient to the Medication Guide for a more thorough description of the use of the Neohaler.

Contraindications and precautions

Arcapta Neohaler, along with all long-acting beta$_2$-agonists, is contraindicated in patients with asthma. Aracapta Neohaler should also not be used in patients with COPD that is deteriorating or in exacerbations of COPD.[5]

Adverse reactions

Throughout clinical trials, the most serious adverse reactions were COPD exacerbation, pneumonia, atrial fibrillation, and angina pectoris. Other adverse effects are oropharyngeal pain, nasopharyngitis, headache, nausea,

and cough. The cough can occur within 15 seconds of inhalation and last for no more than 15 seconds.[5]

Clinical pearls

- Arcapta Neohaler is a pregnancy category C drug.
- The use of Arcapta Neohaler with other beta-blockers can potentially decrease effectiveness in both medications.[5]
- Arcapta Neohaler may cause paradoxical bronchospasms, which may be life-threatening; if this occurs, the Arcapta Neohaler must be stopped immediately and alternative treatment started. Patients should be instructed to seek emergency treatment if necessary.
- Caution must be taken when using Arcapta Neohaler with other adrenergic medications, as well as xanthine derivatives, corticosteroids, and diuretics.
- QT prolongation may occur if Arcapta Neohaler is used in combination with MAO inhibitors, tricyclic antidepressants and other agents that prolong the QT interval.
- The capsules must be stored in the blister pack until ready for use, and protected from light and moisture.
- Patients should be provided with the Medication Guide for thorough information about the medication. NP

REFERENCES

1. Feldman G, et al. Efficacy and safety of indacaterol 150 mcg once-daily in COPD: a double-blind, randomized, 12-week study. Pharmacy Medicine, 2010;10:11-20.
2. Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. http://www.goldcopd.org/.
3. LaForce C, et al. Indacaterol provides sustained 24h bronchodilation on once-daily dosing in asthma: a 7-day dose-ranging study. *Allergy* 2008;63:103-111.
4. Anon. FDA News Release. FDA approves Arcapta Neohaler to treat chronic obstructive pulmonary disease. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm261649.htm.
5. Arcapta Neohaler Prescribing Information. Novartis, 2011. www.pharma.us.novartis.com/products/pi/pdf/arcapta.pdf.

Jennifer M. Belavic is a clinical pharmacist in the Trauma Intensive Care Unit, University of Pittsburgh Medical Center, Presbyterian Hospital, Pittsburgh, PA.

Consult the manufacturer's complete drug product label before prescribing any of the drugs discussed.

The author and planners have disclosed that they have no financial relationships related to this article.

DOI-10.1097/01.NPR.0000410276.29621.85