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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