Olmesartan and Intestinal Adverse Effects in the ROADMAP Study

To the Editor: We read the article by Rubio-Tapia and colleagues[1] with great interest. In this article, the authors describe the occurrence of severe spruelike enteropathy in 22 patients, all of whom received olmesartan (predominantly 40 mg/d) besides other drugs. All patients had long-lasting diarrhea (3-53 months) and weight loss (2.5-50 kg). Many patients also experienced nausea and vomiting (68% of patients), abdominal pain (50%), bloating (41%), and fatigue (68%). Interestingly, these symptoms disappeared after use of olmesartan was stopped. The authors draw the conclusion that olmesartan may directly be involved in spruelike enteropathy. However, our observation in a large group of diabetic patients treated with 40 mg of olmesartan daily does not support this conclusion. We detected no association between treatment with 40 mg of olmesartan once daily and the occurrence of intestinal adverse effects in 2232 patients treated for a median of 3.2 years in the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study.

The largest prospective, randomized, double-blind study with olmesartan is the ROADMAP study.[2,3] In this study, patients with type 2 diabetes were treated with 40 mg of olmesartan (n=2232) or placebo (n=2215) once daily for a median of 3.2 years, and the occurrence of microalbuminuria (interpreted as an early sign of kidney and vascular damage) was the primary end point. We now analyzed the treatment-emergent adverse events (TEAEs) reported by the study physicians. For this analysis, we selected all intestinal illnesses that typically present with diarrhea and selected all symptoms and conditions that were related to abdominal discomfort, such as pain (Table). A total of 78 patients (3.5%) in the olmesartan arm and 94 (4.2%) in the placebo arm had at least 1 episode of diarrhea or diarrhea-associated diseases. We also observed no difference between the groups in the occurrence of any intestinal TEAE. The incidence of abdominal pain or related symptoms was also comparable (Table). In the olmesartan group, 127 patients (5.7%) experienced at least 1 episode of abdominal discomfort vs 125 (5.6%) in the placebo group. The reported incidences of fatigue and weight decrease were also similar. Furthermore, we determined whether more patients prematurely terminated study participation because of intestinal or abdominal discomfort–related TEAEs. Three patients in the olmesartan group (all 3 having diarrhea) and 3 patients in the placebo group (2 having diarrhea and 1 having gastroenteritis) stopped taking the study medication because of specific gastrointestinal findings. Eight additional patients in each of the 2 study arms stopped taking the study medication because of abdominal discomfort–associated TEAEs not specifically linked to the gastrointestinal tract.

In summary, in more than 2200 patients taking high-dose olmesartan for more than 3 years, we did not observe an intestinal effect of olmesartan. In the ROADMAP study, we could not find a link between the occurrence of diarrhea-associated complications and the intake of 40 mg/d of olmesartan. This finding might be because spruelike enteropathy is a rare event. Indeed, the 22 reported cases in the report by Rubio-Tapia et al came from 16 different states and were diagnosed at the Mayo Clinic during a time frame of 3 years. We cannot rule out the possibility

TABLE. Gastrointestinal TEAEs Reported in the ROADMAP Database

Event	No. (%) of patients		*P* value
	Olmesartan, 40 mg (n=2232)	Placebo (n=2215)	
Intestinal-associated TEAE	78 (3.5)	94 (4.2)	.20
Diarrhea	51 (2.3)	52 (2.3)	
Gastroenteritis	17 (0.8)	25 (1.1)	
Colitis	1	6 (0.3)	
Enteritis	2 (0.1)	4 (0.2)	
Gastroduodenitis	4 (0.1)	2 (0.1)	
Colitis, ulcerative	2 (0.1)	2 (0.1)	
Duodenitis	2 (0.1)	2 (0.1)	
Gastrointestinal disorder	3 (0.1)	1	
Gastrointestinal infection	1	3 (0.1)	
Enteritis, infectious	0	2 (0.1)	
Abdominal discomfort–associated TEAE	127 (5.7)	125 (5.6)	.95
Abdominal pain	61 (2.7)	52 (2.3)	
Upper	26 (1.2)	24 (1.1)	
Lower	2 (0.1)	1	
Location not reported by physician	33 (1.4)	27 (1.2)	
Dyspepsia	34 (1.5)	29 (1.3)	
Nausea	30 (1.3)	34 (1.5)	
Vomiting	13 (0.6)	13 (0.6)	
Flatulence	6 (0.3)	9 (0.4)	
Abdominal discomfort	4 (0.2)	4 (0.2)	
Irritable bowel syndrome	2 (0.1)	3 (0.1)	
Epigastric discomfort	2 (0.1)	2 (0.1)	
Gastrointestinal pain	1	0	
Fatigue	25 (1.1)	20 (0.9)	
Weight decrease	17 (0.8)	11 (0.5)	

ROADMAP = Randomised Olmesartan and Diabetes Microalbuminuria Prevention; TEAE = treatment-emergent adverse event.

Mayo Clin Proc. ■ December 2012;87(12):1230-1232
www.mayoclinicproceedings.org ■

that in this very rare disease the intestinal renin-angiotensin system plays a role; however, our data from the ROADMAP database did not identify a link between olmesartan use and the occurrence of gastrointestinal disease.

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Potential Competing Interests: Both authors have received honoraria for lectures from Daiichi-Sankyo. Dr Haller is a medical advisor to Daiichi-Sankyo and was supported by research grants.

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http://dx.doi.org/10.1016/j.mayocp.2012.10.005

Small Bowel Histopathologic Findings Suggestive of Celiac Disease in an Asymptomatic Patient Receiving Olmesartan

To the Editor: Rubio-Tapia et al[1] recently reported a possible association of olmesartan therapy with an unexplained severe enteropathy symptomatically resembling celiac disease (CD) or sprue. The 22 patients described were seen at Mayo Clinic in the relatively short period of August 1, 2008, to August 1, 2011. The usual presentation was chronic diarrhea and weight loss, sometimes requiring hospitalization. Onset of symptoms was months to years after initiation of olmesartan treatment. Intestinal biopsy specimens from 15 patients revealed villous atrophy and variable degrees of mucosal inflammation. Five patients had evidence of colonic inflammation. Most remarkably, a gluten-free diet did not resolve symptoms, whereas both marked symptomatic improvement and resolution of histopathologic findings occurred on withdrawal of olmesartan therapy.

We describe a patient who had been taking olmesartan for 3 years at which time small bowel histopathologic findings suggesting CD were documented, but symptoms of CD enteropathy were absent. This anecdotal observation suggests the possibility that olmesartan could be associated with histopathologic findings for a substantial period before the onset of enteropathy or alternatively that such histopathologic findings might persist for years without the onset of symptoms.

A 59-year-old man experienced mild, normochromic, normocytic anemia in 2007. Workup revealed an isolated vitamin B_{12} deficiency (172 pg/mL), which was ascribed to long-term ranitidine therapy for gastroesophageal reflux and which responded to oral vitamin B_{12} supplementation at 1000 μg/d. However, the anemia did not improve. The gastrin level was 41 pg/mL (reference range, <100 pg/mL); the intrinsic factor antibody test result was negative.

Coincidentally, the patient underwent upper gastrointestinal endoscopy for symptoms consistent with worsening gastric reflux. The only macroscopic finding was nodularity in the duodenal bulb consistent with prominent Brunner glands, which was attributed to acid wash. However, a biopsy specimen from the second portion of the duodenum revealed mild expansion of the lamina propria and increased intraepithelial lymphocytes (IELs) with no significant villous blunting, suggesting (but not diagnostic of) possible CD. The patient reported no diarrhea but had occasional mild constipation. He had a first-degree cousin with CD, but no other family members were known to have CD. Findings from a workup for CD were unremarkable, including negative tissue transglutaminase antibody results (0.9 AU; reference range, <7.0 AU), normal total IgA level (127 mg/dL; reference range, 50–500 mg/dL), normal vitamin K_1 level (1.16 ng/mL; reference range, 0.10-2.10), normal prothrombin time, and negative *Helicobacter pylori* antibody results. He was HLA-DQ2 positive but HLA-DQ8 negative.

Because the findings were unusual, a repeated upper endoscopy and a colonoscopy were performed in August 2010. The small bowel gross appearance was unchanged; the colonic examination findings were unremarkable. A small bowel biopsy specimen revealed increased IELs with mild villous blunting (interpreted as unchanged from the prior study); the colonic biopsy results were normal. The tissue transglutaminase antibody test result was again negative, and the total IgA level was normal.

A stool specimen for *Giardia* and *Cryptosporidium* immunoassays, obtained because of an episode of prolonged (6 weeks' duration) diarrhea during international travel 10 years previously, produced negative results. A trial of a gluten-free diet was considered, but the patient elected not to pursue this given the absence of symptoms, the uncertain diagnosis, and the logistical difficulties of dietary adherence during frequent domestic and international travel.

Hypertension had been diagnosed in 2003, and therapy with losartan was initiated. In 2004, losartan therapy was discontinued, and olmesartan therapy, 20 mg/d, was begun. Olmesartan therapy was well tolerated, and the hypertension was well controlled. On publication of the article by Rubio-Tapia et al, olmesartan was identified as a possible cause of the unusual findings. Olmesartan therapy will be discontinued, with monitoring of vitamin B_{12} levels and consideration for repeated upper gastrointestinal endoscopy.

Although Rubio-Tapia et al are careful to avoid claiming a proven causal relationship between olmesartan therapy and the observed spruelike enteropathy, the data are highly suggestive of more than just a coincidental association. The authors posit that the long interval between initiation of olmesartan therapy and onset of symptoms of enteropathy, as observed in their patients, could be consistent with cell-mediated immunity damage. They further suggest that a potential mechanism for the enteropathy could relate to inhibitory effects of angiotensin II receptor antagonists on transforming growth factor β action because transforming growth factor β is important in gut immune homeostasis.

Another interesting observation by the authors is that 68% of their patients