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Systematic review: sprue-like enteropathy associated with olmesartan

G. Ianiro*, S. Bibbò*, M. Montalto*, R. Ricci†, A. Gasbarrini* & G. Cammarota*

*Department of Internal Medicine, Division of Internal Medicine and Gastroenterology, School of Medicine and Surgery, A. Gemelli Hospital, Catholic University, Rome, Italy.
†Institute of Histopathology, School of Medicine and Surgery, A. Gemelli Hospital, Catholic University, Rome, Italy.

Correspondence to:
Dr G. Cammarota, Institute of Internal Medicine, A. Gemelli Hospital, Catholic University, Largo A. Gemelli, 8, 00168 – Roma, Italy.
E-mail gcammarota@rm.unicatt.it

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SUMMARY

Background
The onset of a sprue-like enteropathy in association with olmesartan therapy has been recently reported.

Aims
To perform a systematic review of the literature and describe three additional cases of olmesartan-associated enteropathy.

Methods
Electronic and manual bibliographic searches were performed to identify original reports in which subjects who were undertaking olmesartan developed a sprue-like enteropathy. Because of the scarcity of studies with adequate sample size, case series with less than 10 patients and case reports were also considered. Data extraction was performed independently by two reviewers.

Results
A total of 11 publications met our pre-defined inclusion criteria, for an overall number of 54 patients (including our series). Almost all patients presented with diarrhoea and weight loss. Normocytic normochromic anaemia and hypoalbuminaemia were the commonest laboratory defects at presentation. Antibody testing for coeliac disease was always negative. Variable degrees of duodenal villous atrophy were present in 98% of patients, while increased intra-epithelial lymphocytes were documented in only 65% of cases. After discontinuation of olmesartan, all reported patients achieved resolution of signs and symptoms.

Conclusions
Although the available evidence is limited, the olmesartan-associated sprue-like enteropathy may be considered as a distinct clinical entity, and should be included in the differential diagnosis when serological testing for coeliac disease is negative.

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INTRODUCTION

Coeliac disease is the most common cause of villous atrophy and increase in intra-epithelial lymphocytes (IELs) in the small bowel.[1] However, these histopathological findings are also caused by other disorders, such as Crohn's disease, enteric infections (e.g. *Giardia lamblia*), collagenous sprue, tropical sprue, common variable immunodeficiency, autoimmune enteropathy and haematological malignancies.[2] Villous atrophy and malabsorption have been reported also as a side-effect of immunosuppressant drugs (in particular, azathioprine, methotrexate, neomycin and mycophenolate mofetil).[3–6]

Olmesartan medoxomil is an angiotensin II receptor blocker used for the management of hypertension, available in Western Countries since 2002.[7] A sprue-like enteropathy associated with olmesartan has been first described in 2012 by Rubio-Tapia *et al.*,[8] and similar cases have since been reported. To date, the pathogenic mechanism of olmesartan-associated enteropathy is still unknown.

Here, we have performed a systematic review of sprue-like enteropathy occurring during treatment with olmesartan and also report three additional cases. Furthermore, we assessed all published reports through a systematic review of literature.

Case series

Case #1. A 60-year old man presented with weight loss and nonbloody diarrhoea. Apart from arterial hypertension, treated with olmesartan since 3 years, his medical history was unremarkable. Physical examination was normal, as well as routine blood and stool exams. Total type A immunoglobulins (IgA) were normal. Both antibody testing for coeliac disease (e.g. transglutaminase and endomisium antibodies) and DQ2/DQ8 HLA search were negative. Colonoscopy findings were normal. Upper endoscopy showed a nodular appearance of the mucosa and a complete flattening of villi. Histopathological examination confirmed the absence of any villous pattern, but without increase in IELs. Neither gluten-free diet nor steroid administration improved symptoms. After reading the report by Rubio-Tapia *et al.*,[8] we hypothesised the possible causative role of olmesartan in the development of such findings. Olmesartan was therefore withdrawn and replaced with ramipril. One week after, diarrhoea ceased and the patient began to gain weight. At 3-month follow-up, full recovery of duodenal villi was documented both at endoscopic assessment and at histopathological analysis.

Case #2. A 59-year old man was admitted to our hospital because of severe fatigue, weight loss and diarrhoea. He was respectively taking insulin because of diabetes mellitus type II and olmesartan because of arterial hypertension. Abdomen physical examination was normal, as well as fasting blood sugar. Laboratory evaluation revealed hypochromic microcytic anaemia and hypoalbuminaemia. Stool exams were negative. Suspecting a neoplastic aetiology, we performed a colonoscopy (that was unremarkable) and an upper endoscopy that showed a severe hypotrophy of duodenal villous pattern. The histological assessment documented a partial villous atrophy, without increase in IELs. Patient therefore underwent full laboratory testing for coeliac disease, including transglutaminase and endomisium antibodies, total blood IgA, human leucocyte antigen (HLA) assessment, without any relevant finding. Anyway, a gluten-free diet was started, without clinical success. We therefore attempted to switch from olmesartan to amlodipine. Afterwards, the patient experienced first disappearance of diarrhoea and then weight gain. The 3-month follow-up upper endoscopy showed the growth of duodenal villi that was confirmed at histopathological evaluation.

Case #3. A 78-year old woman was hospitalised because of fatigue, dyspnoea and nonbloody diarrhoea. She had formerly been diagnosed with coeliac disease, because of an histological finding of total villous atrophy and increase in IELs, even though testing for anti-transglutaminase and endomysial antibodies and typing for HLA DQ2/DQ8 were negative. Since 2010, the patient was receiving a gluten-free diet, without any further follow-up. She was also on olmesartan and furosemide because of arterial hypertension. Physical examination revealed a diffused body oedema, with ascites and pleural effusion. Laboratory assessment revealed normochromic normocytic anaemia and severe hypoalbuminaemia. Total IgA, anti-endomysial and transglutaminase antibodies were within normal range. Cardiac and liver ultrasonography were unremarkable, and a CT scan confirmed the presence of diffuse tissue oedema. At upper endoscopy, total atrophy of duodenal villi was observed, together with a nodular mucosal pattern. Histological assessment confirmed total villous atrophy, but without increase in IELs (Figure 1a). In the suspicion of olmesartan-associated sprue-like enteropathy previously misdiagnosed as seronegative coeliac disease, we changed olmesartan to barnidipine. After 2 weeks, diarrhoea disappeared and anasarca improved markedly. After 2 months,

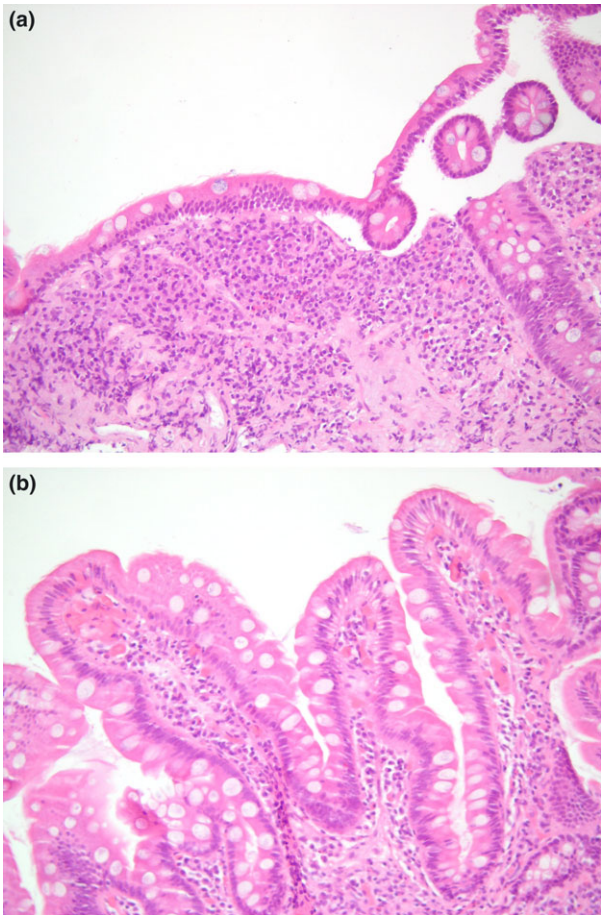

Figure 1 | Histology before (a) and after (b) suspension of olmesartan in case 3 (haematoxylin-eosin, original magnification 200×).
In (a), complete absence of duodenal villi without increasing of IELs; in (b), partial reconstitution of villi.

anaemia improved and serum albumin returned into normal range. Tissue oedema had disappeared almost completely. Moreover, follow-up endoscopy showed a patchy partial recovery of duodenal villi; histological analysis confirmed the presence of partial villous atrophy (Figure 1b).

METHODS

This systematic review was conducted, when possible, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[9]

Eligibility criteria

All the original reports in which the development of sprue-like enteropathy was documented in patients of any age being treated with olmesartan were considered for inclusion. Studies evaluating treatments other than olmesartan were excluded, as well as those including patients without enteropathy treated with olmesartan. In the case of mixed cohorts, only data from patients treated with olmesartan were taken into account. We did not include animal model studies or non-original reports. Because of the likely scarcity of studies with adequate sample size, also case series with less than 10 patients and case reports were considered, without year- span limits. No language restriction was used in the search filter. We included also data presented only as abstracts at conferences.

Information sources and search strategy

A literature search was performed using the following electronic databases: PubMed, SCOPUS, Web of Science (ISI), the Cochrane Library. The last search was run on 19 February 2014. The term 'olmesartan' was matched with the following words: 'villous' OR 'villar' OR 'villous atrophy' OR 'villar atrophy' OR 'enteropathy' OR 'sprue-like' OR 'spruelike' OR 'celiac' OR 'coeliac' OR 'sprue' OR 'diarrhea' OR 'diarrhoea'. All the terms were searched both as keywords and Medical Subject Headings (MeSH). The bibliographies of relevant (according to titles and abstracts) articles were hand-searched to provide additional references. Records from the following yearly symposia were hand-searched to find pertinent abstracts: United European Gastroenterology), 2008–2013; Digestive Disease Week, 2001–2013; European Crohn's and Colitis Organization Congress, 2007–2013; Crohn's and Colitis Foundation of America Annual Scientific Meeting, 2003–2013. When necessary, authors of articles were also contacted for clarifications or for missing information about their data.

Study selection

Titles and abstract were independently assessed from two reviewers (G.I. and S.B.) to determine the eligibility of the studies. Both investigators checked the fulfilment of inclusion and exclusion criteria; in the case of doubt, the full text of articles was retrieved and reviewed. A third author (G.C.) arbitrated in all the cases of a lack of agreement.

Data collection process

Data from eligible studies were independently extracted by two reviewers (G.I. and S.B.), then cross-checked. Discrepancies were rectified by consensus. When articles grouped patients from a previous study and newly enrolled ones, only the latter were considered. In the case of mixed cohorts, only data regarding patients treated with olmesartan were included for the analysis.

Data extracted from each primary study are shown in Table 1. Study references and citations were collected in Endnote software application version 6.0 (Thomson Reuters, New York, NY, USA). A data collection form was designed in Microsoft Excel 2007 (Microsoft, Redmond, WA, USA).

RESULTS

Characteristics of included studies

After literature search and review of titles and abstracts, 11 articles met our pre-defined inclusion criteria.[2, 8, 10–18] All of them were Western case series or case reports published between 2012 and 2014. All but one[10] have been published as full-text articles. A list of the excluded studies and reasons for exclusion, as well as the flow diagram of study selection, are available from the corresponding author upon request. Data from our case series were also considered for the final analysis. Therefore, a total of 12 articles (including the present article) have been included for analysis. Table 1 summarises findings from all studies reporting the onset of an olmesartan-associated enteropathy.

Characteristics of patients

A total of 54 patients, equally distributed between both genders (27 males; 27 females) developed a sprue-like enteropathy during treatment with olmesartan. The mean age was 69 (range: 47–87). The mean duration of olmesartan therapy was reported in 5[8, 10, 11, 14, 15] of 13 studies (including our series), ranging between 6 months and 7 years.

Clinical presentation

Almost all patients whose symptoms had been reported presented with diarrhoea (36 of 38 patients) (95%) and weight loss (34 of 38 patients) (89%). Other common symptoms were fatigue (21 of 38) (56%), nausea and vomiting (17 of 38) (45%), abdominal pain (14 of 38) (37); bloating (11 of 38) (29%). Less frequent symptoms were reflux symptoms, loss of appetite, mild constipation.

Laboratory evaluation

Normocytic normochromic anaemia (17 of 38 individuals) (45%) and hypoalbuminaemia (15 of 34) (39%) were the most diffused laboratory defects at presentation. Only one patient from our series showed microcytic hypochromic anaemia. When performed, the HLA assessment found presence of DQ2 or DQ8 haplotypes in 33 of 46 patients. Anti-transglutaminase and -endomysial antibodies were respectively searched in 49 and 33 patients, and were both always negative. Enterocyte antibodies were tested in 21 patients, resulting positive (with atypical pattern) in three cases.

Endoscopic appearance

The majority of included articles did not describe the endoscopic pattern of olmesartan-associated sprue-like enteropathy. Upper endoscopy showed nodularity in the duodenal bulb in one patient,[11] and duodenal ulcers in another one[14] while Stanich *et al.* did not find changes in the duodenal pattern.[15] In our series, all endoscopic exams were performed with an high-definition scope (EPK-I scope, Pentax Medical, Tokyo, Japan), using both i-scan technology and water-immersion technique for the assessment of the duodenal villous pattern and driving of biopsy sampling. Two of three patients showed a nodular appearance of the mucosa and marked villous atrophy. In the remaining patient, a partial flattening of duodenal villi was found.

Histopathological findings

Flattening of the duodenal villous pattern was the most common histopathological finding, being observed in 53 of 54 (98%) patients. Respectively, total villous atrophy occurred in 28 patients and partial villous atrophy in 22 patients (52% and 41%, respectively). In three patients,[2] the degree of villous flattening was not assessed. In one patient,[18] no villous atrophy was observed. Increased duodenal IELs, according to the modified Marsh's classification modified by Oberhuber (>40 IELs/100 enterocytes),[19] were found in 34 of 52 (65%) patients. All patients from our series showed normal duodenal IELs. In addition, a thickened subepithelial collagen layer, as occurs in collagenous sprue, was identified in the duodenum of 18 of 54 (33%) patients.

Clinical and histopathological outcomes

In all but four[11, 15–17] studies, patients were administered a gluten-free diet after being misdiagnosed as coeliac disease. Gluten withdrawal did not improve symptoms in 45 of 46 (98%) patients, being successful in only one case.[2] Steroid administration was attempted in 20 patients, leading to amelioration of symptoms in 19 (95%) of them; one patient from our series did not respond to steroid treatment.

After discontinuation of olmesartan, 100% of patients achieved resolution of diarrhoea (clinical response). Weight changes were reported in only three studies,[8, 14, 16] plus in our series: a total of 21 of 27 (78%) patients experienced weight gain after stopping olmesartan. Twenty-seven patients underwent a follow-up upper

Table 1 | Studies reporting patients with olmesartan-associated sprue-like enteropathy

Author (Reference)	*n* (M)	Age (yr) or mean age with range	Years of olmesartan intake or mean with range	Symptoms and laboratory findings (*n*)	HLA DQ2 or DQ8 positive (*n*)	TTG/EMA positive (*n*)	Anti-enterocyte antibodies positive (*n*)	Endoscopic findings (*n*)	Duodenal histology at diagnosis (*n*)	Amelioration of symptoms after after GFD (*n*)	Amelioration after steroid administration (*n*)	Clinical amelioration/ histological recovery after suspension of olmesartan (*n*)
de Fonseka[10]	1 (1)	60	7	Diarrhoea Weight loss Anaemia norm. Hypoalbuminaemia	0	0/0	NT	NR	PVA IELs	0	0	1/NR
Rubio-Tapia *et al.*[8]	22 (9)	69 (47–81)	3 (0.5–7)	Diarrhoea (22) Weight loss (22) Anaemia norm (14) Hypoalbuminaemia (10) Nausea and vomiting: 15/22. Abdominal pain: 11/22 Bloating: 9/22 Fatigue: 15/220)	17 of 21 tested	0/0 of 9 tested	3 of 19 tested	NR	TVA in 15 PVA in 7 SCD in 7 IELs in 13 (9 TVA and 4 PVA)	0	NR	22/17 of 18 tested
Talbot [11]	1 (1)	59	3	Anaemia norm.	1	0/NT	NT	Nodularity in the duodenal bulb	PVA IELs	NT	NT	NA
De Gaetani *et al.*[2]	16 (8)	67 (52–83)	NR	NR	14 of 15 tested	0/0	NT	NR	TVA in 8 PVA in 5 NSDVA in 3 SCD in 11 IELs in 11 (7TVA, 2PVA, 2 NSDVA)	1	16	15/2 of 2 tested
Dreifuss *et al.*[12]	1 (1)	64	NR	Diarrhoea Weight loss Bloating	0	0/0	NT	NR	PVA IELs	0	NT	1/NR
Nielsen *et al.*[13]	1 (0)	62	NR	Diarrhoea Weight loss Nausea and vomiting Abdominal pain Bloating	1	0/0	0	NR	TVA SCD IELs	0	NT	1/1
Nunge *et al.*[14]	1 (0)	81	NR	Diarrhoea Weight loss Hypoalbuminaemia	1	0/0	0	Duodenal ulcers	TVA IELs	0	1	1/NR
Stanich *et al.*[15]	1 (0)	57	NR	Diarrhoea Hypoalbuminaemia Nausea and vomiting Abdominal pain	1	0/0	NT	Normal duodenal pattern	TVA IELs	NT	NT	1/NR
Gaur *et al.*[16]	1 (1)	61	5	Diarrhoea Weight loss Abdominal pain Fatigue	NT	0/NT	NT	NR	PVA IELs	NT	1	1/NR
Tran and Li[17]	1 (1)	NR	NR	Diarrhoea Weight loss	0	0/NT	NT	NR	TVA IELs	NT	NT	1/NR
Theophile *et al.*[18]	5 (3)	82 (78–87)	NR	Diarrhoea (4) Weight loss (4) Fatigue (2)	NT	NT/NT	NT	NR	PVA in 4 NV in 1 IELs in 2 (2PVA); NR in 3	NR in 3 pts; NA in 1* No improvement of symptoms in 1	NT	5/2 of 3 tested

Table 1 | (Continued)

Author (Reference)	*n* (M)	Age (yr) or mean age with range	Years of olmesartan intake or mean with range	Symptoms and laboratory findings (*n*)	HLA DQ2 or DQ8 positive (*n*)	TTG/EMA positive (*n*)	Anti-enterocyte antibodies positive (*n*)	Endoscopic findings (*n*)	Duodenal histology at diagnosis (*n*)	Amelioration of symptoms after after GFD (*n*)	Amelioration after steroid administration (*n*)	Clinical amelioration/ histological recovery after suspension of olmesartan (*n*)
Present study	3 (2)	66 (59–80)	3	Diarrhoea (3) Weight loss (2) Anaemia norm. (1) Anaemia micr. (1) Hypoalbuminaemia (2) Fatigue (3)	0	0/0	NT	Nodularity of mucosa: 2/3. TVA in 2 PVA in 1	TVA in 2 PVA in 1 IELs in 0	0	0 of 1 tested; NT in 2 cases	3/3

n, number of subjects; yr, years; TTG, transglutaminase antibodies; EMA, anti-endomysial antibodies; GFD, gluten-free diet; NT, not tested; NR, not reported; NA, not available; TVA, total villous atrophy; PVA, partial villous atrophy; IELs, more that 40% intra-epithelial lymphocytes; NSVA, not specified degree of villous atrophy; SCD, subepithelial collagen deposition; NV, normal villi.

* Concomitant discontinuation of olmesartan and start of GFD.

endoscopy after olmesartan suspension and in 25 (93%) of them a complete recovery of duodenal histology (including normalisation of both villous pattern and IELs infiltrates) was observed. None of the patients underwent olmesartan re-challenge to prove a causality relationship with sprue-like enteropathy.

DISCUSSION

Olmesartan intake has been recently associated with the development of a sprue-like enteropathy, mainly characterised by diarrhoea, weight loss and variable degrees of duodenal mucosa damage. In the present study, we performed a systematic review of the literature, including in the analysis three additional cases of olmesartan-associated enteropathy we diagnosed.

Our search found a total of 11 studies, all of which were case reports or series: this represents a limitation of our systematic review. Overall, 54 patients, equally distributed between men and women, have developed a sprue-like enteropathy associated with olmesartan treatment for arterial hypertension. Mean duration of olmesartan therapy was 3.3 years. Most common symptoms were diarrhoea and weight loss. Normocytic normochromic anaemia and hypoalbuminaemia were the most diffused laboratory alterations, being present in slightly more than a half of patients. Anti-endomysial and -transglutaminase antibodies were negative in 100% of patients, whereas the anti-enterocyte antibodies were positive, when tested, and with atypical pattern, in only three subjects. Similarly to the data shown by Rubio-Tapia,[8] HLA DQ2 or DQ8 haplotype was present in 72% of patients. Since in the normal population the DQ2/DQ8 prevalence is estimated at 30–40%,[20] our data suggest a possible role for genetics also in olmesartan-induced enteropathy.

Endoscopic pattern has been described by few authors only. We have already shown the effectiveness of both water-immersion technique[21] and i-scan technology[22] in the evaluation of duodenal villous pattern. Applying such tools, we found in two patients a nodular appearance of the duodenal mucosa (in addition to total villous atrophy), confirming data by Talbot *et al.* Since this finding has been reported in only three of 54 patients, it cannot be considered an endoscopic hallmark of sprue-like enteropathy. However, endoscopic features of the disease has been described just in four reports, and nobody except us made use of advanced endoscopic image techniques. Further studies should therefore include the application of endoscopic magnification tools for a better definition of such clinical entity.

Interestingly, variable degrees of villous atrophy were present in all patients but one (98%), whereas an increase in IELs infiltration into the duodenal mucosa was documented in only 65% of cases. In addition, a thickened subepithelial collagen band was found in the duodenum of one third (33%) of patients. If confirmed by subsequent, larger series, these findings may help to distinguish between coeliac disease and olmesartan-induced enteropathy from a histopathological perspective.

Such histological features may also suggest some conjectures about the pathogenic pathway of olmesartan-induced enteropathy, and its differences from coeliac disease.

Coeliac disease is an autoimmune disorder which is induced, in genetically pre-disposed people, by the ingestion of gluten which is rich in proline and glutamine. It

is characterised by an inflammatory reaction, primarily in the upper small intestine, with features of infiltration of the lamina propria and the epithelium with chronic inflammatory cells and progressive villous atrophy.[23] In the olmesartan-associated sprue-like enteropathy, the flattening of villi is instead not always associated with increase in IELs and inflammation.

The mechanisms underlying olmesartan-associated enteropathy are not known. At the present time, it is only possible to make some assumptions that have only a speculative value. Villous atrophy in the olmesartan enteropathy might be the result of a pro-apoptotic effect of angiotensin II on intestinal epithelial cells. Renin-angiotensin system is known to regulate fluid and electrolyte absorption in the human gut. Angiotensin II binds to two receptor forms, called AT1 and AT2, with different properties. AT1 receptor is expressed throughout the whole alimentary tract, while the AT2 receptor is expressed only in some tracts, particularly in the duodenum and jejunum.[24] Briefly, AT1 receptor activates growth-promoting factors and mediates major effects of angiotensin II, while AT2 receptor induces opposite effects.[25] Recently, Sun *et al.* have shown that angiotensin II promotes apoptosis of enterocytes through binding to AT2 receptor and consequent up-regulation of pro-apoptotic protein (Bax and GATA-6) associated with a down-regulation of Bcl-2, an anti-apoptotic protein.[26] In addition, drug-induced AT1 receptor blocking has been shown to exert translocation of AT2 receptors from cytosol to external membrane in presence of high concentrations of angiotensin II in rat smooth muscle cells; such behaviour may favours binding of angiotensin II to AT2 receptors.[27] Olmesartan shows high affinity for AT1 receptors. In case of AT1 receptor saturation by olmesartan, circulating angiotensin II could bind only AT2 receptor, with consequent pro-apoptotic effect. Apoptosis of enterocytes may ultimately lead to villous atrophy without inflammatory reaction and increase in IELs.

After the discontinuation of olmesartan, clinical remission occurred in 100% of patients, and almost all of them showed histological recovery of the duodenum (although if follow-up duodenal biopsy sampling has been performed in only a half of all cases). Steroid treatment induced improvement of symptoms in 19 patients, but none of them underwent subsequent endoscopic and histological assessment.

Olmesartan-associated sprue-like enteropathy may be considered as an adverse drug reaction. However, a cause–effect relationship should be classified only as probable according to the Naranjo probability scale, since neither olmesartan nor placebo have been reintroduced in none of the patients.[28]

In conclusion, olmesartan-associated sprue-like enteropathy may be considered as a distinct clinical entity, and should be included in the differential diagnosis of seronegative villous atrophy. Considering the worldwide use of olmesartan as anti-hypertensive treatment, olmesartan-associated sprue-like enteropathy may theoretically be widespread, and the clinical gastroenterologist should be aware of this. Up to now, however, only a few cases have been described, and scarcity of available data does not allow a correct definition of the disease. Areas of interest include the assessment of pathogenic pathways (including the role of the DQ2/DQ8 haplotypes), as well as of endoscopic and histological hallmarks of the disease.

AUTHORSHIP

Guarantor of the article: None.

Author contributions: Gianluca Ianiro, Stefano Bibbò and Giovanni Cammarota were involved in the study concept and design; in the analysis and interpretation of data; in drafting of the manuscript; in the critical revision of the manuscript, and in describing the clinical history of two reported cases. Massimo Montalto was involved in reporting the clinical history of a patient, and in the critical revision of the manuscript. Riccardo Ricci was involved in the histopathological analysis of the reported patients. Antonio Gasbarrini was involved in the critical revision of the manuscript. All authors approved the final version of the manuscript.

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