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Blockers of Angiotensin Other Than Olmesartan in Patients With Villous Atrophy: A Nationwide Case-Control Study

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Abstract

Objective: To examine the association between the previous use of nonolmesartan angiotensin receptor blockers (ARBs) or any angiotensin-converting enzyme inhibitor (ACEI) and subsequent villous atrophy (VA) in patients with small-intestinal VA as compared with general population–matched controls.

Patients and Methods: A case-control study was used to link nationwide histopathology data on 2933 individuals with VA (Marsh grade 3) to the Swedish Prescribed Drug Register to examine the association between the use of ACEIs as well as the specific use of ARBs other than olmesartan and subsequent VA. Olmesartan is not available in Sweden, so this exposure was not examined. All individuals with VA had biopsies performed between July 1, 2005, and January 29, 2008, and matched on age, sex, calendar period of birth, and county of residence to 14,571 controls from the general population.

Results: Use of nonolmesartan ARBs was not associated with VA (odds ratio, 0.84; 95% CI, 0.64-1.09; P=.19). Neither was VA associated with a previous medication of any ACEI (odds ratio, 1.08; 95% CI, 0.90-1.30; P=.41). Restricting the analysis to individuals with repeated prescriptions for ACEIs or ARBs revealed only marginally changed risk estimates for VA.

Conclusion: The lack of association between the use of ACEIs and nonolmesartan ARBs and subsequent VA suggests that these medications are not a major risk factor for the development of VA in the general population.

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A duodenal biopsy showing villous atrophy (VA) has long been considered a diagnostic hallmark of celiac disease (also known as celiac sprue).[1] In celiac disease, dietary gluten causes small-intestinal VA and inflammation. Celiac disease is prevalent in 1% to 2% of the Western population.[1,2] Although celiac disease is by some margin the most common cause of VA, several additional causes of VA exist, for example, tropical sprue, infective gastroenteritis, and immunodeficiency states.[3]

In 2012, Rubio-Tapia et al[4] first described 22 patients taking olmesartan medoxomil, an angiotensin receptor blocker (ARB) used for the treatment of hypertension, who developed spruelike enteropathy. These patients, suffering from chronic diarrhea and weight loss accompanied with small-intestinal VA or inflammation, showed a marked clinical improvement after discontinuing olmesartan. Although these patients' intestinal histology resembled that of celiac disease, none of these patients had characteristics entirely consistent with celiac disease, that is, positive celiac disease serology and/or a symptomatic improvement on a gluten-free diet. Although questioned by some,[5,6] a number of case series[7,8] and 1 national case finding study[9] have since then reported additional cases of olmesartan-associated spruelike enteropathy. Some data have also suggested that other ARBs, besides olmesartan, may induce similar outcomes.[9] Drug-induced enteropathy is a challenging, often overlooked, differential diagnosis toward celiac disease. Despite this, there are few general population–based data on the previous use of angiotensin-converting enzyme inhibitors (ACEIs) and ARBs other than olmesartan before the development of VA.

The main objective of this study was to examine the association between the previous use of nonolmesartan ARBs as well as any ACEI and subsequent development of VA in patients

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with small-intestinal VA as compared with general population—matched controls. To differentiate the use of these drugs in patients with VA, we also examined their usage in patients with VA as compared with individuals with milder small-intestinal histopathology: small-intestinal inflammation without VA or normal small-intestinal mucosa but positive celiac disease serology.[1]

PATIENTS AND METHODS

In this case-control study, we linked nationwide histopathology data on individuals undergoing small-intestinal biopsy to the Swedish Prescribed Drug Register to examine the association between the use of nonolmesartan ARBs or any ACEI and the subsequent development of VA.

Study Population

Between 2006 and 2008, we searched the computerized register of Sweden's 28 pathology departments to identify individuals with small-intestinal VA (Marsh grade 3).[10,11] The biopsies were performed between July 1969 and January 2008.[12] A detailed account of the data collection process has been described elsewhere.[10,13] In an earlier validation study on a randomly selected sample of patients in our cohort, 95% (108 of 114) of the patients with VA had later received a clinical diagnosis of celiac disease.[10]

In the present study, we used the same data set described in our previous study of mortality identifying 29,096 patients with VA.[14] The government agency Statistics Sweden then matched each individual with VA with up to 5 controls from the general population for age, sex, calendar period of birth, and county of residence. The number of controls was decided after consultations with the government agency Statistics Sweden. After the exclusion of individuals with data irregularities (see our previous report[14]), we identified 144,522 controls.

Patients with VA and their matched controls were then linked to the Swedish Prescribed Drug Register (established on July 1, 2005).[15] Through this linkage, we identified 2933 patients with VA who had biopsies performed between July 1, 2005 (the start of the Prescribed Drug Register), and January 29, 2008 (the end of the study period), and 14,571 matched controls.

Using Swedish computerized pathology data, we identified a secondary control group of individuals with small-intestinal inflammation (Marsh grades 1-2) but without VA and individuals with normal small-intestinal mucosa (Marsh grade 0) but positive celiac disease serology.[13] Data on individuals with normal mucosa and positive celiac disease serology were regional and obtained from the ascertainment areas of 8 Swedish university hospitals covering approximately half of the Swedish population.[13] *Positive celiac disease serology* was defined as a positive IgA or IgG antigliadin antibody, endomysial antibody, or tissue transglutaminase test less than 180 days before or no later than 30 days after a normal biopsy result (and with no previous or subsequent biopsy showing VA or inflammation).[13] In total, this secondary control group included 2738 individuals (2118 individuals with inflammation and 620 individuals with normal mucosa but positive celiac disease serology).

Use of ARBs and ACEIs

The Swedish Prescribed Drug Register contains prospectively recorded individual data on more than 99% of all dispensed prescribed drugs in Sweden.[15]

We collected data on the use of any ACEI (Anatomical Therapeutic Chemical [ATC] code, C09) as well as the specific use of ARBs other than olmesartan (ATC codes, C09C and C09D) from July 1, 2005 (launch of the Prescribed Drug Register), through January 29, 2008 (end of the study period), and up to the date of the biopsy (and the corresponding date in matched controls). Olmesartan is not available in Sweden, so this exposure was not studied in this population-based investigation.

Statistical Analyses

We used conditional logistic regression to estimate odds ratios (ORs) and 95% CIs. Each stratum (1 individual undergoing biopsy and up to 5 matched controls) was analyzed separately before a summary OR was calculated.[16] This statistical approach therefore eliminates the effect of sex, age, county, and calendar year on our ORs.

In analyses on the specific use of nonolmesartan ARBs and subsequent VA, other types of ACEIs were not considered. For the usage of both ARBs and any ACEI, we performed stratified analyses by sex and by age at the time of biopsy showing VA (0-19, 20-39, 40-59, and ≥60 years). In this study, we choose to also include children because national prescription

TABLE 1. Descriptive Characteristics of Individuals With Small-Intestinal Villous Atrophy[a]

Characteristic	Value
Total no. of patients	2933
Sex, n (%)	
Women	1796 (61.2)
Men	1137 (38.8)
Median age at study entry (y) (range)	28 (0-94)
Age (y), n (%)	
0-19	1218 (41.5)
20-39	566 (19.3)
40-59	583 (19.9)
60+	566 (19.3)
Year, n (%)	
2005[b]	819 (27.9)
2006	1828 (62.3)
2007[c]	274 (9.3)
2008[d]	12 (0.4)

[a]Reference individuals have not been included in the table because their age, sex, and entry year distributions were identical to those of individuals with villous atrophy (due to matching).
[b]Beginning of study period: July 1, 2005.
[c]Most of the pathology departments delivered data on individuals with small-intestinal pathology undergoing biopsy up to the beginning of year 2007. The remaining pathology departments reported histopathology data up to the end of 2007 or very early 2008. For this reason, our data included fewer individuals with villous atrophy who had biopsies performed in 2007 than in 2006.
[d]End of study period: January 29, 2008.

data indicate that more than 1000 Swedish children per year are treated with an ACEI.[17] To evaluate potential causality, we estimated the dose- and time-dependent association between ARB/ACEI medication and VA in 2 separate analyses: (1) when individuals had received at least 2 prescriptions of any ARB/ACEI and (2) when an ARB/ACEI had been prescribed at least 1 year (>365 days) before biopsy. Education level has been associated with overall drug utilization[18] and health care utilization (and ascertainment of small-intestinal VA).[19] In a subanalysis, we therefore adjusted for education using 7 predefined education categories determined by Statistics Sweden.

To differentiate the use of ARBs/ACEIs in patients with VA, we also examined their usage in individuals with small-intestinal inflammation without VA (Marsh grades 1-2) and individuals with normal small-intestinal mucosa (Marsh grade 0) but positive celiac disease serology. In this subanalysis, we used logistic regression adjusted for age at the time of biopsy (showing VA, inflammation, or normal mucosa), sex, and calendar year of study entry to estimate ORs and 95% CIs.

Post Hoc Analyses

Although most studies implicating drug-induced spruelike enteropathy implicate olmesartan, 2 studies have reported cases of VA associated with nonolmesartan ARBs, irbesartan and valsartan, respectively.[9,20] We, therefore, collected data on the specific use of irbesartan (ATC code, C09CA04) and valsartan (ATC code, C09CA03).

In a post hoc analysis, we specifically examined the association between the previous use of ARBs/ACEIs among 2118 individuals with small-intestinal inflammation without VA (Marsh grades 1-2) as compared with matched controls from the general population (n=10,442) (see matching procedure described above for patients with VA).

We have previously shown that patients with celiac disease with small-intestinal VA have a more favorable cardiac risk profile, including decreased risk of hypertension, as compared with the general population.[21] Therefore, to examine the susceptibility to confounding by indication, we contrasted the use of ARBs/ACEIs by examining the association between VA and previous antihypertensive therapy with calcium channel blockers. Data on the use of any calcium channel blocker (ATC code, C08) were collected from the Prescribed Drug Register between July 1, 2005, and January 29, 2008, and up to the date of biopsy showing VA (and the corresponding date in matched controls).

For analyses on the previous use of ARBs/ACEIs in individuals with VA, we examined for interactions between sex and exposure via the inclusion of multiplicative interaction terms in an unconditional logistic regression model adjusted for age, sex, and calendar year.

Statistical significance was defined as 95% CIs for risk estimates not including 1.0 and P values of $<.05$. SPSS (version 22.0) was used for all statistical analyses.

Ethics

This study was conducted in accordance with national and institutional standards and was approved by the Regional Ethical Vetting Board in Stockholm.

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TABLE 2. Odds Ratios for Previous Use of ARBs in Individuals With Villous Atrophy as Compared With General Population–Matched Controls[a,b]

Characteristic	Villous atrophy (%)	Controls (%)	Odds ratio	95% CI	*P*
ARBs[c]	66 of 2933 (2.3)	387 of 14,571 (2.7)	0.84	0.64-1.09	.19
Sex					
Male	41 of 1137 (3.6)	187 of 5645 (3.3)	1.09	0.77-1.55	.62
Female	25 of 1796 (1.4)	200 of 8926 (2.2)	0.61	0.40-0.92	.02
Repeated prescriptions of ARBs	64 of 2931 (2.2)	378 of 14,562 (2.6)	0.83	0.63-1.09	.18
Use of ARBs >1 y before biopsy	22 of 2889 (0.8)	119 of 14,303 (0.8)	0.93	0.59-1.49	.78

[a]ARB = angiotensin receptor blocker.
[b]Odds ratios estimated through conditional logistic regression. Through this statistical approach all analyses were carried out stratumwise and thereby conditioned on age at the time of biopsy (and corresponding date in controls), calendar period, sex, and county of residence.
[c]Use of ARBs (Anatomical Therapeutic Chemical code, C09C) between July 1, 2005, and January 29, 2008.

RESULTS

Of the 2933 individuals with VA, some 60% were women. The median age at biopsy was 28 years (1715/2933 [58.5%] of those with VA had biopsies performed in adulthood) (Table 1).

Use of ARBs

A total of 66 individuals with VA (2.3%) and 387 controls (2.7%) had an earlier record of medication with a nonolmesartan ARB, equivalent to an OR of 0.84 for subsequent VA (95% CI, 0.64-1.09). None of the children with VA had a previous treatment with an ARB. Among adults with VA, ORs did not differ appreciably according to age at the time of biopsy (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). Adjustment for education level revealed an unchanged OR (adjusted OR, 0.84; 95% CI, 0.64-1.11; *P*=.22). As compared with sex-matched controls, we found a significantly decreased risk estimate for VA in women with previous treatment with an ARB (OR, 0.61; 95% CI, 0.40-0.92) that was not found in men (OR, 1.09; 95% CI, 0.77-1.55). The *P* value for interaction (sex×ARB) in an unconditional logistic regression model was .04. We found no association between VA and repeated prescriptions of ARBs or treatment initiated at least 1 year (>365 days) before biopsy (Table 2).

ORs for the previous use of ARBs did not differ appreciably according to calendar year at the time of biopsy (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

USE OF ANY ACEI

Of the 2933 individuals with VA, 165 (5.6%) had received at least 1 prescription of any ACEI before biopsy showing VA as compared with 762 of 14,571 (5.2%) among the general population–based controls, corresponding to an OR of 1.08 (95% CI, 0.90-1.30) for subsequent development of VA (Table 3). Restricting our analysis to individuals with VA who had biopsies performed in adulthood, we found largely unchanged risk estimates (OR, 1.08; 95% CI, 0.89-1.30; *P*=.44). Adjustment for education level revealed largely unchanged OR (adjusted OR, 1.12; 95% CI, 0.93-1.35; *P*=.25). The association between the use of any ACEI and subsequent VA was similar in men and women (men: OR, 1.22, 95% CI, 0.95-1.56; women: OR, 0.94; 95% CI, 0.71-1.25), as compared with sex-matched controls. The *P* value for interaction (sex×ACEI) in an unconditional logistic regression model was .21.

We found no indication of a dose-response effect for individuals with repeated prescriptions of ACEIs (OR, 1.06; 95% CI, 0.88-1.28). As expected, treatment with ACEIs was very rare among children and was increasingly more common according to age at the time of biopsy. Among those aged 20 to 39 years at the time of biopsy, 6 individuals with VA (1.1%), as compared with 7 controls (0.2%), had previously been treated with any ACEI (OR, 3.82; 95% CI, 1.41-10.38). In none of the remaining age bands, nor in stratified analyses by calendar year at time of biopsy, did we find an association between the previous use of ACEIs and subsequent development of VA (Supplemental Table 3 and Supplemental Table 4, respectively, available online at http://www.mayoclinicproceedings.org).

TABLE 3. Odds Ratios for Previous Use of Any ACEI in Individuals With Villous Atrophy as Compared With General Population–Matched Controls[a,b]

Characteristic	Villous atrophy (%)	Controls (%)	Odds ratio	95% CI	*P*
Any ACEI[c]	165 of 2933 (5.6)	762 of 14,571 (5.2)	1.08	0.90-1.30	.41
Sex					
Male	99 of 1137 (8.7)	418 of 5645 (7.4)	1.22	0.95-1.56	.12
Female	66 of 1796 (3.7)	344 of 8926 (3.9)	0.94	0.71-1.25	.66
Repeated prescriptions of any ACEI	160 of 2928 (5.5)	751 of 14,560 (5.2)	1.06	0.88-1.28	.52
Use of ACEI >1 y before biopsy	47 of 2815 (1.7)	238 of 14,047 (1.7)	1.01	0.72-1.41	.98

[a]ACEI = angiotensin-converting enzyme inhibitor.
[b]Odds ratios estimated through conditional logistic regression. Through this statistical approach all analyses were carried out stratumwise and thereby conditioned on age at the time of biopsy (and corresponding date in controls), calendar period, sex, and county of residence.
[c]Any ACEI (Anatomical Therapeutic Chemical code, C09) used between July 1, 2005, and January 29, 2008.

Subanalyses

In a number of preplanned subanalyses, we also examined the use of ARBs/ACEIs in patients with VA as compared with individuals with small-intestinal inflammation without VA and individuals with normal small-intestinal mucosa but positive celiac disease serology. Overall, we identified 2738 individuals with these potentially prodromal stages of VA. In this secondary control group, 1732 (63%) were women and the median age at the time of biopsy was 41 years.

Using logistic regression analysis adjusting for sex, age, and calendar year of study entry, we found only marginally changed ORs for the previous use of any ACEI in individuals with VA as compared with individuals with mucosal inflammation or with normal biopsy result but positive celiac disease serology (adjusted OR, 1.08; 95% CI, 0.87-1.35) (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org). Neither did we find a statistically significant association between VA and the repeated use of any ACEI medication as compared with individuals with mucosal inflammation or normal mucosa but positive celiac disease serology (adjusted OR, 1.07; 95% CI, 0.85-1.34).

Overall, the use of ARBs was not related with subsequent development of VA as compared with individuals with small-intestinal inflammation or normal mucosa but positive celiac disease serology (Supplemental Table 6, available online at http://www.mayoclinicproceedings.org).

Post Hoc Analyses

In a post hoc analysis, 7 individuals with VA (0.2%) and 37 controls (0.3%) had an earlier record of irbesartan (ATC code, C09CA04), equivalent to an OR of 0.93 for subsequent development of VA (95% CI, 0.42-2.09; *P*=.87). Looking specifically at the earlier use of valsartan (VA: 4 of 2933 [0.1%]; controls: 38 of 14,571 [0.3]) revealed a slightly lower OR for subsequent development of VA (OR, 0.52; 95% CI, 0.19-1.44; *P*=.21).

Of the 2118 individuals with small-intestinal inflammation without VA, 111 (5.2%) had an earlier record of medication with a nonolmesartan ARB, as compared with 341 of 10,442 (3.3%) controls from the general population (OR, 1.63; 95% CI, 1.31-2.03; *P*<.001). We largely found similarly increased ORs for subsequent small-intestinal inflammation without VA after repeated prescriptions of ARBs (OR, 1.62; 95% CI, 1.30-2.02; *P*<.001); however, we found no increased risk after ARB treatment initiated at least 1 year (>365 days) before biopsy (OR, 1.09; 95% CI, 0.73-1.64; *P*=.66). In individuals with intestinal inflammation without VA, OR for previous ACEI treatment was 1.57 (95% CI, 1.33-1.86; *P*<.001) (repeated use of ACEIs: OR, 1.57; 95% CI, 1.32-1.86; *P*<.001; ACEI treatment initiated at least 1 year before biopsy: OR, 1.17; 95% CI, 0.88-1.58; *P*=.28).

Finally, to contrast the use of ARBs/ACEIs, we examined the previous use of calcium channel blockers in individuals with VA (86 of 2933 [2.9%]) as compared with general population–based controls (502 of 14,571 [3.4%]) (OR, 0.83; 95% CI, 0.66-1.06; *P*=.13)

DISCUSSION

In this study, we examined the association between blockers of the angiotensin pathway and VA. Our study involved almost 3000

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individuals with VA, and overall we found no positive association between the previous use of ARBs or ACEIs and the subsequent development of VA in the general population; nor did we find a relationship between these drugs and VA when restricting our definition of exposure to multiple prescriptions. Neither did we find an association between the previous use of ARBs/ACEIs in individuals with VA and the subsequent development of VA as compared with individuals with milder small-intestinal histopathology.

Olmesartan is not used in Sweden, but a large number of individuals are treated with nonolmesartan ARBs and a positive finding here would have larger health implications than an effect restricted to olmesartan. Although the bulk of recent case reports and series implicating drug-induced spruelike enteropathy implicate olmesartan, a recent French study[9] included 1 case of nonolmesartan (irbesartan)-associated VA, and there are also case reports of valsartan- and telmisartan-associated VA.[20,22] Subtle histologic abnormalities short of VA have been reported with the use of olmesartan, but not with the use of other ARBs.[23] It therefore has been a pressing concern whether this recently described spruelike enteropathy is a class effect or is unique to (or more closely associated with) olmesartan. Our study, which includes 2933 patients with VA and 14,571 matched controls who were exposed to ACEIs and nonolmesartan ARBs, found no association between these drugs and VA.

Olmesartan appears to cause a spruelike enteropathy, but it has not been shown to trigger celiac disease per se. In a chart validation of a randomly selected sample of patients from our cohort, 95% of those with VA later received a clinical diagnosis of celiac disease.[10] However, it is likely that before the first report of this clinical entity in June 2012,[4] patients with this condition would be misdiagnosed with celiac disease. Indeed, the initial case series describing olmesartan-associated enteropathy arose from referral centers for celiac disease because many of these patients were initially thought to have nonresponsive or refractory celiac disease.[4,24] Therefore, we believe that a spruelike enteropathy would be detectable in an analysis of patients with VA who had biopsies performed before 2012. The fact that we found no association between the use of ARBs/ACEIs and VA suggests that spruelike enteropathy is not commonly triggered by these drugs.

Instead, the findings of our study are more consistent with the randomized clinical trial by Menne and Haller[6] who were unable to detect an increased risk of enteropathy in patients prescribed olmesartan. That study included a median follow-up of 3.2 years, and olmesartan-associated enteropathy can develop after even 10 years of drug exposure.[9] It is possible that nonolmesartan ARBs may trigger an enteropathy that we were unable to detect because of the relatively short drug exposure time in our study.

Our null findings in regard of subsequent development of VA can be interpreted in several ways. First, the available nonolmesartan drugs used in Sweden may not be associated with VA. The mechanism underlying olmesartan-induced enteropathy is unknown, but it has been hypothesized to be the result of a proapoptotic effect of angiotensin II on intestinal epithelial cells.[7] Speculatively, this apoptotic effect may hence be limited to olmesartan. Second, several articles have linked olmesartan to serology-negative VA.[24] Our data collection was based on mucosal abnormalities and not primarily serology, but an earlier validation of a subset of patients with VA from our cohort found that 88% had a positive celiac serology at the time of biopsy (defined here as tissue transglutaminase test/endomysial antibody but also positive antigliadin antibody because our cohort stretches back to 1969).[10] On interviewing 180 gastroenterologists and 68 pediatricians at the time of data collection (year 2008), 86% and 100%, respectively, reported that a positive serology was part of their diagnostic algorithm in at least 8 of 10 patients.[10] Hence the proportion of serology-negative individuals in our study is low, potentially adding to our null findings. Third, as noted above, if ARBs induce VA only after a long period of use, we may have missed a positive association. The Swedish Prescribed Drug Register that was used to ascertain ARB medication has been in use only since mid-2005 and hence we had a short follow-up of patients.

Because patients with celiac disease with small-intestinal VA may have a reduced risk of hypertension,[21,25] we carried out a sensitivity analysis revealing no statistically significant association (P=.13) between VA and previous treatment with calcium channel blockers. These results argue against confounding by indication as a sole cause of our null findings.

In post hoc analyses, we found positive associations between subsequent small-intestinal inflammation without VA and previous treatment with ARBs/ACEIs. However, these statistically significant increased risk estimates were confined to treatment initiated within 1 year before biopsy and one explanation for these findings could be that some individuals with multiple preexisting morbidity (including cardiovascular disease) undergo small-intestinal biopsy as part of a general investigation.

This study has some strengths and limitations. Among the strengths are the large numbers of patients with VA and that data on ARB use were collected from an independent source (the Swedish Prescribed Drug Registry). Although we cannot rule out that a small proportion of individuals with VA in this study were false-positive (an earlier blinded validation study found that Swedish pathologists correctly identify 90% of all VA cases),[10] a misclassification rate of 10% should not drive the risk estimate down to 1.08 (95% CI=0.90-1.30) and 0.84 (95% CI=0.64-1.09) for previous use of ACEIs and ARBs, respectively.

Although olmesartan has often been linked to clinically severe celiac like enteropathy,[4] we lacked individual-based information on symptom severity in our participants. However, when examining the patient charts of 118 random individuals with VA, some 79% had gastrointestinal symptoms. Hence, it is unlikely that our null findings are due to lack of classical symptoms[2] in our cohort. If nonolmesartan ARBs cause enteropathy as a very rare, long-term adverse effect, our study is unlikely to have the statistical power or follow-up time to detect this effect.

CONCLUSION

We found no increased risk of VA in Swedish individuals with a previous record of nonolmesartan ARB use or ACEI use. Future studies should elucidate the distinct features by which olmesartan, more so than other members of this drug class, induces VA.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **ACEI** = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **ATC** = Anatomical Therapeutic Chemical (pharmaceutical classification); **OR** = odds ratio; **VA** = villous atrophy

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REFERENCES

1. Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for coeliac disease and related terms. *Gut*. 2013;62(1):43-52.
2. Walker MM, Murray JA, Ronkainen J, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. *Gastroenterology*. 2010;139(1):112-119.
3. Dewar DH, Ciclitira PJ. Clinical features and diagnosis of celiac disease. *Gastroenterology*. 2005;128(4, Suppl 1):S19-S24.
4. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe sprue-like enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.
5. Greywoode R, Braunstein ED, Arguelles-Grande C, Green PH, Lebwohl B. Olmesartan, other antihypertensives, and chronic diarrhea among patients undergoing endoscopic procedures: a case-control study. *Mayo Clin Proc*. 2014;89(9):1239-1243.
6. Menne J, Haller H. Olmesartan and intestinal adverse effects in the ROADMAP study. *Mayo Clin Proc*. 2012;87(12):1230-1231: author reply 1232.
7. Ianiro G, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: sprue-like enteropathy associated with olmesartan. *Aliment Pharmacol Ther*. 2014;40(1):16-23.
8. Bhat N, Anupama NK, Yelsangikar A, Vizhi K. Olmesartan-related sprue-like enteropathy. *Indian J Gastroenterol*. 2014;33(6):564-567.
9. Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. *Aliment Pharmacol Ther*. 2014;40(9):1103-1109.
10. Ludvigsson JF, Brandt L, Montgomery SM, Granath F, Ekbom A. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. *BMC Gastroenterol*. 2009;9:19.
11. Marsh MN. Grains of truth: evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. *Gut*. 1990;31(1):111-114.
12. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls

in healthcare and medical research. *Eur J Epidemiol*. 2009; 24(11):659-667.
13. Ludvigsson JF, Brandt L, Montgomery SM. Symptoms and signs in individuals with serology positive for celiac disease but normal mucosa. *BMC Gastroenterol*. 2009;9:57.
14. Ludvigsson JF, Montgomery SM, Ekbom A, Brandt L, Granath F. Small-intestinal histopathology and mortality risk in celiac disease. *JAMA*. 2009;302(11):1171-1178.
15. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726-735.
16. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
17. Statistics Sweden. Statistical database. www.socialstyrelsen.se/statistik/statistikdatabas. Accessed December 2, 2014.
18. Weitoft GR, Rosén M, Ericsson O, Ljung R. Education and drug use in Sweden—a nationwide register-based study. *Pharmacoepidemiol Drug Saf*. 2008;17(10):1020-1028.
19. Westin M, Ahs A, Bränd Persson K, Westerling R. A large proportion of Swedish citizens refrain from seeking medical care—lack of confidence in the medical services a plausible explanation? *Health Policy*. 2004;68(3):333-344.
20. Herman ML, Rubio-Tapia A, Wu T, Murray JA. A case of severe sprue-like enteropathy associated with valsartan. *ACG Case Rep J*. 2015;2(2):92-94.
21. Emilsson L, Carlsson R, Holmqvist M, James S, Ludvigsson JF. The characterisation and risk factors of ischaemic heart disease in patients with coeliac disease. *Aliment Pharmacol Ther*. 2013; 37(9):905-914.
22. Cyrany J, Vasatko T, Machac J, Nova M, Szanyi J, Kopacova M. Letter: telmisartan-associated enteropathy—is there any class effect? *Aliment Pharmacol Ther*. 2014;40(5):569-570.
23. Lagana SM, Braunstein ED, Arguelles-Grande C, Bhagat G, Green PH, Lebwohl B. Sprue-like histology in patients with abdominal pain taking olmesartan compared with other angiotensin receptor blockers. *J Clin Pathol*. 2015;68(1):29-32.
24. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: a diagnostic and therapeutic dilemma. *Am J Gastroenterol*. 2013;108(5):647-653.
25. West J, Logan RF, Card TR, Smith C, Hubbard R. Risk of vascular disease in adults with diagnosed coeliac disease: a population-based study. *Aliment Pharmacol Ther*. 2004;20(1):73-79.