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.

Jan Menne, MD
Hermann Haller, MD
Medical School Hannover
Hannover, Germany

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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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

had HLA-DQ2, which was found in the current patient as well and is consistent with their hypothesis that the presence of DQ2 might increase the risk of olmesartan-associated enteropathy.

The finding of intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa has been recognized as an increasing diagnostic problem with a wide differential diagnosis.[2] Brown et al[2] reported in 2006 that "up to 2.5% of proximal small intestinal mucosal biopsies display increased IELs (>25 IELs per 100 epithelial cells) in the absence of villus architectural change. In most cases this is due to immunologic activation of the lymphocytes that are normally resident in the epithelium. The causes for this increase in numbers of IELs are multiple and include reactions to intraluminal antigens and small intestinal manifestations of autoimmune or other allied diseases." Drugs suggested as a cause of this finding include nonsteroidal anti-inflammatory drugs and proton pump inhibitors; however, the strength of the association is weak.[2]

The findings in the patient who is the subject of this case report are similar to those of the patients described by Rubio-Tapia et al, with the notable exception of the absence (to date) of symptomatic enteropathy. In particular, the laboratory evaluation results for CD were negative in the setting of nondiagnostic histopathologic findings. Although anecdotal, these observations lead to the hypothesis that olmesartan, and perhaps other angiotensin II receptor antagonists, could be a cause of intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa. Furthermore, the observation raises intriguing questions about the likely natural history of this phenomenon, assuming it is validated by other observers in larger numbers of patients. For example, would such patients ultimately become symptomatic? Is the risk of small intestinal malignant tumors increased? These and other questions about this entity should be addressed by properly designed, prospective studies.

George Harrison Talbot, MD
Talbot Advisors LLC
Anna Maria, FL

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In reply: We appreciate the communication from Drs Menne and Haller regarding their review of the gastrointestinal adverse events in the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study. The lack of excess adverse effects relating to the gastrointestinal system in individuals enrolled in the ROADMAP study, half of whom were actively treated with olmesartan, puts our report in perspective. Their data suggest that the association we had described is likely quite rare. This finding should be reassuring for both prescribers and patients who are doing well with olmesartan. Drs Menne and Haller rightly point out that our report was based on patients drawn from a wide referral base. Rare associations of other drug therapies can be clinically important, yet not seen in many of the often quite large initial clinical trials. In particular, Drs Menne and Haller report on just more than 2200 individuals exposed to olmesartan (40 mg) followed up for a mean of 3 years, or approximately 6600 years of patient follow-up. Our research reported on a relatively small number of patients (22 total) who were drawn from a likely much larger population of individuals taking olmesartan. Further, the population from which our patients were drawn likely had more heterogeneous clinical characteristics than permitted by the strict inclusion criteria used in the ROADMAP study. We have since identified more patients with a similar syndrome, including 1 patient with diabetes who was prescribed olmesartan for microalbuminuria prevention (ie, a profile similar to that of the patients enrolled in the ROADMAP research). Larger postmarketing surveillance studies will be necessary, along with other studies, for example, pharmacogenetic studies, to understand the mechanisms of this important, albeit rare, association.

In his letter, Dr Talbot described a 59-year-old man who had abnormal intestinal biopsy findings (intraepithelial lymphocytosis on a first biopsy specimen and intraepithelial lymphocytosis with mild villous blunting on a subsequent biopsy specimen) without diarrhea and also had "symptoms consistent with worsening gastric reflux" and mild constipation. This profile suggests the possibility of a spectrum of severity in olmesartan-associated enteropathy. In addition to diarrhea, many of our patients also experienced upper gastrointestinal tract symptoms, such as abdominal pain, nausea, and vomiting. Other clinical characteristics of Dr Talbot's reported case are consistent with our observations. Demonstration of complete recovery of the mucosa of the duodenum after suspension of olmesartan therapy in his patient will be required to support an association between olmesartan and histologic abnormalities in the absence of symptomatic malabsorption.

Alberto Rubio-Tapia, MD
Margot L. Herman, MD
Joseph A. Murray, MD
Mayo Clinic
Rochester, MN

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