ISMP Adverse Drug Reactions

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*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.

STATIN-INDUCED LUNG INJURY

Statin-induced lung injury (SILI) is an uncommon but serious pulmonary complication of statin therapy. SILI was initially reported in the medical literature in 1995¹ and additional case reports followed. In 2007 an analysis of the US Food and Drug Administration (FDA) Adverse Reporting System data concerning statin use and SILI was performed.² The findings demonstrated a group of disorders with similar pathological findings including cellular infiltration, scarring and/or architectural disruption of the pulmonary parenchyma

involving alveolar lining cells, small and large airways, endothelial basement membranes, and occasionally the pleura. This group of pulmonary effects was found to occur in 0.01% to 0.4% of patients treated with statins and demonstrates that the clinical features of SILI vary widely.

The authors completed an investigation of 12 previously reported cases of SILI as well as 4 cases diagnosed at their institution. The authors' analysis demonstrated that simvastatin was the most common statin reported to cause lung injury; however, of the 4 patients at their

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

institution, 3 patients received rosuvastatin and 1 received atorvastatin. The most common symptoms patients reported were fever, dyspnea, and cough. The onset of lung injury varied widely from the start of statin treatment, ranging from 0.25 to 120 months. Upon onset of symptoms, statins were discontinued and steroids were administered in 15 of the 16 patients. Clinical or radiologic improvement was noted in 10 patients receiving steroids. Because of severe lung injury, rechallenge with statins was not performed. However, 1 patient experienced increased dyspnea 1 week after inadvertent re-administration of rosuvastatin prescribed by a physician with no knowledge of the patient's history of SILI. Of the remaining 6 patients with unfavorable outcome, 2 had slowly progressive disease complicated by persistent dyspnea. Four patients died from respiratory or cardiac failure, including 1 patient who received continuous simvastatin therapy.

The authors' analysis indicates that the patients with clinical symptoms of cough and/or fever had a favorable outcome. It may be that the presence of such acute symptoms prompts the patient to seek medical help and avoid delay in diagnosis and treatment. However, these clinical symptoms, in addition to thoracic radiological findings, may mimic pulmonary infection and confuse physicians who are unaware of SILI. The authors recommend a high index of suspicion of SILI; the presence of pulmonary phospholipidosis, shown by a foamy appearance of the majority of alveolar macrophages which stain positive for Sudan black in bronchoalveolar lavage fluid, may be of considerable value in diagnosing SILI. In addition, the high-resolution CT (HRCT) findings in SILI are nonspecific but may be of prognostic value. Alveolar infiltrates, especially ground-glass opacity, indicate favorable outcome, whereas fibrosis shown on HRCT suggests an unfavorable outcome.

The authors outline the current research questions concerning SILI that remain: What are the underlying mechanisms of SILI? What are the risk factors for the occurrence of SILI? How can health care professionals become more aware of SILI in their clinical practice?

Huang LK, Tsai MJ, Tsai HC, et al. Statin-induced lung injury: diagnostic clues and outcome. *Postgrad Med*. 2013;89:14-19.

COLCHICINE-INDUCED RHABDOMYOLYSIS CAUSED BY INTERACTION WITH CLARITHROMYCIN

A 59-year-old man with a history of pulmonary tuberculosis about 40 years prior presented with generalized myalgia and fever. Behçet disease had been diagnosed 15 months prior, and the patient was treated with methotrexate and colchicine (0.6 mg every 12

hours). Behçet's disease is a triad of aphthous ulcers, genital ulcerations, and ocular inflammation. Three months prior to his admission, methotrexate was discontinued because of elevated liver enzymes, and his liver function had normalized within 2 months. The patient developed nasal congestion and chronic cough as well as rhinosinusitis. Clarithromycin 500 mg every 12 hours was initiated. Nine days after starting treatment, he developed myalgia and weakness in both legs along with a febrile sensation. Despite treatment with analgesics, his myalgia had worsened and involved other extremities.

Upon admission, his liver enzymes were elevated (aspartate aminotransferase, 227 IU/L; alanine aminotransferase, 564 IU/L), but neither cytopenia nor renal impairment was observed. The patient's creatinine kinase and myoglobin concentrations were markedly elevated at 766 IU/L and 1,393 ng/mL, respectively. After conservative management, his subsequent liver enzymes, myoglobin, and creatinine kinase concentrations decreased while his muscle pain and weakness gradually disappeared within 2 weeks. The patient was discharged without colchicine therapy.

According to the FDA's safety data for colchicine-related deaths, 117 of the 169 fatal cases were within the therapeutic dosage range and more than half were reported in patients concomitantly using clarithromycin.³ Clarithromycin can increase the oral bioavailability of colchicine by increasing its absorption by inhibiting P-glycoprotein in enterocytes and can increase colchicine accumulation by decreasing the activity of CYP3A4, which is involved in colchicine metabolism. The authors warn that pharmacologic interactions between colchicine and clarithromycin and other drugs that inhibit CYP3A4 and/or P-glycoprotein can cause serious adverse reactions. Health professionals should be vigilant for these potentially life-threatening interactions.

Kim JB, Kim S, Yoon SY, et al. Colchicine-induced rhabdomyolysis caused by interaction with clarithromycin in a patient with Behçet disease. *J Clin Rheumatol*. 2012;18(8):453-454.

DISULFIRAM ETHANOL REACTION MIMICKING ANAPHYLACTIC, CARDIOGENIC, AND SEPTIC SHOCK

A 65-year-old man was admitted to the intensive care unit (ICU) for shock. The patient had no pertinent past medical history except for alcohol abuse and was asymptomatic until midday when he consumed 500 mL of wine. Within 30 minutes he fainted and was taken to the emergency department. Upon admission, the patient's consciousness returned to normal but his blood pressure was 80/60 mm Hg, heart rate 110 beats

per minute (bpm), respiratory rate 25 breaths per minute, oxygen saturation of 99% on room air, and a temperature of 36°C (96.8°F). The patient displayed diffuse erythema on his chest and face, without mucosal swelling or pruritus. Anaphylaxis was suspected, and the patient immediately received 0.1 mg of intravenous epinephrine along with aggressive fluid resuscitation. Worsening circulatory failure warranted high-dose norepinephrine (0.8 mcg/kg/min) infusion. ECG was suggestive of an acute myocardial infarction but coronary angiography was normal. Because of hypothermia (35.5°C [95.9°F]) and intense shivering, toxic shock syndrome was suspected and intravenous broad-spectrum antibiotics were initiated (ceftriaxone and clindamycin). Upon his admission to the ICU, lab results revealed metabolic acidosis (pH 7.33, bicarbonate 17.2 mmol/L, and arterial blood lactate 8.7 mmol/L), but procalcitonin, high-sensitivity troponin, and other routine lab tests were within normal limits. Blood ethanol concentration was 0.9 g/L measured 6 hours after ingestion.

Additional history was elicited from the patient, and it was discovered that he erratically self-medicated with disulfiram and that he had ingested 500 mg of disulfiram 1 hour before his alcohol intake. Within 2 hours after ICU admission, his circulatory status dramatically improved and he was gradually weaned off of norepinephrine. Cutaneous manifestations, lactic acidosis, and ECG abnormalities also resolved within 6 hours. All cultures remained sterile, and antibiotics were discontinued. The patient was discharged to home the next day without any medications. The diagnosis was severe disulfiram ethanol reaction.

The disulfiram ethanol reaction is widely known, but the manifestation is expected to be mild but unpleasant with the patient experiencing headache, flushing, and nausea as a deterrent to further ethanol ingestion. Severe vasodilatory shock has been reported rarely in the literature, with only 1 case describing ST-segment depression. This case is unique; the patient experienced effects that mimicked anaphylactic, cardiogenic, and septic shock that resolved relatively rapidly after ICU admission.

Moachon L, Arnould MA, Perruche F, et al. Disulfiram ethanol reaction mimicking anaphylactic, cardiogenic and septic shock. *Am J Emerg Med.* 2013;31(1):270.e1-270.e3.

WEIGHT GAIN WITH ABDOMINAL ENLARGEMENT IN A PATIENT RECEIVING TOCILIZUMAB

A 56-year-old woman with rheumatoid arthritis (RA) and Sjögren syndrome was initiated on tocilizumab in November 2010 after a long course of disease and failure (due to lack of efficacy or unacceptable

adverse effects) of numerous synthetic disease-modifying antirheumatic drugs, 3 anti-tumor necrosis factor (TNF) drugs, and rituximab. Upon initiation of therapy with tocilizumab (*Actemra*) 320 mg, the patient weighed 43 kg (94.8 lbs; body mass index [BMI] 16.8). The patient also received prednisone 10 mg daily, which had been part of her long-term background regimen. In February 2011, the patient complained of persistent abdominal distention and pain. Abdominal ultrasound, CT, gastroscopy, and colonoscopy did not reveal a cause for the pain. The patient reported no change in her appetite or eating habits and her weight was 52 kg (114.6 lbs; BMI 20.3). The patient experienced moderate improvement in RA activity, and tocilizumab therapy was continued.

In May 2011, the patient presented with worsening diffuse abdominal pain and her appearance had changed dramatically. Prominent trunk fat deposition was now apparent and her weight was now 56 kg (123.5 lbs; BMI 21.9). Her anterior abdominal wall was tender and her skin was distended. Ultrasound of the abdominal wall revealed significant diffuse fat deposition in the subcutaneous area. Tocilizumab was discontinued at this time. Three months later (August 2011), the patient noted significant improvement in her abdominal pain and distention and her weight had decreased by 5 kg (11 lbs). However the patient required an increase in her prednisone dose to 20 mg daily to treat her RA. Because of worsening joint disease, the patient agreed to receive another infusion of tocilizumab in November 2011. Two weeks after administration, she presented again with abdominal pain and new weight gain of 3 kg (6.6 lbs). She refused further tocilizumab treatment and was then maintained on prednisone 10 mg/daily. During follow-up, the patient's abdominal distention gradually diminished and pain disappeared, however her weight did not decrease significantly and remained at 52 kg (114.6 lbs; BMI 20.3) as of September 2012.

Tocilizumab is a humanized monoclonal antibody to the interleukin-6 (IL-6) receptor. Although weight gain has been thought to be a potential adverse effect of IL-6 receptor blockade, it has not been reported in patients receiving tocilizumab. This case represents a patient who gained more than 30% of her initial weight as well as significant abdominal fat accumulation. The weight gain also reoccurred upon reintroduction of tocilizumab therapy.

Younis S, Rosner I, Rimar D, et al. Interleukin 6 blockade-associated weight gain with abdominal enlargement in a patient with rheumatoid arthritis. *J Clin Rheum.* 2013;19(1):48-49.

NILOTINIB-ASSOCIATED ACUTE PANCREATITIS

A 69-year-old Caucasian male was admitted to the hospital for abdominal pain. Six days prior to admission, he began treatment with nilotinib for recently diagnosed chronic myelogenous leukemia (CML). He had been receiving nilotinib 300 mg twice daily. He had no history of smoking or alcohol abuse and no known allergies. He had been receiving simvastatin, aspirin, and enalapril for at least the last 5 years. His abdominal pain had begun after the first dose of nilotinib and gradually worsened prior to admission. The patient denied recent alcohol use or abdominal trauma. Lab test results revealed elevated white blood cell (WBC) count of 33,370/ μ L, amylase 152 IU/L, serum lipase 308 IU/L, and serum lactate dehydrogenase 308 IU/L. The patient had baseline serum amylase and lipase determined prior to nilotinib initiation, and they were within normal limits. Serum bilirubin levels were slightly elevated at 1.7 mg/dL and serum triglyceride levels were within normal limits at 121 mg/dL. An abdominal CT scan demonstrated normal liver, a slightly enlarged spleen with normal appearance, and thickening of the pancreatic tail with infiltration of the surrounding fat. All of these findings are consistent with pancreatitis. Nilotinib was immediately discontinued, and the patient had no oral intake for a day and was treated with intravenous fluids and analgesics. The next day, the abdominal pain decreased and serum amylase, lipase, and bilirubin all decreased and returned to normal 2 weeks later.

Nilotinib is a second-generation tyrosine kinase inhibitor (TKI). TKI administration has been associated with an increase in serum amylase and/or lipase.

This case report describes acute pancreatitis, which was confirmed by clinical, radiologic, and laboratory studies after initiation of nilotinib. Even though the patient had been receiving simvastatin and enalapril and these agents are associated with pancreatitis, it is unlikely that these agents played a part in the development of pancreatitis. He had been receiving these drugs for at least 5 years and was reinitiated on these agents without incident.

The authors state that nilotinib should be considered as capable of causing acute pancreatitis. The determination of baseline amylase and lipase serum levels prior to nilotinib initiation should be the standard of care, and clinicians should be alert for this rare phenomenon.

Engel T, Justo D, Amitai M, et al. Nilotinib-associated acute pancreatitis. *Ann Pharmacother*. 2013;47(1):e3.

REFERENCES

1. Hill C, Zeitz C, Kirkman B. Dermatomyositis with lung involvement in a patient treated with simvastatin. *Aust N S Z J Med*. 1995;25:745-746.
2. Fernandez AB, Karas RH, Alsheikh-Ali AA, et al. Statins and interstitial lung disease: a systematic review of the literature and of food and drug administration adverse event reports. *Chest*. 2008;134:824-830.
3. US Food and Drug Administration. Information for health professionals: new safety information for colchicine (marketed as *Colcrys*). 2009. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm174315.htm>. Accessed February 11, 2013. ■