

Coeliac disease enteropathy and symptoms may be aggravated by angiotensin receptor blockers in patients on a gluten-free diet

Neil O'Morain¹  | Eileen Shannon¹  | John McManus¹ | Vanessa Warner¹ | Hilary Leeson¹  | Helen O'Donovan¹ | Brian Egan² | Valerie Byrnes¹

¹Department of Gastroenterology, Galway University Hospital, Galway, Ireland

²Department of Gastroenterology, Mayo General Hospital, Castlebar, Ireland

Correspondence

Neil O'Morain, Department of Gastroenterology, Galway University Hospital, Galway, Ireland.
Email: neilmoran@gmail.com

Abstract

Background: Angiotensin receptor blocker-associated enteropathy (ARB-e) is an increasingly recognised clinical entity with symptoms and histological findings identical to coeliac disease (CD). There is evidence to suggest immune-mediated mucosal injury in ARB-e with a high prevalence of DQ2/DQ8; however, as IgA anti-tissue transglutaminase (anti-TTG) is usually negative, an insult other than TTG-mediated injury is suspected. The impact of ARBs on disease activity in patients with CD is not known.

Objective: To assess the effect of ARB exposure on patients with established CD.

Methods: A patient record search of 1142 individual patients attending a dedicated coeliac clinic from 2010 to the present identified 59 patients treated with ARB. Those with CD confirmed by serology (TTG + ve/EMA + ve) and histopathology (Marsh criteria) were included ($n = 40$, 0.52%). Data collected included disease duration, compliance with gluten-free diet (GFD), reported symptoms (diarrhoea, weight loss and abdominal pain), surrogate markers of absorption (Vitamin D, Iron, Calcium and Haemoglobin), in addition to anti-TTG titre and histological grade at last follow up. Patients were age and sex-matched in a 1:2 ratio with CD patients not taking ARBs (controls), with comparable rates of disease duration and compliance with GFD.

Results: The ARB and control groups were matched in terms of age (mean 66.2 years) and gender (female 63%). Strict compliance with GFD was reported in 55% and 56%, respectively. Persistent symptoms were reported in 10/40 (25%) of the ARB group compared with 7/82 (9%) of controls ($p = 0.0181$). There were lower rates of mucosal healing (Marsh grade 0) in the ARB group (36% $n = 11$) compared to controls (55%, $n = 33$). There was no significant difference in anti-TTG titres. Surrogate markers of absorption were comparable across the groups, except for Vitamin D which was lower in those taking olmesartan ($p = 0.0015$).

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Conclusions: ARBs may aggravate the enteropathy and lead to increased symptoms in patients with bone fide diagnosed CD following a GFD.

KEYWORDS

angiotensin receptor blocker, anti-TTG, ARB-enteropathy, coeliac disease, enteropathy, gluten-free diet, MARSH

Key summary

Summarise the established knowledge on this subject

- Angiotensin receptor blocker-associated enteropathy (ARB-e) is an increasingly recognised clinical entity with symptoms and histological findings identical to coeliac disease (CD).
- The exact cause of mucosal injury in ARB-e is unknown however there is evidence to suggest immune-mediated mucosal injury in ARB-e with a high prevalence of DQ2/DQ8, however as anti-tissue transglutaminase (TTG) is usually negative, an insult other than TTG-mediated injury is suspected. The impact of ARBs on disease activity in patients with CD is not known.

What are the significance and/or new findings of this study?

- Coeliac patients who take ARBs are more likely to have persistent symptoms and lower rates of mucosal healing than their age-matched coeliac controls. This observation appears to be independent of TTG mediated injury, akin to that reported in non-coeliac populations.
- ARB use in patients with established coeliac disease may confound the interpretation of clinical and histological response to a gluten-free diet.

INTRODUCTION

Angiotensin receptor blocker-associated enteropathy (ARB-e) is an increasingly recognised clinical entity that presents insidiously with symptoms and histological findings almost identical to coeliac disease (CD). The association between angiotensin receptor antagonist use and enteropathy was first described in 2012 in a case series which identified 22 patients who developed a severe sprue-like enteropathy with concomitant olmesartan medoxomil® therapy.¹ These patients developed chronic diarrhoea and weight loss, however had negative coeliac serology despite evidence of mucosal injury and did not respond to a gluten-free diet. This enteropathy was noted to be transient and resolved completely upon removal of the offending medication. Since then, a host of publications have appeared both confirming this ARB-e as a new clinical entity²⁻⁹ but also implicating other ARBs, though perhaps not as severe as olmesartan, but nonetheless demonstrating a class effect.¹⁰⁻¹⁶ Many patients with an initial diagnosis of 'serology negative' CD were reclassified as having an ARB-e.^{11,12,17-21} While the risk of developing ARB-e in individuals taking ARB medication is extremely low,^{22,23} the prevalence of ARB-e is likely to be underreported.¹⁷

The pathophysiology of ARB-e and indeed the exact cause of mucosal injury remains largely unexplained. There is evidence to suggest an immune-mediated process with a higher prevalence of the HLA-DQ2/DQ8 gene alleles in affected individuals compared to the baseline population.¹⁻³ However, as anti-tissue transglutaminase (anti-TTG) is usually negative^{6,24} an insult other than,

or in combination with, TTG-mediated injury is suspected. Potential coeliac markers (anti-TG2 deposits and specific intraepithelial leukocytes) have been identified in a subset of these patients, which have been shown to persist following withdrawal of ARB, suggesting affected individuals may indeed carry an underlying susceptibility.^{25,26} There is generally a relatively long period (months-years) from initiation of the drug to the manifestation of disease, with longer durations to diagnosis associated with more severe presentations.⁷ This might suggest that the pathological process is cell-mediated rather than a hypersensitivity reaction.^{1,4,17,22}

Most reported cases to date have demonstrated negative coeliac serological markers, however, transient increases in anti-TTG titres at symptom onset have been documented, indicating that positive markers do not completely out rule ARB-e.²⁷ While the association between ARBs and enteropathy is now well recognised, there is a paucity of data regarding the impact of ARBs on disease activity in patients with established CD.²⁸ Indeed, established coeliac patients on an ARB with ongoing symptoms or histologic injury, in spite of strict adherence to a gluten-free diet (GFD) may be misdiagnosed with refractory CD. We have observed the presence of 'pseudo refractory' CD in two such patients while on ARB therapy. Symptoms and histological injury resolved completely following withdrawal of ARB therapy. In light of this, we elected to identify a cohort of patients with established CD exposed to ARBs and review the clinical, biochemical and histological markers of disease severity when compared to coeliac patients not exposed to this class of drugs.

METHODS

Patient selection

This was a retrospective single centre case-control study. A patient record search of 1142 individual patients attending a dedicated coeliac out-patient clinic from January 2010 to May 2019 identified 59 patients who were undergoing treatment with an ARB. Only those with CD confirmed by serology (both anti-TTG + ve and EMA + ve) and histopathology (Marsh criteria ≥ 1) and on a GFD were included. Patients without a bone fide diagnosis of CD, referred to the clinic specifically for assessment of possible ARB-e were excluded. Patients who may have been on an ARB at the time of diagnosis of CD irrespective of the anti-TTG titre were also excluded (Figure 1). Therefore, only those with a definitive diagnosis of CD prior to ARB initiation were included.

Data collection

Coeliac serology (anti-TTG and EMA) and histopathology (Marsh grade) of all included patients were reviewed to confirm the diagnosis of CD according to current international guidelines.²⁹ Information from patients' most recent outpatient clinic encounter including anti-TTG titre, biochemical tests, and histopathology was included for analysis. Symptom review including diarrhoea, weight loss, abdominal pain as well as surrogate markers of small bowel absorption (Vitamin D, Iron, Calcium, and Haemoglobin) was also recorded. The presence of mucosal healing (Marsh 0) and non-healing mucosa (Marsh ≥ 1) were compared across the two groups.

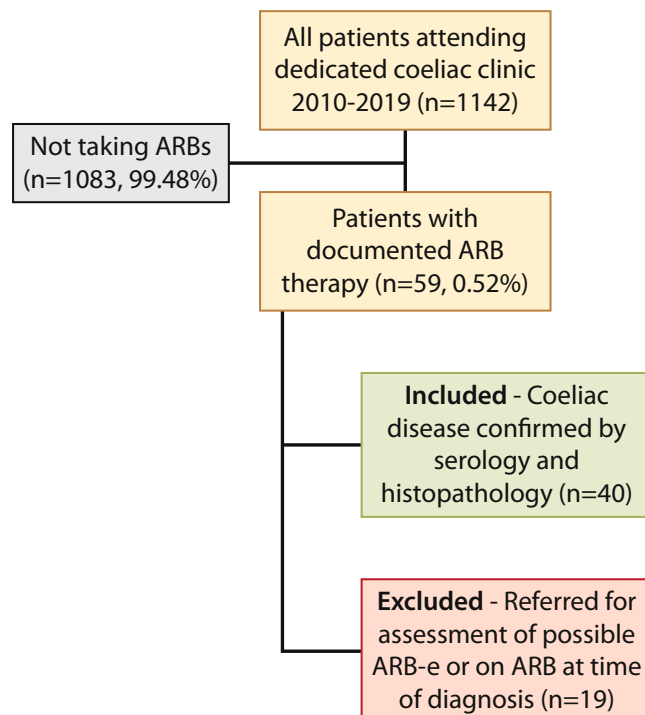


FIGURE 1 Flow sheet of patients identified for inclusion

Control group

Patients were age and sex-matched in a 1:2 ratio with CD patients selected from a prospectively managed database who were never exposed to ARBs. Controls were also selected to match the ARB group in terms of disease duration and compliance to the GFD.

Olmesartan sub-group

The available data in published case reports and case series to date suggests a more pronounced enteropathy with olmesartan and negative coeliac serology when compared with other ARBs. We, therefore, performed a sub-group analysis of our coeliac patients taking olmesartan and compared this with other ARBs as well as controls to determine whether this sub-group might bias the overall comparison between subjects and controls.

Statistical analysis

Descriptive statistics were used to calculate measures of central tendency in the form of means for continuous variables (e.g., age, duration symptoms, and disease activity biomarkers) and proportions for categorical variables (e.g., compliance with GFD, presence of symptoms, coeliac serology, Marsh staging index). Distribution of continuous variables were expressed in the form of standard deviation. A comparison between groups (ARB vs. control, olmesartan vs. control and olmesartan vs. non-Olmesartan ARBs) was performed using a chi-square test for categorical variables and two sample unpaired t-test for continuous variables given the normal distribution of values. Two-sided testing was performed given the potential bi-directional nature of association under study and results were considered significant with a p -value < 0.05 .

Ethics

This study was approved by the Galway University Hospital Clinical Research Ethics Committee on the 1st of December 2020 (Ref: C.A. 2518). Written, informed consent was not required for this study by the Ethics committee. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

RESULTS

Demographics

A total of 40/1142 patients (0.52%) were identified (26 female, 63%) who met the inclusion criteria of a confirmed diagnosis of CD and subsequent treatment with an ARB. Olmesartan accounted for 25%

of all ARBs ($n = 10$). Non-olmesartan ARBs included telmisartan ($n = 13$, 33%), valsartan ($n = 6$, 15%), losartan ($n = 8$, 20%) and candesartan ($n = 3$, 7%). There were 82 patients included in the control group (52 female, 63%). Demographic data and reported compliance with GFD were similar in both groups (Table 1), while disease duration was longer in the control group (13.3 vs. 8.2 years).

Symptoms

Persistent symptoms were reported in 25% ($n = 10/40$) of the ARB group compared with 9% ($n = 7/82$) of controls ($p = 0.018$) (Figure 2). There was no difference in symptoms reported between olmesartan (20%) and other ARBs (27%) ($p = 0.19$).

Marsh grade

Follow up histopathology was available for analysis in 75% ($n = 30$) and 73% ($n = 60$) in the ARB and control group respectively. The mean time from diagnosis to the most recent histological follow-up was 39.9 months (SD 25.3) for the ARB group and 48.4 months (SD 32.6) for the control group. Complete mucosal healing (Marsh 0) was present in 36% ($n = 11/30$) in the ARB group compared to 55% in the control group ($n = 33/60$) ($p = 0.04$) (Figure 3). Incomplete mucosal healing or persistent villous atrophy (Marsh ≥ 1) was reported in 63% ($n = 19/30$) in the ARB group in contrast with the

control group (45%, $n = 27/60$) despite not reaching statistical significance ($p = 0.18$).

Coeliac serology

Anti-TTG titres were positive in 6% ($n = 5/82$) of the control group compared with 10% ($n = 4/40$) of those taking ARBs ($p = 0.42$). The mean duration of GFD at the time of most recent anti-TTG

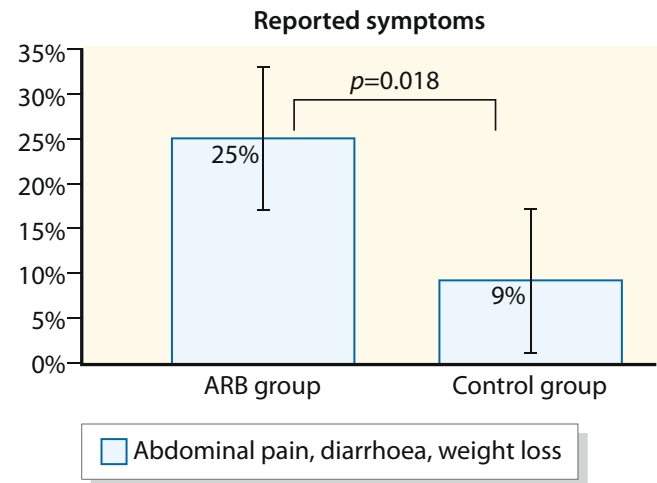


FIGURE 2 Frequency of symptoms reported in angiotensin receptor blockers and Control Groups

TABLE 1 Demographic data and disease characteristics of included patients

	Olmesartan ($n = 10$) Group 1	Other ARBs ($n = 30$) Group 2	P value (groups 1 vs 2)	All ARBs ($n = 40$) Group 3	Control ($n = 82$) Group 4	P value (groups 1 vs 4)	P value (groups 3 vs 4)
Mean age (years)	62.8 (SD 16.49)	67.3 (SD 10.82)	0.37	66.2 (SD 12.04)	66.2 (SD 12.3)	0.42	1.0
Mean duration of disease (years)	6.5 (SD 3.98)	9.9 (SD 11.03)	0.35	8.2 (SD 8.66)	13.3 (SD 9.42)	0.02	0.07
Compliance GFD (%)	60 (6/10)	53 (16/30)	0.7	55 (22/40)	56 (46/82)	0.72	0.26
Symptoms (%)	20 (2/10)	27 (8/30)	0.19	25 (10/40)	9 (7/82)	0.28	0.0181
Positive coeliac serology- not index (%)	0 (0/10)	13 (4/30)	0.23	10 (4/40)	6 (5/82)	0.42	0.42
Marsh staging (%)							
- 0	20 (2/10)	30 (9/30)	0.54	36 (11/30)	55 (33/60)	0.1	0.04
- 1	10 (1/10)	13 (4/30)	0.8	16 (5/30)	8 (5/60)	1.0	0.62
- 3	50 (5/10)	30 (9/30)	0.54	48 (14/30)	37 (22/60)	0.18	0.13
- n/a	20 (2/10)	27 (8/30)		25 (10/40)	27 (22/82)		
HB	13.2 (SD 2.39)	12.7 (SD 1.48)	0.44	12.8 (SD 1.74)	12.8 (SD 1.44)	0.45	1.00
Vitamin D	44.2 (SD 21.8)	69.9 (SD 27.6)	0.01	67 (SD 27.0)	65.6 (SD 19.3)	0.0015	0.74
Iron	14.8 (SD 12.73)	13.5 (SD 10.05)	0.74	13.78 (SD 7.46)	13.8 (SD 7.77)	0.72	0.98
Calcium	2.35 (SD 0.78)	2.36 (SD 0.08)	0.94	2.36 (SD 0.08)	2.36 (SD 0.09)	0.9	1.0

Notes: Marsh n/a—histology not available. These were put in bold/italics to signify p values, The p values in old were statistically significant. The values in red were highlighted as statistically significant values (i.e., values <0.05).

Abbreviations: ARBs, angiotensin receptor blockers; GFD, gluten-free diet; HB, haemoglobin.

assessment was 57.3 months (SD 39.9) for the ARB group and 61.4 months (SD 38.6) for the control group. Further analysis revealed negative anti-TTG serology in all patients taking olmesartan ($n = 10$, $p = 0.42$) as well as those taking losartan ($n = 8$) and valsartan ($n = 6$) (Table 2), while positive anti-TTG serology was identified in a subset of those taking telmisartan ($n = 3/13$) and candesartan ($n = 1/3$).

Surrogate markers of absorption

Surrogate markers of small bowel absorption were comparable across the groups, except for 25 hydroxyvitamin D3 which was lower

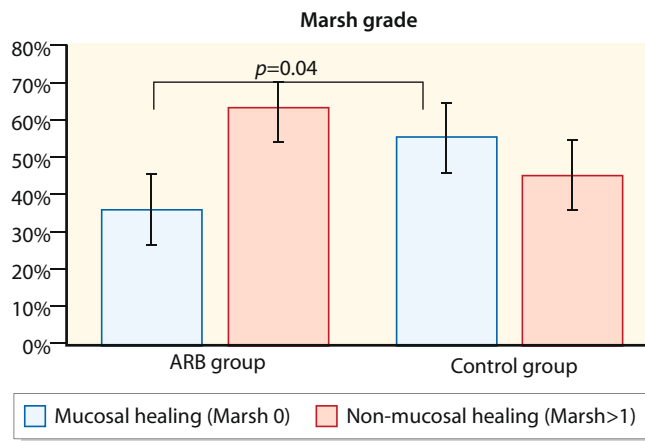


FIGURE 3 Comparison of Marsh Grade in angiotensin receptor blockers and Control Groups

TABLE 2 Clinical, serological and histological features for each class of ARB

	Olmesartan ($n = 10$)	Telmisartan ($n = 13$)	Losartan ($n = 8$)	Valsartan ($n = 6$)	Candesartan ($n = 3$)
Mean age (years) (SD)	62.8 (16.5)	66.4 (11.1)	65.3 (11.2)	70.2 (13.4)	71 (4.6)
Female	5	9	5	4	2
Mean duration of disease (years) (SD)	6.5 (3.98)	9.76 (12.5)	11 (12.8)	10.5 (9.6)	7.7 (1.5)
Compliance GFD (%)	60	76	25	50	33
Symptoms (%)	20	30	38	16	0
Positive TTG (%)	0	23	0	0	33
Marsh staging (%)					
0	20	23	25	50	33
1	10	8	12.5	0	66
3	50	46	37.5	0	0
n/a	20	23	25	50	0
Haemoglobin (g/dl)	13.2 (2.4)	12.6 (1.4)	13.4 (1.4)	12.4 (1.5)	11.4 (1.9)
25 (OH) Vitamin D (nmol/L) (SD)	44.2 (21.8)	71.3 (29.1)	64.8 (25.4)	85.2 (14.8)	52.3 (42.2)
Iron (mol/L) (SD)	14.8 (8.45)	12.3 (3.85)	14.8 (10.7)	15.3 (8.45)	n/a
Calcium (mmol/L) (SD)	2.35 (0.08)	2.36 (0.09)	2.36 (0.06)	2.38 (0.08)	2.13 (0.14)

Abbreviations: ARBs, angiotensin receptor blockers; GFD, gluten-free diet; TTG, anti-tissue transglutaminase.

(44.2 nmol/L) in the olmesartan group compared to other ARBs (69.9 nmol/L) ($p = 0.01$) and controls (65.5 nmol/L) ($p = 0.0015$) (Table 1).

DISCUSSION

This study evaluates the effects of ARB exposure in patients with CD following a gluten-free diet. We sought to determine whether ARB-e may represent a new and important consideration in the investigation of non-responsive or non-healing CD. Prior reports of ARB-e as a distinct clinical entity mimicking that of CD suggested a higher incidence in HLA DQ2/DQ8 positive individuals but heretofore data on the impact of ARBs in established CD was unknown. We have shown that ARB exposure is associated with persistent mucosal damage and this appears to be a class effect rather than that confined to olmesartan induced enteropathy.

CD patients exposed to ARBs report increased symptoms of abdominal pain, weight loss and diarrhoea compared to controls (25% vs. 9%, $p = 0.018$). Moreover, ARB exposed patients have lower rates of mucosal healing with only 36% of such patients achieving a Marsh grade of 0 compared with 55% of controls. Increased rates of ongoing mucosal injury, as defined by Marsh ≥ 1 , were also recorded in the ARB exposed group. Failure to reach statistical significance was likely affected by the small sample size but such findings suggest the entity of an additional ARB-e or an aggravation of the coeliac related enteropathy, as a result of exposure to ARB.

Interestingly, this injury does not appear to be driven by a TTG induced response as evidenced by the low (telmisartan/candesartan) or negative (olmesartan/losartan/valsartan) TTG serology recorded

in these patients. Moreover, the rate of positive serology was equivalent to that in the control group (6% and 10%, respectively). This would suggest that a different mechanism of action is at play, similar to that observed in the non-coeliac population.

It is important to recognise the possibility of drug-induced enteropathy at an early stage in the investigation of non-responsive CD as withdrawal of the offending medication should lead to prompt resolution of symptoms and mucosal healing, thus avoiding escalation of investigations and inappropriate initiation of a treatment algorithm. The evaluation of ARB related non-responsive CD should always be considered, particularly in elderly coeliac patients, who are the most commonly exposed to such a class of anti-hypertensive drug.³⁰

The possibility that inadvertent gluten contamination could account for variations in reported symptoms, serological markers and histological changes is inherent in any study of disease activity in CD. Indeed, this has been particularly challenging in the definition of primary endpoints in clinical trials assessing novel pharmacological agents, with no single measure of disease activity widely accepted.³¹ In this context, validated patient reported outcomes (e.g., symptoms based) have been increasingly considered as acceptable standards for evaluating disease activity in CD.^{31,32} Strict compliance with a GFD in this study was comparable across the two groups and consistent with levels of reported compliance in other studies.³³ We, therefore, posit the risk of gluten contamination was equivalent in both groups and unlikely to account for variation observed.

There are some limitations to the study that should be reported. The sample size in this study, while relatively small, is considerable given the obscure and rare nature of the interaction studied. Nonetheless, the effect of such a small sample size on statistical significance must be acknowledged. Indeed, the retrospective nature of the study does introduce the possibility of selection and information bias, which cannot be overcome with a larger sample size. A validated questionnaire to evaluate compliance with GFD was not employed, rather individual recall of exposure was relied upon which in itself has its inherent risks. This however was similar across the two groups.

CONCLUSION

This retrospective observational case-control study reports the confounding effect of ARB use on the interpretation of symptoms and lack of mucosal healing in established coeliac patients. We demonstrate that ARB exposed coeliac patients are more likely to have persistent symptoms and ongoing mucosal injury than their age and sex-matched non-exposed coeliac controls. Furthermore, this study confirms a class effect rather than a phenomenon unique to olmesartan. This observation appears to be independent of TTG mediated injury, akin to that reported in non-coeliac populations. Screening for ARB exposure is paramount during the assessment of non-responsive CD. Indeed, we propose drug withdrawal and

alternative anti-hypertensive drug use in such cases of 'pseudo-refractory' CD.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Neil O'Morain  <https://orcid.org/0000-0003-2542-9455>

Eileen Shannon  <https://orcid.org/0000-0003-2391-8757>

Hilary Leeson  <https://orcid.org/0000-0002-1692-9207>

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