CLINICAL VIGNETTE

Olmesartan-Associated Enteropathy

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Case Report

A 72-year-old female presented with non-bloody diarrhea. Her medical history includes diabetes mellitus type 2, hypertension, breast cancer status post-right mastectomy, radiation, and chemotherapy. The diarrhea started one year ago when she started chemotherapy. It persisted despite being off chemotherapy for a year. Metformin was reduced without improvement in her symptoms. Her past medical history also included anxiety, depression, hyperthyroidism (iodine-induced), osteoporosis, glaucoma, herpes zoster, kidney stones, and a posterior cerebral artery aneurysm status post clipping. Her medications included Anastrozole, Olmesartan 40mg daily (which she had been on for at least a year), Hydrochlorothiazide, Metoprolol, Metformin 500mg daily, Glipizide, Sertraline 50mg daily, Simvastatin 20mg daily, Xalatan, Omega 3, and Vitamin D. Her physical exam was normal, including abdominal exam. Laboratory data showed WBC 3.6, Hgb 12.9, normal TSH of 1.1 and albumin of 4.5. Colonoscopy showed small hemorrhoids. Her medications were reviewed, and she had a trial of discontinuation of Olmesartan due to concerns for enteropathy. She was switched to Benazepril for her hypertension. Her diarrhea resolved within days after stopping Olmesartan.

Discussion

Olmesartan is an angiotensin II receptor blocker (ARB) that is used for treatment of hypertension; it is used alone or in combination of with other antihypertensives. It is also marketed as Benicar, Benicar-HCT, Azor, Tribenzor, and generics.[1] It was first approved in 2002 in the United States and in 2003 in the European Union.[2] It can cause a sprue-like enteropathy that is characterized by weight loss and chronic diarrhea, and the symptoms can take months to years to develop.[1] Olmesartan-associated enteropathy was first reported in 2012. Other angiotensin II receptor blockers have not been known to cause enteropathy. The exact etiology is unclear but thought to be due to an increase in Cytotoxic CD8+ T cells or a dysfunctional intestinal regulatory mechanism that normally suppresses CD8 T cells.[3]

There have been case reports and case series of Olmesartan causing sprue-like enteropathy. In a systematic review of these reports, almost all the patients had diarrhea (95%) and weight loss (89%).[4] Other symptoms include fatigue (56%), nausea and vomiting (45%), abdominal pain (37%), and bloating (29%). The mean age of the affected patients was 69, and mean therapy duration of Olmesartan was 3.3 years (range 6 months to 7 years). The most common laboratory abnormalities were a normochromic normocytic anemia (45%) and hypoalbuminemia (39%).[4] Antibody testing for celiac disease was negative in all patients. Histopathology showed variable degrees of duodenal villous atrophy (98% cases) and increased intra-epithelial lymphocytes (65% cases). All these patients had resolution of their signs and symptoms after discontinuation of Olmesartan.[4] In some affected patients, intestinal villi can be normal, but there are usually mild histologic abnormalities present, such as intra-epithelial lymphocytosis and lamina propria lymphocytic infiltration.[5]

Olmesartan is also associated with increased risk of hospitalization that is due to intestinal malabsorption; the relative risk increases with longer exposure to the drug. This is demonstrated in a French, nationwide, observational cohort study that compared Olmesartan to other ARBs and ACE Inhibitors (ACEIs) in patients initiated on these drugs between 2007 and 2012. The primary endpoint was incidence of hospitalization with a discharge diagnosis of intestinal malabsorption. Compared with ACEI, adjusted rate ratio of hospitalization in Olmesartan users was 2.49 (95% CI 1.7-3.57, $p<0.0001$) . The adjusted rate ratio was 0.76 (95% CI 0.39-1.49, $p=0.43$) for treatment duration less than 1 year, 3.66 (95% CI 1.84 to 7.29, $p<0.001$) for treatment duration between 1 and 2 years, and 10.65 (95% CI 5.05-22.46, $p<0.0001$) for treatment duration beyond 2 years. Median length of hospital stay was longer in the Olmesartan group (9 days) than in other ARB group (2 days) and ACEI group (4 days).[2]

Conclusion

Olmesartan can cause a sprue-like enteropathy characterized by chronic diarrhea and weight loss. The symptoms can be severe and life-threatening and can occur months to years after initiation of the drug. Antibody testing for celiac disease will be negative,[4] and there is no response to a gluten-free diet.[3] In patients who test negative for celiac disease and who are on Olmesartan, Olmesartan-associated enteropathy should be in the differential diagnosis. In the United States, this condition is a reportable adverse event to the Food and Drug Administration.[1] Olmesartan is associated with increased risk of hospitalization for intestinal malabsorption.[2] Patients with villous atrophy are more likely to have diarrhea, vomiting, renal failure, hypokalemia, weight loss, and hypoalbuminemia.[5]

Clinical response and histological recovery are expected after discontinuation of the drug.[6]

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