Olmesartan and Drug-Induced Enteropathy

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INTRODUCTION

The constellation of diarrhea, weight loss, and villous atrophy is usually associated with celiac disease, an immune-mediated sensitivity to gluten that results in damage to the intestinal villi, contributing to malabsorption and gastrointestinal (GI) disorders.[1] The diagnosis of celiac disease involves serologic testing for immunoglobulin A tissue transglutaminase antibodies (IgA tTGA) with subsequent upper endoscopy and small-bowel biopsy for confirmation.[1]

Given the association of gluten with celiac disease, patients must maintain a life-long gluten-free diet. However, in individuals without an elevated IgA tTGA and who do not respond to a gluten-free diet, celiac disease is a less likely diagnosis. Testing for other suspected causes such as common variable immunodeficiency, autoimmune enteropathy, microscopic colitis, pancreatic exocrine insufficiency, bacterial overgrowth, GI infections, intestinal cancers, irritable bowel disease, small-bowel strictures, collagenous sprue, Crohn's disease, and tropical sprue may be warranted.

Another possible cause of villous atrophy has recently garnered more attention—drug-induced enteropathy. Reports of damage to the intestinal villi by pharmaceuticals have been described with azathioprine (Imuran, Prometheus), mycophenolate mofetil (CellCept, Roche), methotrexate, neomycin, and colchicine (Colcrys, Takeda).[2–6] The oral angiotensin-receptor blocker (ARB) olmesartan medoxomil (Benicar, Daiichi Sankyo) can now been added to the compendium of drugs linked to sprue-like enteropathy. The earliest evidence of olmesartan-induced sprue-like enteropathy was identified in August 2012, and a few reports were published subsequently.[7–9]

Olmesartan, approved by the FDA on April 25, 2002, is one of several ARBs used for the treatment of hypertension (Table 1).[10,11] No other ARBs, angiotensin-converting enzyme (ACE) inhibitors, or direct renin inhibitors have been associated with the development of villous atrophy. Reports published by the Mayo Clinic provided enough support for the FDA to institute label changes addressing this adverse event in July 2013 for all olmesartan single-ingredient and combination products (Table 2).[12] The FDA's warning states this medication has been associated with severe, chronic diarrhea and weight loss, with evidence of villous atrophy, in patients exposed to olmesartan over months to years.[12] Health care practitioners should exclude other causes of sprue-like enteropathy before considering olmesartan as a cause.

PATHOPHYSIOLOGY

The mechanisms associated with drug-induced diarrhea are diverse. Causes include acid suppression, which can precipitate an increased risk; infectious pathogens; drug-induced hypomotility or hypermotility,[5] drugs that affect water and electrolyte transport; and the osmotic potential of lactulose and sorbitol, common ingredients in laxatives that induce diarrhea.

Most often, diarrhea as a side effect of medications occurs independently of damage to the intestinal mucosa. How-

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Table 1 Single-Ingredient Angiotensin II Receptor Blockers

Generic Name	Brand Name	Time to Peak Concentration (Hours)	Bioavailability (%)	Elimination Half-Life (Hours)
Azilsartan	Edarbi (Arbor)	1.5–3	60	11
Candesartan	Atacand (AstraZeneca)	3–4	15	5–9
Eprosartan	Teveten (AbbVie, Solvay)	1–2	13	5–9
Irbesartan	Avapro (Bristol-Myers Squibb)	1.5–2	60–80	11– 15
Losartan	Cozaar (Merck)	1/3–4*	33	1.5–2/6–9*
Olmesartan	Benicar (Daiichi Sankyo)	1–2	26	13
Telmisartan	Micardis (Boehringer Ingelheim)	0.5–1	42–58	24
Valsartan	Diovan (Novartis)	2–4	25	6

*Losartan: active metabolite E-3174.
Data from Dana WJ, et al. *Drug Information Handbook,* 2013.[11]

Table 2 Olmesartan Products

Generic Name	Brand Name	FDA Approval Date
Olmesartan medoxomil	Benicar	April 25, 2002
Olmesartan medoxomil/hydrochlorothiazide	Benicar HCT	June 5, 2003
Olmesartan medoxomil/amlodipine	Azor	September 26, 2007
Olmesartan medoxomil/ amlodipine/hydrochlorothiazide	Tribenzor	July 23, 2010

ever, when villous involvement and malabsorption are present, the damage is defined as sprue-like enteropathy.

Celiac disease refers only to diarrhea experienced as a result of intestinal villous atrophy caused by exposure to gluten, whereas drug-induced enteropathy occurs independent of gluten intake. Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss, as well as abdominal pain, fatigue, bloating, nausea, vomiting, and anemia.

Olmesartan-induced enteropathy can develop months to years after the initiation of therapy and, in severe cases, can lead to hospitalization. Because of the lag time between olmesartan initiation and symptom development, the mechanism is unlikely to be an allergic type-1 hypersensitivity response.[9]

A possible mechanism is a cell-mediated immune response. As an ARB, olmesartan can increase circulatory levels of angiotensin II, which can induce gene expression of transformation growth factor (TGF)-beta. The increase in TGF-beta in the GI tract may be responsible for damage to the intestinal epithelial cells and mucosal immune system.[9] Given that all ARBs cause an increase of angiotensin II, this effect does not explain why sprue-like enteropathy has only been seen with olmesartan.

At present, other ARBs do not appear to carry an increased risk of enteropathy, according to the FDA's assessment of Mini-Sentinel and Centers for Medicare & Medicaid Services (CMS) claims data of International Classification of Disease, Ninth Revision (ICD-9) codes for celiac disease after a minimum of 2 years' exposure to ARBs.[12] The number of diagnoses of celiac disease was higher with olmesartan compared with the use of all other ARBs. However, because of the limited number of events observed and the possibility of invalid coding of celiac disease, caution is warranted in interpreting this information.

INCIDENCE AND LITERATURE REVIEW

In 2012, approximately 10.6 million prescriptions were dispensed for olmesartan, and nearly 2 million patients received a prescription for the single or the combination product from community pharmacies in the U.S.[13] The incidence of adverse effects reported by Daiichi Sankyo related to olmesartan in premarketing clinical trials was similar to those of placebo.[10] The only adverse effect linked to olmesartan reported in the prescribing information with greater frequency than placebo was dizziness (3% vs. 1%, respectively).

According to an evaluation of adverse events in the published literature, case series, and other data received by the FDA's Adverse Event Reporting System (FAERS), symptoms related to enteropathy, including nausea, vomiting, diarrhea, weight loss, and electrolyte abnormalities, appeared to be associated with olmesartan. Through FAERS, the agency identified 23 patients who presented with late-onset diarrhea and significant weight loss. All patients improved clinically when olmesartan therapy was stopped. Ten patients had a positive rechallenge.[12]

Between the years 2008 and 2011, physicians from the Mayo Clinic treated 22 patients from 17 states with life-threatening GI symptoms, commonly seen in patients with celiac disease.[7] Patients experienced chronic diarrhea with intestinal inflammation and abnormalities; 14 patients required hospitalization for their symptoms. These patients lost an average of 18 kg (almost 40 pounds), and one patient lost 57 kg (about 125 pounds). Although some patients' medical histories included celiac disease, serologic measurements performed by the physicians did not confirm this diagnosis. The patients also did not respond to gluten-free diets. All patients were taking 10 to 40 mg of olmesartan daily, and most patients received 40 mg daily. The duration of treatment ranged from several months to several years. When olmesartan was discontinued, symptoms dramatically improved in all patients. All patients experienced clinical weight gain (a mean increase of 12.2 kg). Intestinal biopsies from 18 of the 22 olmesartan-treated patients showed improvement when the medication was stopped.

In another case series of 72 patients with villous atrophy and negative celiac serology, 26% had drug-induced enteropathy.[8] Of 19 patients with drug-induced enteropathy,16 patients were using olmesartan. In three patients, mycophenolate and methotrexate was the cause of the enteropathy. Of the patients who received olmesartan, follow-up data were available for 15 patients. All 15 patients improved after olmesartan was discontinued, and some patients had resumed a gluten diet without any negative consequences. One patient's symptoms reoccurred after olmesartan was reinitiated.

Stanich et al. reported on a 57-year-old woman who had nausea and vomiting for 3 weeks.[14] Her medical history is described below.

Case Study 1

A patient arriving from another facility after a stay of 15 days had experienced up to five episodes of bilious emesis and five to 10 episodes of large, watery stools each day. Her medical history included hypertension and gastroesophageal reflux disease (GERD), for which she was taking olmesartan, amlodipine (e.g., Norvasc), bisoprolol (e.g., Zebeta, Duramed/Barr), hydrochlorothiazide, and omeprazole (Prilosec, AstraZeneca).

She was given a trial of empirical antibiotics, but her symptoms did not resolve. Studies to detect infected stool and colonoscopy were negative. Total parental nutrition, which had been initiated at a previous facility, was continued. Endoscopic biopsy revealed sprue-like enteropathy with diffuse villous blunting, crypt hyperplasia, and an increase in intraepithelial lymphocytes. Olmesartan had been withheld during her hospitalization because it was not on the formulary. While she was awaiting IgA tTGA testing, her symptoms began to improve. Additional test results were negative for the *HLA DQ2/8* gene associated with celiac disease.

The patient continued to improve. By the 6th day, she was tolerating oral intake and ready for discharge by hospital day 7.

Two weeks after discharge, although enteroscopy was not performed, the patient reported complete resolution of symptoms and olmesartan had not been reinitiated.

DIAGNOSIS

All patients taking olmesartan or olmesartan combination products who experience severe or chronic diarrhea or significant weight loss should contact their health care professional regardless of how long they have been taking the drug. Individuals with chronic diarrhea, weight loss, or malabsorption should be evaluated for celiac disease prior to the removal of gluten from their diet. Evaluation of IgA tTGA, with an accompanying test for IgG-deamidated gliadin peptides (DGPs), if considered appropriate, should be performed in patients with a high suspicion of celiac disease.[9]

If serologic results are positive, a small-bowel biopsy may be warranted. Patients following a gluten-free diet with negative celiac serology may undergo additional *HLA DQ2/DQ8* testing to determine genetic susceptibility to celiac disease. If the results are negative, celiac disease should be excluded from the differential diagnosis.[9]

In patients with drug-induced enteropathy, an upper endoscopy with small-bowel biopsy may reveal sprue-like histological features, ranging from a mild alteration characterized only by increased intraepithelial lymphocytes to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia. The diagnosis is supported if symptoms do not resolve on a gluten-free diet.

In patients without celiac disease or other likely causes, a thorough review of their medications should be performed to rule out drugs associated with villous atrophy. Besides olmesartan, these agents include azathioprine, mycophenolate, methotrexate, neomycin, and colchicine. Discontinuation or substitution of the offending agent should be considered based on benefit versus risks.

TREATMENT

If olmesartan is the cause of sprue-like enteropathy, the medication should be discontinued and an alternative antihypertensive agent should be prescribed. Discontinuation of olmesartan should result in clinical improvement of symptoms and may improve histological features of the intestinal villi. At this time, it would be reasonable to try an alternative ARB or ACE inhibitor to treat hypertension in patients with diabetes or chronic kidney disease because of their nephroprotective and proteinuric benefits.

Case Study 2

A middle-aged man presented to our hospital with diarrhea and a weight loss of more than 4 kg (10 pounds). He was admitted for an evaluation of celiac disease because he was experiencing numerous episodes of watery, nonbloody diarrhea several times a day. He denied any other symptoms of infection, recent travel, ill contacts, or change in diet or medications.

The patient's medical history included hypertension. Recent colonoscopy results did not show evidence of microscopic colitis or inflammatory bowel disease. He was taking olmesartan 40 mg daily for hypertension.

Dehydration developed as a result of the diarrhea, and his serum creatinine level rose to 1.7 mg/dL. No medications were used to control his diarrhea during hospitalization; however, olmesartan was discontinued.

Esophagogastroduodenoscopy revealed villous blunting and atrophy, with increased intraepithelial lymphocytes. Abdominal and pelvic computed tomography did not suggest a pancreatic abnormality or malignancy. An IgA tTGA level and *HLA-DQ2* genetic testing were performed in order to confirm a diagnosis of celiac disease.

Upon a later review, all of his serologic markers were negative. No clear cause of his diarrhea was established. On hospital day 3 (i.e., 2 days after olmesartan was discontinued), his GI symptoms continued to improve. Testing was continued to determine a cause of the diarrhea. Within 2 days, the patient's symptoms completely resolved.

On hospital day 6, the patient was ambulating and tolerating oral intake. He was discharged later that day. At the time, the medical team was not aware of the association between olmesartan and sprue-like enteropathy. Therefore, no additional follow-up evaluation was performed after hospital discharge; it was unclear whether the patient started taking olmesartan again at home. Subsequent outcomes are not known.

In the editor's (M. B. K.) personal correspondence with Joseph A. Murray, MD, in 2013, he identified 60 cases of olmesartan-associated sprue-like enteropathy. Dr. Murray, along with his coauthors Rubio-Tapia et al., had identified 22 patients at the Mayo Clinic in Rochester, Minnesota.[7] Since that time, they have identified one case of potential valsartan-induced sprue-like enteropathy. The valsartan case was presented at the 78th American College of Gastroenterology meeting in San Diego, California, on October 15, 2013.[15] This case report is described next.

Case Study 3

A 71-year-old woman presented with watery diarrhea, nighttime fecal incontinence, and abdominal pain, along with a weight loss of 27 kg over a period of 5 years. Duodenal biopsies showed villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. She did not respond to a gluten-free diet. Numerous GI tests showed an inflamed and edematous bowel. Capsule endoscopy revealed villous atrophy along 75% to 90% of the small intestinal mucosa.

The patient received a 10-day course of tetracycline for bacterial overgrowth in the small intestine without resolution of symptoms. Follow-up biopsy results at 1 and 2.5 years were unchanged. It was recommended that she stop taking valsartan (Diovan). Within days, the diarrhea, bloating, and abdominal pain resolved. A year later, the villous architecture had normalized. There was no rechallenge; however, drug-induced sprue-like enteropathy, similar to that reported with olmesartan, was suspected to be the cause.

CONCLUSION

An association between olmesartan and sprue-like enteropathy has been observed in several case series and reports. Patients 57 to 81 years of age, irrespective of gender, have experienced weight loss of up to 40 kg while taking this drug. Although the mechanism precipitating this adverse effect remains uncertain, it is essential to consider olmesartan-associated enteropathy in patients with biopsy-proven villous atrophy when no other cause can be found.

Because observational studies do not provide the strongest evidence, further clinical investigation is required to evaluate the specific mechanisms of olme-

sartan-associated enteropathy. In addition, similar findings have not been consistently noted with other ARBs. Whether this association is limited to olmesartan needs to be confirmed.

In summary, treatment with olmesartan was suspended in patients presented in the two case series published by Rubio-Tapia et al.[7] and by DeGaetani et al.[8] To avoid a recurrence of sprue-like enteropathy, the researchers did not introduce olmesartan again. Alternative antihypertensive medications, such as calcium-channel blockers (e.g., amlodipine) or diuretics (e.g., hydrochlorothiazide), were started in appropriate situations without ill effects.[7,9]

Although olmesartan has been on the market for more than a decade, cases of olmesartan-induced sprue-like enteropathy have been reported only since 2012. Millions of people have used olmesartan. Careful consideration of patients' medication regimens is warranted when severe and chronic diarrhea and weight loss are unexplained by other known causes of enteropathy. Greater awareness of olmesartan-induced sprue-like enteropathy, as with other drug-induced diseases, can help to divert expenditures from invasive or high-priced procedures and laboratory testing, to relatively simple and quick trials of drug discontinuation. Accurately identifying olmesartan-induced sprue-like enteropathy is helpful, because drug discontinuation and substitution of another agent or ARB are necessary for treatment.

REPORTING ADVERSE DRUG REACTIONS

All adverse drug reactions (ADRs) should be reported to MedWatch at 1-888-INFO-FDA, 1-888-463-6332, or online. The FDA 3500 Voluntary Adverse Event Report Form can be easily accessed online for reporting ADRs at www.fda.gov/Safety/Medwatch/HowToReport/ucm085568.htm.

The FDA is interested in serious reports that include any of the following patient outcomes: death; life-threatening condition; initial hospitalization; prolonged hospitalization; disability or permanent damage; congenital anomalies or birth defects; and other serious conditions for which medical or surgical intervention is needed to prevent one of the aforementioned outcomes.

In addition, the FDA is interested in any unlabeled ADRs for new drugs (e.g., usually those approved within the previous 2 years).

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