ISMP Adverse Drug Reactions

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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.

TICAGRELOR-INDUCED PNEUMONITIS AND SUBSEQUENT PULMONARY HEMORRHAGE

A 56-year-old male was admitted to the hospital following his second bout with hemoptysis over a 48-hour period. Ten days prior, the patient had begun taking aspirin 100 mg daily and ticagrelor (*Brilinta*) 90 mg twice daily following coronary artery stenting. At the time of admission, the patient did not exhibit shortness of breath, chest pain, fever, or infectious symptoms. He did not have any prior history of bleeding. A medication history revealed that the patient was receiving diltiazem, rosuvastatin, and a fluticasone and salmeterol inhaler. The patient had a pulse of 80 bpm, blood pressure of 132/91 mm Hg, respiratory rate of 24 breaths/min, and an oxygen saturation of 90% on room air. On examination, the

patient had coarse crackles bilaterally throughout his lower lung fields. His complete blood count (CBC) and indicators of renal and hepatic function were all within normal limits along with an international normalized ratio (INR) of 1.1. A CT scan of the chest revealed bilateral ground-glass opacities consistent with peribronchovascular pulmonary hemorrhages. The diffusion capacity was elevated, which is consistent with fresh hemorrhage.

Ticagrelor was temporarily stopped, and the patient was referred for a bronchoscopy. The bronchoscopy demonstrated edematous airways and frank blood in the lower lobes of the patient's lungs. Bronchiolar lavage demonstrated frank blood with no pathogens identified. At this time, ticagrelor was restarted and the patient's hemoptysis recurred.

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Ticagrelor was then discontinued and clopidogrel was started due to the patient's high risk of stent thrombosis, but he continued to experience ongoing hemoptysis. Twenty-five days after starting ticagrelor, the patient underwent open lung biopsy and elective coronary artery bypass grafting (CABG) to allow safe cessation of clopidogrel. Following the CABG, the patient's hemoptysis ceased and he was discharged on aspirin monotherapy. Six weeks postoperatively, the patient had experienced no further hemoptysis and diagnostic imaging of his chest showed marked improvement.

Ticagrelor has a more rapid onset and more pronounced platelet inhibition than clopidogrel. Although dyspnea is often reported in patients receiving ticagrelor, pulmonary hemorrhage has not been previously reported in the literature. The rapid onset of hemoptysis and alveolar hemorrhage within 14 days following initiation of ticagrelor, with associated relief of symptoms with discontinuation of ticagrelor and recurrence when the drug was restarted, are strong factors in the argument that it was the causative agent in this patient. Additionally, the histopathologic evidence of a lung injury pattern that is consistent with drug-induced injury and resolution of changes on CT scan at follow-up effectively rule out other potential diseases as a cause of the patient's pulmonary hemorrhage. The patient ultimately had a significant pulmonary hemorrhage due to drug-induced pneumonitis with ticagrelor and aspirin.

The authors point out that the mechanism by which ticagrelor induced lung injury in this patient is unclear. It has been hypothesized that the reversible nature of platelet inhibition with ticagrelor could lead to sequestration of overloaded, exhausted platelets in the pulmonary circulation, with subsequent disruption of endothelial function. The authors also mention that since this side effect is obviously rare, some unusual genetic factor related to the binding or action of ticagrelor is likely to be a contributing factor. Additional reports are needed to evaluate the potential risk profile of this adverse effect.

Whitmore TJ, O'Shea JP, Starac D, et al. A case of pulmonary hemorrhage due to drug-induced pneumonitis secondary to ticagrelor. *Chest*. 2014;145(3):639-641.

DRUG RASH WITH EOSINOPHILIA DUE TO BOCEPREVIR

A 56-year-old African woman with chronic hepatitis C complicated with cirrhosis and cryoglobulinemia type 2 with severe sensory and motor neuropathy received boceprevir (*Victrelis*). The patient was also co-infected with HIV. Her HIV regimen for the pre-

vious 8 months included raltegravir, tenofovir disoproxil, and emtricitabine and was well tolerated with good efficacy. The patient's chronic hepatitis C treatment was interferon alfa-2a (PegIFN) and ribavirin for 4 weeks, without adverse effects; then boceprevir was added to her regimen. The patient had a good response to treatment and her viral load decreased from 1.3×10^7 IU/mL to 30 IU/mL in 12 weeks.

Eight weeks after boceprevir was added to the patient's regimen, she developed a generalized maculopapular widespread rash with facial edema. She also had a fever of 40°C (104°F) and appearance of lymphadenopathies. Testing revealed eosinophilia up to 3×10^9 cells/L (reference range, 0-0.45 cells $\times 10^9$ /L) and no biological inflammatory syndrome. The patient also had a doubling of the GGT level compared to values before treatment. Histological exam was consistent with a drug rash reaction. A CT scan of the thorax and the abdomen revealed several swollen lymph nodes located in the abdomen and inguinal areas.

HCV treatment was stopped, and topical steroids were started. These were sufficient to relieve symptoms. Cutaneous and systematic symptoms disappeared within a few weeks, however the eosinophilia persisted for more than 7 weeks. Boceprevir was considered the causative agent due to the occurrence of the symptoms 8 weeks after beginning the drug; the generalized maculopapular rash with facial edema, fever, lymphadenopathy, and eosinophilia; and the improvement following interruption of boceprevir treatment. The role of PegIFN and ribavirin was not considered, because the patient had been receiving it more than 12 weeks without adverse effect.

The authors point out that the patient presented with the signs and symptoms of drug rash with eosinophilia (DRESS). DRESS is characterized by a long delay between the initiation of the drug (3-8 weeks) and by its long duration (more than 2 weeks) with flares even after drug discontinuation. Its pathophysiology is the consequence of the immune response against herpes virus (HHV6, EBV, and CMV) reactivation. Risk factors for DRESS include personal and family history of DRESS, African American origin, and HIV infection.

The authors state that their patient had the DRESS risk factors of African origin and HIV infection. No study specifically focuses on the comparison of DRESS rates in African and HIV populations. Some authors have suggested a role of genetic factors and a vitamin D deficiency in the African population. In the HIV population, genetic factors are also sug-

gested; antiretroviral drugs include drugs that have been associated with DRESS. Rare cases of DRESS due to raltegravir and tenofovir disoproxil have been reported, but these treatments were not considered the cause of this patient's DRESS because she had been receiving them for more than 8 months.

Samain A, Duval-Modeste AB, Joly P, et al. First case of drug rash eosinophilia and systemic symptoms due to boceprevir. *J Hepatol.* 2014;60:891-893.

HEPATITIS C REACTIVATION AFTER STARTING INFlixIMAB

A 50-year-old female was started on infliximab (*Remicade*) 5 mg/kg intravenous (IV) infusion at weeks 0, 2, and 6 and then every 8 weeks for recurrent fistulizing Crohn's disease. The patient had mild elevations in her transaminases before infliximab, with an alanine aminotransferase (ALT) level of 84 IU/L (reference range, 10-35 IU/L) and an aspartate aminotransferase (AST) level of 55 IU/L (reference range, <35 IU/L). Viral hepatitis serology revealed no evidence of active or prior hepatitis B virus (HBV) infection. Her anti-hepatitis C virus (HCV) antibody was positive by enzyme immunoassay. HCV RNA was negative on 2 separate occasions, 3 months and 7 weeks before infliximab treatment, suggesting either prior infection or a false positive. The patient's liver was mildly enlarged and diffusely fatty on CT scan of the abdomen with IV contrast. The patient had a history of alcohol abuse; it was felt that her mild elevation of transaminases was most likely related to nonalcoholic fatty liver disorder.

Five weeks after the first dose of infliximab, the patient experienced a significant rise in her transaminases, with an ALT of 346 IU/L and an AST of 143 IU/L. A repeat HCV RNA at week 7 was positive with a viral load of 6,110 IU/mL with an HCV genotype of 1a. An abdominal ultrasound revealed fatty infiltration of the liver and no new abnormalities. A serological workup revealed no acute viral hepatitis A or B. Other than infliximab, she was taking no new medications. The patient reported that she briefly experimented with IV drugs in the early 1970s, but she had no recent IV drug abuse or other risk factors for viral hepatitis.

The patient elected to continue treatment with infliximab, to which she responded well with the eventual closure of her colocutaneous fistula and healing of her luminal Crohn's disease. The patient's AST and ALT stabilized at 1.5 to 2 times the upper limit of normal 3 months after infliximab treatment.

Hepatitis C viremia persisted at 20 months after treatment with infliximab, indicating the development of chronic HCV infection. A liver biopsy 8 months after treatment with infliximab showed a striking degree of microvascular steatosis and mixed inflammatory infiltration. The patient was offered treatment for her HCV with pegylated interferon, ribavirin, and a protease inhibitor. Because of other concurrent medical issues, the patient chose not to initiate HCV treatment.

Infliximab is a monoclonal antibody with specific activity for human tumor necrosis factor-alpha (TNF α). The specific activity of infliximab is high-affinity binding to TNF α receptors and neutralizing TNF α activity. Although TNF α is proinflammatory, it is also an important cytokine in immune response against viral infection. Treatment with anti-TNF α therapy has been associated with reactivation of several latent viral infections including HBV, which can be fulminant and fatal. The authors postulate that their patient developed reactivation of HCV infection after infliximab treatment. She had 2 negative HCV RNA tests before treatment with infliximab, making it unlikely that the negative HCV RNA was falsely negative.

Huang M, Huang L. Reactivation of hepatitis C viral infection after treatment with infliximab. *J Clin Gastroenterol.* 2014;48(2):189.

HYDRALAZINE-ASSOCIATED IMMUNE GLOMERULONEPHRITIS

The authors present a case series of 4 patients, all receiving hydralazine, who presented to a large, Midwestern academic medical center with acute kidney injury, nephritic urine sediment, and the simultaneous presence of autoantibodies suggesting both drug-induced lupus and drug-induced vasculitis. All of the patients had evidence of pauci-immune glomerulonephritis on kidney biopsy. Pauci-immune glomerulonephritis is the most common type of rapidly progressive glomerulonephritis and refers to the paucity or absence of immune deposits seen on immunofluorescence.

Drug-induced lupus is a well-known adverse effect of hydralazine; drug-induced pauci-immune glomerulonephritis is a rare but preventable entity in the hypertensive population. The 4 patients in the case series were Caucasian women older than 60 years of age (range, 64-83 years) who were receiving hydralazine for more than 12 months (range, 13-24 months) at a dose of 150 mg once daily or more (dose

range, 150-300 mg/day). On initial presentation, all patients had evidence of acute kidney injury with nephritic sediment associated with high serum titers of anti-neutrophil cytoplasmic antibody (ANCA). All of the patients underwent kidney biopsy that revealed pauci-immune glomerulonephritis.

The authors point out that an interesting feature in each of the patients was the simultaneous presence of multiple autoantibodies. The pathogenesis of hydralazine-induced pauci-immune glomerulonephritis and vasculitis is not well understood. A proposed mechanism is that hydralazine accumulates in neutrophils, binds to myeloperoxidase, and induces cytotoxic products and neutrophil apoptosis. The simultaneous presence of various autoantibodies as seen in this case series suggests that apoptotic blebs of neutrophils could be a source of immunogens. However, the pathologic potential of ANCA and other antibodies is controversial, because not all patients with these antibodies develop clinical abnormalities.

Although discontinuation of hydralazine use may be sufficient to reverse disease activity in hydralazine-associated lupus, immunosuppression is often required to manage ANCA-associated vasculitis syndrome. All 4 of the patients in this case series received a steroid and cyclophosphamide for 3 months, as each patient's renal function returned to normal. It should be noted that antibodies including antinuclear antibody (ANA) and ANCA may persist for many years after the resolution of this syndrome. The authors emphasized that this case series draws attention to the possibility of pauci-immune glomerulonephritis/vasculitis in patients taking hydralazine and highlights the presence of multiple antibodies. This case series also questions the long-term use of hydralazine, especially in an elderly female population.

Suneja M, Baiswar S, Vogelgesang SA. Hydralazine associated pauci-immune glomerulonephritis. *J Clin Rheumatol*. 2014;20(2):99-102.

FLUOROQUINOLONES AND RETINAL DETACHMENT

A retrospective population-based cohort study was conducted with more than 356,000 patients to evaluate the risk of retinal detachment with the use of fluoroquinolones versus the use of amoxicillin. The authors extracted data from the Taiwan National Health Insurance Research Database from 1998 through 2010. Uncommon adverse effects of quinolones include seizure, tendon rupture, torsades de pointes, hepatotoxicity, and dysglycemia. An asso-

ciation between the use of oral quinolones and retinal detachment has been recently described in several anecdotal reports and a population-based study by Etminan et al. The authors speculated that because fluoroquinolones are well distributed in the vitreous cavity, they may have a deleterious effect on the collagen or connective tissue. There are 3 types of retinal detachment – exudative, tractional, and rhegmatogenous. Each has a distinct pathogenesis and associated risk factors. The presumed mechanism of fluoroquinolones on connective tissue is similar to that of rhegmatogenous retinal detachment (RRD).

The study population received fluoroquinolone therapy for a median of 3 days. Patients were 59.2% female and were on average 47 years of age. Approximately 41% of the prescriptions for fluoroquinolones were for the treatment of respiratory tract infections. The authors assessed the risk of RRD during the 90 days after completion of fluoroquinolone therapy. During the 90-day period, 96 patients (0.054%) receiving fluoroquinolones developed RRD. The median interval between use of the fluoroquinolone and the onset of RRD was 35.5 days.

Ofloxacin was the most commonly prescribed fluoroquinolone during the study period, followed by norfloxacin, ciprofloxacin, and levofloxacin. The risk of RRD differed based on the fluoroquinolone evaluated. Ciprofloxacin had the highest risk of RRD followed by levofloxacin, norfloxacin, and ofloxacin. The interval between fluoroquinolone use and the onset of RRD was 28 days for ciprofloxacin, 48.5 days for levofloxacin, 37 days for norfloxacin, and 44 days for ofloxacin.

The exact mechanism by which fluoroquinolones increase the risk for RRD remains unclear. Fluoroquinolone-associated tendinopathy has been suggested as a possible mechanism. Some of the mechanisms that have been considered are an ischemic vascular process or direct toxicity to collagen. Because the retina is attached to the vitreous body collagen fibers, it has been proposed that the presence of fluoroquinolones in the vitreous body may interfere with collagen synthesis, resulting in retinal detachment.

Kuo SC, Chen YT, Lee YT, et al. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: A population-based cohort study. *Clin Infect Dis*. 2014;58(2):197-203.

Etminan M, Forooghian F, Brophy JM, et al. Oral fluoroquinolones and the risk of retinal detachment. *JAMA*. 2012;307:1414-1419. ■