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Falgun Gosai
Adult Hospitalist, SFMC Peoria, Illinois, falgungosai7799@gmail.com

Neha Gosai
Avalon School of medicine, Curacao.

BRIEF REPORT

Angiotensin Receptor Blockers Associated Enteropathy- Brief Report

Neha Gosai [a], Falgun Gosai [b,*]

[a] Avalon School of Medicine, Curaçao
[b] Adult Hospitalist, SFMC Peoria, Illinois, USA

Abstract

The current literature has shown equivocal results regarding the association of Olmesartan and other angiotensin receptor blockers (ARBs) use and the presence of Celiac sprue-like enteropathy (CSLE). Various factors affecting the association are- patient population under study, geographic area, and duration of use of medication. Various case reports/ case series and observational studies have shown the mixed results regarding an association. We have tried to answer a question what exists in the literature regarding the angiotensin receptor blockers related sprue like enteropathy.

Keywords: ARB, Sprue like enteropathy, Diarrhea, Olmesartan

1. Angiotensin receptor blockers associated enteropathy- does it really exist?

The current literature has shown equivocal results regarding the association of Olmesartan and other angiotensin receptor blockers (ARBs) use and the presence of Celiac sprue-like enteropathy (CSLE). Various factors affecting the association are-patient population under study, geographic area, and duration of use of medication.

2. When to suspect celiac sprue-like enteropathy

The presence of enteropathy symptoms like chronic diarrhea, malabsorption, and weight loss in the absence of celiac serology may suggest the possibility of CSLE.[1] The laboratory findings of hypoalbuminemia, electrolyte imbalances, and negative stool cultures are supportive. The duodenal biopsy may reveal variable degree of duodenal villous atrophy with increased intra-epithelial lymphocytes or rarely eosinophils-same as classical celiac sprue.[2] The lack of response to gluten-free diet also supports the diagnosis of CSLE. Discontinuation of the culprit medication improves not only symptoms but also the histological features of CSLE.[3]

3. Background of ARBs

For the last decade and a half, ARBs have been widely used for their cardiovascular benefits. In 2010, a study from Mayo clinic showed that among patients with CSLE, 25% were on Olmesartan (OM).[4] The subsequent case series and various other studies have also shown the higher rate of CSLE with various ARBs use. In 2011, the Food and Drug Administration (FDA) requested a Mini-Sentinel modular program report of risk assessment because the number of cases of CSLE among users of Olmesartan was higher than expected in the FDA adverse event report system. However, the incidence of CSLE was found to be similar between all ARBs, including OM.[4] Nevertheless, in July 2013, the FDA issued a 'Drug Safety Communication' approving a label change to include CSLE linked to OM.

4. How do they do it?

Even though, several mechanisms by which ARBs might increase the risk of enteropathy have been proposed, the exact mechanism is still unknown.

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* Corresponding author at:
E-mail address: falgungosai7799@gmail.com (F. Gosai).

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Table 1. Studies showing significant association of Olmesartan (OM) and CSLE.

Study	Type of study	Biopsy proven CSLE	Results
Y H Dong et al.[9]	Retrospective cohort	No	HR- 1.21(95% CI,1.05–1.40) [OM to the other ARBs
Mickael Basson et al.[10]	Prospective	No	Adjusted rate ratio- 2.49(95% CI,1.73–3.57), P < 0.0001[for discharge diagnosis of intestinal malabsorption- OM to other ARBS]

Table 2. Studies showing no significant association Olmesartan (OM) and CSLE.

Study	Type of study	Biopsy proven CSLE	Outcomes
Seng Chan Yu et al.[11]	Prospective cohort	No	Adjusted rate ratio- 0.33 (95% CI,0.10–1.09, P-0.070) [OM to other ARBS]
Ruby Greywoode et al.[12]	Prospective cohort	yes	No significant history of diarrhea among OM users undergoing EGDs and colonoscopy
Peter Malfertheiner et al.[13]	Prospective cohort	No	RR:2.50, 95% CI,1.21–5.19, P-0.01 [incidence of CSLE among ARBs and OM users]

CSLE and Celiac disease/sprue (CD/CS) share common features like increase in aggregation of CD8+ cells and overexpression of IL-8 to suggest a possible immune mediated process. Delay in the onset of symptoms after initiation of the offending medication points towards cell-mediated immunity damage rather than type-1 hypersensitivity reaction. While Angiotensin receptors type-1 get saturated with ARBs, circulating angiotensin-2 might bind with type 2 receptors and trigger pro-apoptotic affects resulting in cell damage causing enteropathy like picture.[5]

5. The controversy continues

The association between CSLE and the use of OM was initially reported in a case series of 22 patients,[1] followed by a small series of individual case reports. A large observation study from France showed the 2.4 to 3-fold increased risk of hospitalization among OM users with intestinal malabsorption (IM) and CSLE when compared with other ARBs and ACEI.[6] It also reported the prolonged median stay of 9-day with OM use compared to 2 days in other ARBs use. Recent case reports showed the possible association between other ARBs and enteropathy-valsartan, irbesratan, telmisartan, losartan etc. This finding has suggested the class effect hypothesis.[8] The observation cohort from Germany and Italy showed the class effect of ARB for association with CSLE.[9] It also reported that the incidence rate of intestinal malabsorption was relatively low among OM, other ARBs and ACEI users (3.1, 8.8 and 2.3 per 100 person years). In contrast to above mentioned studies, no difference in the events of diarrhea or malabsorption was found between use of OM and the controls in the large randomized controlled ROADMAP trial.[7] Further details of studies regarding the association are described in tables (Table 1 showing association and Table 2 showing no association).

Few explanations for the conflicting results had been proposed. There has been a concern for the use of different ICD codes to describe unspecified intestinal malabsorption or SLE or for the enrolment of the patients. Many studies did not consider the presence of the confounders (presence of Diabetes in ROADMAP trial). There is a limited data on outpatient scenario of CSLE or intestinal malabsorption among the ARBs or ACEI users. These factors could explain difference in outcomes of various studies.

6. Take home message

Considering the widespread use of Olmesartan, and other ARBs and ACEI, even the low incidence of Sprue-like enteropathy may have a significant impact on the patient population. All patients receiving this group of medications should be educated about the symptoms associated with CSLE. All clinicians should be vigilant about the clinical entity of CSLE and should consider discontinuation of the culprit agent for clinical and histological recovery in the affected patients.

Conflict of interest

The authors do not have any conflict of interest to disclose.

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