Clinical Gastroenterology and Hepatology 2018;16:584–585

RESEARCH CORRESPONDENCE

Regional Patterns of Olmesartan Prescription and the Prevalence of Duodenal Villous Atrophy Throughout the United States

Eugenia N. Uche-Anya,[*] Peter H. R. Green,[*] Robert M. Genta,[‡,§] and Benjamin Lebwohl[*,‖]

[*]Celiac Disease Center, Department of Medicine, Columbia University Medical Center, New York, New York; [‡]Miraca Life Sciences Research Institute, Irving, Texas; [§]Baylor College of Medicine, Houston, Texas; [‖]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York

A severe, sprue-like enteropathy has been described in patients exposed to olmesartan.[1] Although histologically similar to celiac disease, patients typically are seronegative and only respond to drug cessation. Studies suggest that olmesartan-associated enteropathy is a rare adverse event among olmesartan prescription users.[2–4] However, among patients with villous atrophy, it is uncertain whether olmesartan is a rare or common but under-recognized cause.[5] We therefore aimed to determine whether regional variations in olmesartan prescription in the United States exert an ecologic effect on the prevalence of villous atrophy.

Methods

We obtained histologic data containing all duodenal biopsy specimens submitted from patients $\geq$ 18 years to Miraca Life Sciences (Irving, TX), a large national pathology laboratory, from January 2, 2008, to April 30, 2015. All specimens were analyzed and reported by a single group of fellowship-trained gastrointestinal histopathologists. The database does not contain serologic data; therefore, we could not determine which patients had celiac disease, although celiac disease is the most common cause of seronegative villous atrophy in the United States.[5]

We cross-referenced patients' residential ZIP codes from publicly available olmesartan prescription data from the Centers for Medicare and Medicaid Services beneficiaries in 2013.[6] We identified all olmesartan prescriptions by Medicare providers in each ZIP code. These ZIP codes were ranked by quartiles based on the number of olmesartan prescriptions per physician, and again by olmesartan prescriptions per capita. Data containing the number of registered physicians and the residential population in each ZIP code were obtained from the Centers for Medicare and Medicaid Services[6] and US 2010 Census Data,[7] respectively. We compared the prevalence of villous atrophy in each olmesartan prescription quartile using the Cochran–Armitage test for trend. The analysis was repeated, restricting the population to patients older than age 65. The study had 80% power to detect a 0.11% difference in the prevalence of villous atrophy between the lowest and highest quartiles.

Results

There were 443,479 patients $\geq$ 18 years from 729 ZIP codes in 48 states. We excluded 4016 patients from 7 ZIP codes without corresponding olmesartan prescription information available, yielding a remaining sample size of 439,463 individuals from 722 ZIP codes. The median age was 54 years and 67% were female. Of these 439,463 patients, 7556 (1.72%) had villous atrophy. The prevalence of villous atrophy from the lowest to highest quartile of olmesartan prescriptions per capita was 1.69%, 1.83%, 1.66%, and 1.70% ($P = .45$). With olmesartan prescriptions per physician, there was an inverse relationship between increasing olmesartan prescription rates and the prevalence of villous atrophy: 1.77%, 1.75%, 1.76%, and 1.61% ($P = .0056$) (Figure 1). Similarly, for patients $\geq$ 65 years of age, higher quartiles of olmesartan prescriptions per capita/physician were not associated with a higher prevalence of villous atrophy. The prevalence of villous atrophy from the lowest to highest quartile of olmesartan prescriptions per capita was 1.50%, 1.38%, 1.48%, and 1.34% ($P = .22$), and the prevalence of villous atrophy from the lowest to highest quartile of olmesartan prescriptions per physician was 1.45%, 1.40%, 1.45%, and 1.40% ($P = .74$). Results were unchanged when restricted to biopsy specimens submitted in 2011 to 2012.

Discussion

In contrast to a French nationwide cohort study that used individual patient data, this study examined enteropathy on a national level so as to determine if olmesartan

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2017.09.058

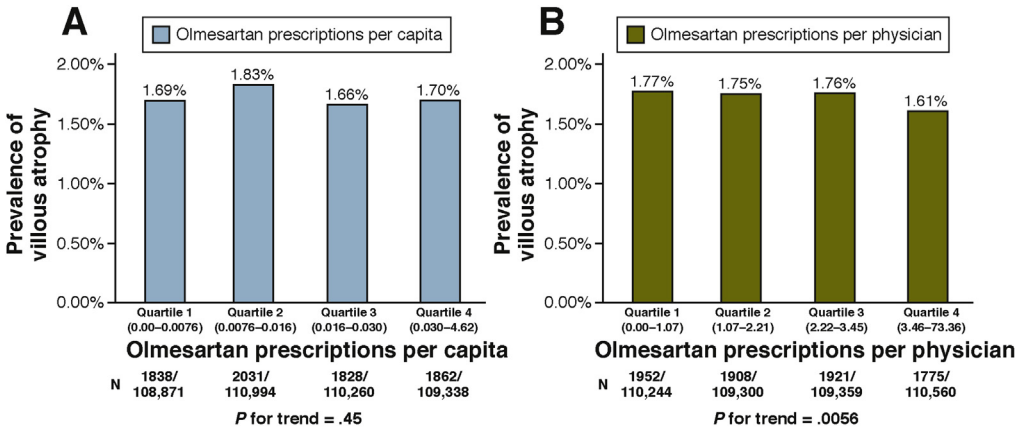

Figure 1. Prevalence of duodenal villous atrophy by olmesartan prescriptions per capita and olmesartan prescriptions per physician.

is a rare or common cause of villous atrophy in the United States.[8] In this analysis, higher regional olmesartan prescription rates were not associated with a higher prevalence of villous atrophy. Because olmesartan enteropathy is seen predominantly in the older population, we repeated the analysis for patients $\geq$ 65 years and found similarly null results. Therefore, despite increasing case reports/series characterizing olmesartan-induced sprue-like enteropathy, olmesartan does not appear to be a major cause of villous atrophy on a national level.

The strengths of this study included its large, nationally representative sample size and uniform methodology of biopsy specimen interpretation. Limitations included its retrospective study design, although a prospective study is impractical to detect what appears to be a rare outcome.[4] In addition, this was an ecologic study and therefore we are unable to make inferences about individual risk. Although designed to be nationally representative, the study likely undersampled patients in ZIP codes with high population densities where endoscopists may be unlikely to send samples to a commercial pathology service. Finally, olmesartan prescription data are limited to Medicare beneficiaries and may not account for other factors affecting physician prescribing behavior such as economics, physician supply, and marketing forces.

In conclusion, there was no relationship between regional rates of olmesartan prescription and the prevalence of villous atrophy. Although clinically significant in the individual, olmesartan enteropathy appears to be an uncommon cause of villous atrophy in the United States.

References

1. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012;87:732–738.
2. Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. Aliment Pharmacol Ther 2014;40:1103–1109.
3. Greywoode R, Braunstein ED, Arguelles-Grande C, et al. Olmesartan, other antihypertensives, and chronic diarrhea among patients undergoing endoscopic procedures: a case-control study. Mayo Clin Proc 2014;89:1239–1243.
4. Menne J, Haller H. Olmesartan and intestinal adverse effects in the ROADMAP study. Mayo Clin Proc 2012;87:1230–1231.
5. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. Am J Gastroenterol 2013;108:647–653.
6. Centers for Medicaid and Medicare Services. Provider utilization and payment data: part D prescriber data CY 2013. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html. Accessed July 25, 2016.
7. U.S. Census Bureau. Census 2010; social explorer. Available at: http://old.socialexplorer.com/pub/reportdata/HtmlResults.aspx?reportid=R11205065. Accessed July 28, 2016.
8. Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. Gut 2016;65:1664–1669.

Reprint requests
Address requests for reprints to: Benjamin Lebwohl, MD, MS, Celiac Disease Center, Columbia University, 180 Fort Washington Avenue, Suite 936, New York, New York 10032. e-mail: BL114@columbia.edu; fax: (212) 305-3738.

Conflicts of interest
The authors disclose no conflicts.