ISMP Adverse Drug Reactions

Ranolazine-Induced Reversible T-Wave Inversions with Prolonged QTc Interval

Progressive Multifocal Leukoencephalopathy Linked to Fingolimod

Losartan-Induced Sprue-like Enteropathy

Nivolumab-Induced Psoriasiform Skin Eruption

Hepatitis B Reactivation with Hepatitis C Treatment with Simeprevir and Sofosbuvir

*Michael A. Mancano, PharmD**

The purpose of this feature is to heighten awareness of specific adverse drug reactions (ADRs), discuss methods of prevention, and promote reporting of ADRs to the US Food and Drug Administration's (FDA's) MEDWATCH program (800-FDA-1088). If you have reported an interesting, preventable ADR to MEDWATCH, please consider sharing the account with our readers. Write to Dr. Mancano at ISMP, 200 Lakeside Drive, Suite 200, Horsham, PA 19044 (phone: 215-707-4936; e-mail: mmancano@temple.edu). Your report will be published anonymously unless otherwise requested. This feature is provided by the Institute for Safe Medication Practices (ISMP) in cooperation with the FDA's MEDWATCH program and Temple University School of Pharmacy. ISMP is an FDA MEDWATCH partner.

RANOLAZINE-INDUCED REVERSIBLE T-WAVE INVERSIONS WITH PROLONGED QTc INTERVAL

A 64-year-old female presented to the hospital with a 2-hour history of chest discomfort. She had a history of coronary artery disease and a prior stent placement. On admission, her EKG revealed sinus bradycardia with an ST elevation. The patient's troponin-T level peaked at 0.22 mg/mL (normal value, <0.01 ng/mL), and creatine phosphokinase was also elevated at 201 U/L (normal value, 60-174 U/L). Coronary angiography revealed a cardiac wall motion abnormality consistent with Takotsubo cardiomyopathy.

Takotsubo cardiomyopathy mimics acute coronary syndrome and is accompanied by transient hypokinesis, dyskinesis, or akinesis of the left ventricular mid-segments, with or without apical involvement. The regional wall-motion abnormalities extend beyond a single epicardial vascular distribution, and a stressful trigger is often, but not always, present. In addition to these findings, the patient's QTc interval on admission was 416 ms.

The patient was initiated on ranolazine (*Ranexa*) 500 mg to treat her chronic anginal symptoms. An EKG was performed a few hours after the patient's

*Chair and Clinical Professor, Department of Pharmacy Practice, Temple University School of Pharmacy, Philadelphia, Pennsylvania; Clinical Advisor, Institute for Safe Medication Practices, Horsham, Pennsylvania

first dose of ranolazine, and it revealed deep T-wave inversions and a prolonged QTc of 505 ms. At this time, the patient's troponin-T and creatine phosphokinase continued to trend downward. Ranolazine was discontinued and 24 hours later an EKG was conducted; it revealed persistent T-wave inversions with decreased amplitude compared to the prior EKG and a QTc interval that decreased to 412 ms.

Ranolazine exerts antianginal and anti-ischemic effects without changing hemodynamic parameters (heart rate or blood pressure). At therapeutic levels, ranolazine inhibits the late phase of the inward sodium channel in ischemic cardiac myocytes during cardiac repolarization reducing intracellular sodium concentrations and thereby reducing calcium influx via $\text{Na}^+/\text{Ca}^{2+}$ exchange. Decreased intracellular calcium reduces ventricular tension and myocardial oxygen consumption. It is thought that ranolazine produces myocardial relaxation and reduces anginal symptoms through this mechanism, although this is uncertain. Prolongation of the QTc interval has been reported with the use of ranolazine but is considered a rare adverse event. In fact, at higher concentrations ranolazine inhibits the rapid delayed rectifier potassium current, thus prolonging the ventricular action potential duration with subsequent prolongation of the QT interval. The patient in this case had only received one dose of ranolazine when she experienced QTc prolongation and T-wave inversion. Ranolazine has been associated with T-wave changes such as notching and decreased T-wave amplitude, however T-wave inversion has not previously been reported with ranolazine. The authors concluded that even though these "adverse effects may be rare and not always apparent in clinical trials, this highlights the importance of postmarketing surveillance."

Kumthekar A, Cossarini F, Shih JC, et al. Ranolazine-induced repolarization changes: A case report. *Am J Med.* 2015;128(7):e3-e5.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY LINKED TO FINGOLIMOD

Fingolimod (*Gilenya*) is an immunomodulator shown to benefit patients with relapsing forms of multiple sclerosis. This type of multiple sclerosis causes attacks or relapses, which are periods of time when symptoms get worse. Fingolimod-phosphate blocks the lymphocytes' ability to emerge from lymph nodes; therefore, the amount of lymphocytes available to the central nervous system is decreased, which reduces central inflammation. The US Food

and Drug Administration (FDA) reports that a case of definite progressive multifocal leukoencephalopathy (PML) and a case of probable PML have been reported in patients taking fingolimod for multiple sclerosis. These are the first cases of PML reported in patients taking fingolimod who had not been previously treated with an immunosuppressant drug for multiple sclerosis or any other medical condition. As a result, information about these recent cases is being added to the fingolimod product labeling.

Progressive multifocal leukoencephalopathy is a rare condition; it is a serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems, including those taking immunosuppressant drugs. Symptoms of PML are diverse and may include progressive weakness on one side of the body; clumsiness; vision problems; confusion; and changes in thinking, personality, memory, and orientation. The progression of deficits can lead to severe disability or death. A magnetic resonance imaging (MRI) scan may find lesions in the brain before symptoms develop.

In an August 2013 Drug Safety Communication from the FDA, it was reported that a patient developed PML after taking fingolimod. PML could not be conclusively linked to fingolimod in this case, because prior to fingolimod treatment the patient had been treated with an immunosuppressant drug that can cause PML and during fingolimod treatment the patient had received multiple courses of intravenous corticosteroids, which can weaken the immune system. Recently the FDA was notified about one patient with PML and one patient with probable PML that occurred during fingolimod treatment without prior or concurrent exposure to other immunosuppressant drugs. The patient with probable PML did not have clinical signs or symptoms suggestive of PML and was diagnosed based on MRI findings compatible with PML and JC virus detected in the cerebrospinal fluid. The second patient was diagnosed with definite PML based on characteristic symptoms, MRI findings, and JC virus in the cerebrospinal fluid. In closing, the FDA urges health care professionals and patients to report side effects involving fingolimod to the FDA MEDWATCH program.

FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug *Gilenya* (fingolimod) in two patients with no prior exposure to immunosuppressant drugs. <http://www.fda.gov/Drugs/DrugSafety/ucm456919.htm>. Accessed October 13, 2015.

Voelker R. Brain disease linked with MS drug. *JAMA*. 2015;314(11):1108.

LOSARTAN-INDUCED SPRUE-LIKE ENTEROPATHY

A 67-year-old male came to the hospital with an 11 kg weight loss that had occurred over the previous 9 months. He reported 4 to 5 episodes of nonbloody diarrhea daily. He stated that he did not have any loss of appetite or change in his gluten-containing diet. A medication history revealed he had been receiving losartan 50 mg daily for the previous 3 years. On physical examination, the patient exhibited abdominal tenderness. Blood tests revealed the patient had anemia and reduced levels of iron, albumin, potassium, calcium, phosphorus, total cholesterol, HDL cholesterol, and triglycerides. Fecal occult blood tests were repeatedly negative. Fecal microbiologic tests for bacteria, parasites, and viruses potentially responsible for diarrhea were also negative. Anti-tissue transglutaminase IgA antibodies were absent and HLA-DQ typing was negative for celiac disease. The patient underwent an esophagogastroduodenoscopy, and biopsies of the duodenum revealed total villous atrophy and inflammation of the lamina propria. The patient was diagnosed with sprue-like enteropathy, which is characterized by diarrhea, weight loss, and villous atrophy that typically is linked to celiac disease. However this patient had tested negative for celiac disease.

Losartan was discontinued at this time. In a few days, the patient's diarrhea decreased without any other intervention. The patient was discharged from the hospital and achieved complete resolution of his diarrhea within 1 week. Over the next 8 months, the patient regained the 11 kg of body weight he had lost over the prior 9 months. The patient continued to eat a gluten-containing diet. The patient had follow-up labs that revealed resolution of anemia and normalization of iron, albumin, potassium, calcium, phosphorus, total cholesterol, HDL cholesterol, and triglycerides. The patient also had 2 follow-up esophagogastroduodenoscopies at 3 months and 11 months after losartan was withdrawn. Histology from duodenal biopsies showed partial to complete reconstruction of villous architecture.

The authors summarize that although sprue-like enteropathy is a rare adverse effect, other angiotensin II receptor blockers have caused sprue-like enteropathy. Two case reports of sprue-like enteropathy have been published with olmesartan and single case reports with irbesartan and valsartan. The authors

point out that their case report with losartan might suggest that sprue-like enteropathy may not be linked to a specific ARB but might be a class effect.

Negro A, Rossi GM, Santi R, et al. A case of severe sprue-like enteropathy associated with losartan. *J Clin Gastroenterol*. 2015;49(9):794.

NIVOLUMAB-INDUCED PSORIASIFORM SKIN ERUPTION

An 80-year-old had been receiving nivolumab (*Opdivo*) 2 mg/kg every 3 weeks for the treatment of unresectable primary mucosal melanoma on the upper lip, palate, and cheeks. The patient was previously healthy without a personal or family history of psoriasis. The patient's tumor on his lip enlarged over the course of the first 2 doses of nivolumab and then began to shrink after the third dose was administered. Immediately following the fourth dose of nivolumab, the patient developed malaise, skin eruption, dysesthesia, and severe pain in his extremities. The patient had a low-grade fever and asymptomatic, sharply bordered, scaly erythematous plaques on his trunk and extremities; eruptions having unclear borders or crusts were also present.

Routine laboratory tests were normal except for a highly elevated C-reactive protein of 11.2 mg/dL (normal value, <0.3 mg/dL). A skin biopsy revealed that some infiltrates tested positive for interleukin 17 or 23. On the third day of hospitalization, the patient developed a high fever, over 39.5°C (103.1°F). The patient was given oral prednisolone (0.7 mg/kg), and his systemic symptoms and skin eruptions improved immediately. After prednisolone therapy was discontinued, the eruptions recurred along with increased C-reactive protein levels and a fever of 37.8°C (100°F). Prednisolone was restarted at a dose of 0.4 mg/kg, which immediately resolved the patient's symptoms again. He was then prescribed 0.1 mg/kg of prednisolone. Three months after the last dose of nivolumab, the patient's lesions on his palate decreased in size and no melanoma cells were found in the biopsy from his upper lip.

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding. The negative PD-1 receptor signaling that regulates T-cell activation and proliferation is therefore disrupted. This releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.

Blocking PD-1 activity results in decreased tumor growth. In clinical trials with nivolumab, cutaneous adverse reactions, which were categorized as rash, vitiligo, pruritus, and acneform eruptions, occurred in about half of patients.

The authors concluded, "Psoriasis and psoriasiform eruptions are well known to occur as a paradoxical reaction during biological therapies for severe psoriasis. The phenomenon is thought to be mediated by the increased production of interferons. The occurrence of the psoriasiform eruptions and systemic illness temporally coincided with the regression of melanoma lesions, suggesting a strong correlation with nivolumab's mechanism of action. Therefore, psoriasiform eruptions may be induced in cases of sufficient nivolumab antitumor activity."

Ohtsuka M, Miura T, Mori T, et al. Occurrence of psoriasiform eruption during nivolumab therapy for primary oral mucosal melanoma. *JAMA Derm.* 2015;151(7):797-799.

HEPATITIS B REACTIVATION WITH HEPATITIS C TREATMENT WITH SIMEPREVIR AND SOFOSBUVIR

A 59-year-old White female with chronic hepatitis C virus (HCV) genotype 1B was started on treatment with simeprevir (*Olysio*), sofosbuvir (*Sovaldi*), and ribavirin. She had been treated in the past with interferon and ribavirin without success. The patient's pretreatment laboratory test results revealed elevated aminotransferase (AST) 235 U/L (normal value, <35 U/L) and alanine transaminase (ALT) 168 U/L (normal range, 10-35 U/L). Her liver biopsy revealed chronic HCV with grade 1 inflammation and stage 2/4 fibrosis. Hepatitis B virus (HBV) surface and core antigens in her liver biopsy were negative. The patient's HBV surface antigen (HBsAg) was nonreactive at this time, with reactive core antibody but absent surface antibody. A HBV DNA level measured 2 years prior was undetectable.

Four weeks after beginning treatment with simeprevir, sofosbuvir, and ribavirin, her HCV level was less than 12 IU/mL, with AST and ALT approaching normal at 38 and 31 U/L, respectively. The patient's ribavirin was discontinued at this time due to anemia. At week 11 of a planned 12-week course of therapy, the patient was found to have an ALT of 2,263 U/L, AST of 2,870 U/L, total bilirubin of 9.1 mg/dL (normal range, 0.3-1 mg/dL), and an international normalized ratio (INR) of 1.9. At this time, repeat HBV serologies revealed a positive HBsAg and a viral load of 29,000,000 IU/mL, however her HCV viral load was undetectable. A transjugular liver biopsy revealed severe hepatitis with necrosis, inflammation, many apoptotic bodies, and extensive periportal and

pericellular fibrosis. HBV surface and core antigens were identified on immunohistochemistry.

The patient was initiated on tenofovir for treatment of HBV on day 3 after presentation. Even with treatment with tenofovir, the patient became increasingly encephalopathic with an increasing INR. The patient was transferred to the intensive care unit, and she underwent liver transplantation 10 days after admission to the hospital. Her hospital course was unremarkable, and she was discharged home 1 week after liver transplantation. The patient's HCV viral load was tested at weeks 12 and 24 after transplant and remained undetectable. The patient's HBV remains suppressed with ongoing tenofovir therapy.

The authors reviewed the known epidemiology that estimates that rates of HCV coinfection in patients with HBV (HBsAg positive) vary from 9% to 30%, depending on geographic region. They theorize that the incidence of isolated HBcAb in HCV-infected individuals is likely even higher because screening programs often only test for HBsAg. They state, "Several studies have shown that HBV and HCV interact with each other and HCV infection can suppress HBV replication. Coinfected patients commonly have lower HBV DNA levels, and decreased hepatic expression of HBsAg and HBV core antigen compared to HBV monoinfected patients." This has led to the hypothesis of reciprocal interaction between viruses where HBV replication is inhibited by HCV. Hence, the potential for reactivation of HBV following HCV treatment has long been a concern.

The authors believe their case represents evidence to support the theory of reciprocal HCV-HBV interaction most frequently characterized by an inhibition of HBV replication by HCV. With the potential inhibitory effect of chronic HCV on HBV eliminated with oral antiviral treatment in their patient, HBV replication was no longer restricted, which led to fulminant HBV reactivation necessitating liver transplantation. The authors warn that this case raises concern for the safety of new direct-acting antiviral drugs in patients coinfecting with HBV and HCV or in those who have chronic HCV infection and isolated HBcAb. It remains unclear whether HBV booster immunization may have prevented this episode. The authors recommend, "Close monitoring and aminotransferases and/or HBsAg or HBV DNA levels may be warranted in such patients during oral interferon-free direct-acting antiviral therapy."

Ende AR, Kim NH, Yeh MM, et al. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: A case report. *J Med Case Rep.* 2015;9(164)1-4. ■