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 al² 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.

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1. Rubio-Tapia A, Herman ML, Lu JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc.* 2012;87(8):732-738.
2. Brown I, Mino-Kenudson M, Deshpande V, Lauwers GY. Intraepithelial lymphocytosis in architecturally preserved proximal small intestinal mucosa: an increasing diagnostic problem with a wide differential diagnosis. *Arch Pathol Lab Med.* 2006; 130(7):1020-1025.

<http://dx.doi.org/10.1016/j.mayocp.2012.09.011>

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 post-marketing 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.

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<http://dx.doi.org/10.1016/j.mayocp.2012.10.006>