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Severe cases of sprue-like enteropathy associated with angiotensin receptor blockers other than olmesartan

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Summary

Background: Sprue-like enteropathy (SLE) has been reported in patients with arterial hypertension who are treated with the angiotensin receptor blocker (ARB) olmesartan. It is currently controversial whether this is a class effect or specific to olmesartan.

Methods: A systematic literature search was conducted in Medline/PubMed, Embase, Web of Science and Scopus without language, publication year or publication status restrictions up to October 2019 to retrieve publications on SLE related to all ARBs excluding olmesartan.

Results: Overall, 17 reports including a total of 21 patients describing SLE cases were identified with the following ARBs: candesartan (n = 1), eprosartan (n = 1), irbesartan (n = 4), losartan (n = 7), telmisartan (n = 4) and valsartan (n = 4). The treatment duration among these ARB-treated patients varied from 2 months to up to 13 years, while the onset of enteropathy-related symptoms ranged from 2 months to 10 years from treatment initiation. The most frequently reported SLE symptoms were as follows: chronic diarrhoea, abdominal symptoms, loss of appetite and weight loss (3-27 kg). Symptomatic treatment with antibiotics, corticosteroids and dietary modifications did not significantly improve the SLE symptoms in patients while on treatment with ARBs. However, diarrhoea resolved in all 21 patients after the withdrawal of ARBs and other gastrointestinal symptoms had resolved on follow-up in all but two patients.

Conclusions: SLE is observed in patients treated with ARBs other than olmesartan. This suggests a class effect in the rare event of patients treated with ARBs developing SLE.

1 | INTRODUCTION

Angiotensin receptor blockers (ARBs) are widely used for the treatment of arterial hypertension. International guidelines for the management of hypertension recommend ARBs as monotherapy or in combination with other anti-hypertensive drugs. ARBs are recognised to be highly effective and appreciated for their favourable safety profile.[1] Their mode of action is via the renin-angiotensin-aldosterone pathway by selectively blocking the action of angiotensin II at the receptor level thereby reducing vasoconstriction.[2]

In 2012, Rubio-Tapia and colleagues reported an association between olmesartan treatment and severe sprue-like enteropathy (SLE), a syndrome characterised by chronic non-bloody diarrhoea, weight loss, the frequent presence of nausea, vomiting, abdominal pain, bloating and fatigue.[3] In the original study, >50% of patients (14/22) required hospitalisation due to the severity of gastrointestinal symptoms and malabsorption. The characteristic histological findings in these patients were partial or total duodenal villous atrophy with crypt architectural distortion.[3] In some patients with olmesartan-induced SLE, chronic inflammatory changes were found

at other locations in the gastrointestinal tract and included microscopic colitis, lymphocytic and collagenous gastritis. Anaemia, hypoalbuminaemia and electrolyte imbalances were frequently detected due to severe malabsorption in the treated patients.[3]

Olmesartan-related SLE presents characteristics similar to coeliac disease. Furthermore, patients with olmesartan-induced SLE often have a positive result on HLA-DQ2/DQ8 testing. However, there are two critical parameters that distinguish olmesartan-related SLE from coeliac disease: patients with olmesartan-related SLE have negative serology (ie absence of antibodies to transglutaminase) for coeliac disease and do not respond to a gluten-free diet. Although a rare condition,[4-6] olmesartan-related SLE is a serious clinical entity that may require hospitalisation.[4]

The onset of olmesartan-related SLE is usually delayed several weeks or even years after starting treatment with olmesartan (mean 3.3 years), but prompt clinical recovery occurs following treatment cessation.[7] In contrast, histological recovery usually takes weeks to several months.[5,8] In the study by Rubio-Tapia and colleagues, all patients showed a clinical response following olmesartan withdrawal and regained weight (median 12.2 kg), while 17 of 21 patients who underwent follow-up biopsies showed histological recovery or improvement.[3] None of the treated patients were restarted on a different ARB after olmesartan withdrawal.[3]

Following the study by Rubio-Tapia and other publications and analysis of pharmacovigilance data, the US Food and Drug Administration included olmesartan-induced SLE as an adverse event in the product label for olmesartan-containing products.[9] Similarly, during the renewal procedure for olmesartan (18 August 2014), the European Authorities requested revisions to the Summary of Product Characteristics (SmPC) to include SLE in Section 4.8 as an undesirable effect with a 'very rare' incidence (<1/10 000), and specific warning on the management of patients who develop chronic diarrhoea when on olmesartan treatment in Section 4.4.[10] Despite the evidence of SLE cases associated with other ARBs (the described variations), these notifications were adopted for olmesartan only.

This report aims to systematically review the published literature and to examine the evidence for SLE related to ARBs other than olmesartan. Special attention is paid to the question of whether olmesartan and other ARBs-related SLE are similar or distinct in their clinical and histological features.

2 | MATERIALS AND METHODS

A comprehensive literature search was conducted electronically to retrieve publications on SLE related to all ARBs including olmesartan, and a systematic review performed. The literature search strategies were developed using the Cochrane Collaboration Handbook, which details the use of the PICO (Population-Intervention-Comparator-Outcome) process, a technique used in evidence-based practice to precisely frame and answer relevant clinical or health care-related questions.[11] The PICO framework approach was adhered to while developing the search strategies, with the resulting questions used to frame the search strategy (Table 1).

TABLE 1 PICO (Population-Intervention-Comparator-Outcome) questions

Patient/population	Patients with sprue-like enteropathy
Intervention	Angiotensin receptor blockers
Comparator	Olmesartan
Outcome	Not defined

The following electronic databases were searched without language, publication year or publication status restrictions up to October 2019: MEDLINE/PUBMED (Appendix 1), EMBASE (Appendix 2), WEB OF SCIENCE (Appendix 3) and SCOPUS (Appendix 4). The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement was used in processing the search results,[12] and duplicates were identified from each of the four databases and managed using the reference management software Zotero. The results were then manually searched by the medical librarian-information specialist who performed the bibliographic research to remove duplicates and articles reporting preclinical studies. The final shortlisted publications were reviewed by Prof. Peter Malfertheiner, a key opinion leader in the field of gastroenterology, hepatology and internal medicine, and articles reporting an association between SLE with ARBs other than olmesartan were selected.

3 | RESULTS

A flow diagram of the search process and results is presented in Figure 1. The literature search identified 19 articles reporting suspected SLE cases associated with ARBs other than olmesartan, of which two were excluded for the following reasons: (a) although one manuscript reported a case of enteropathy possibly associated with candesartan, it was excluded from this review due to paucity of the reported information;[13] and (b) another publication[14] was identified as a duplicate of a case of losartan-related SLE[15] and was therefore excluded. A total of 17 case reports describing severe enteropathy related to ARB intake in 21 patients were included in this review.

SLE was reported in patients receiving candesartan (n = 1),[16] eprosartan (n = 1),[17] irbesartan (n = 4),[18-20] losartan (n = 7),[15,21-25]; telmisartan (n = 4)[26-29] and valsartan (n = 4).[20,30,31]

Table 2 summarises the demographic and clinical data of the 21 patients included in this review. The duration of treatment with ARBs varied from 2 months to 13 years, while the onset of enteropathy symptoms ranged from 2 months to 10 years from ARB treatment initiation. The most frequently reported symptoms were chronic diarrhoea, abdominal discomfort, loss of appetite and weight loss (range: 3-27 kg). All patients required a thorough diagnostic workup, while hospitalisation due to SLE-related conditions was reported for eight patients.

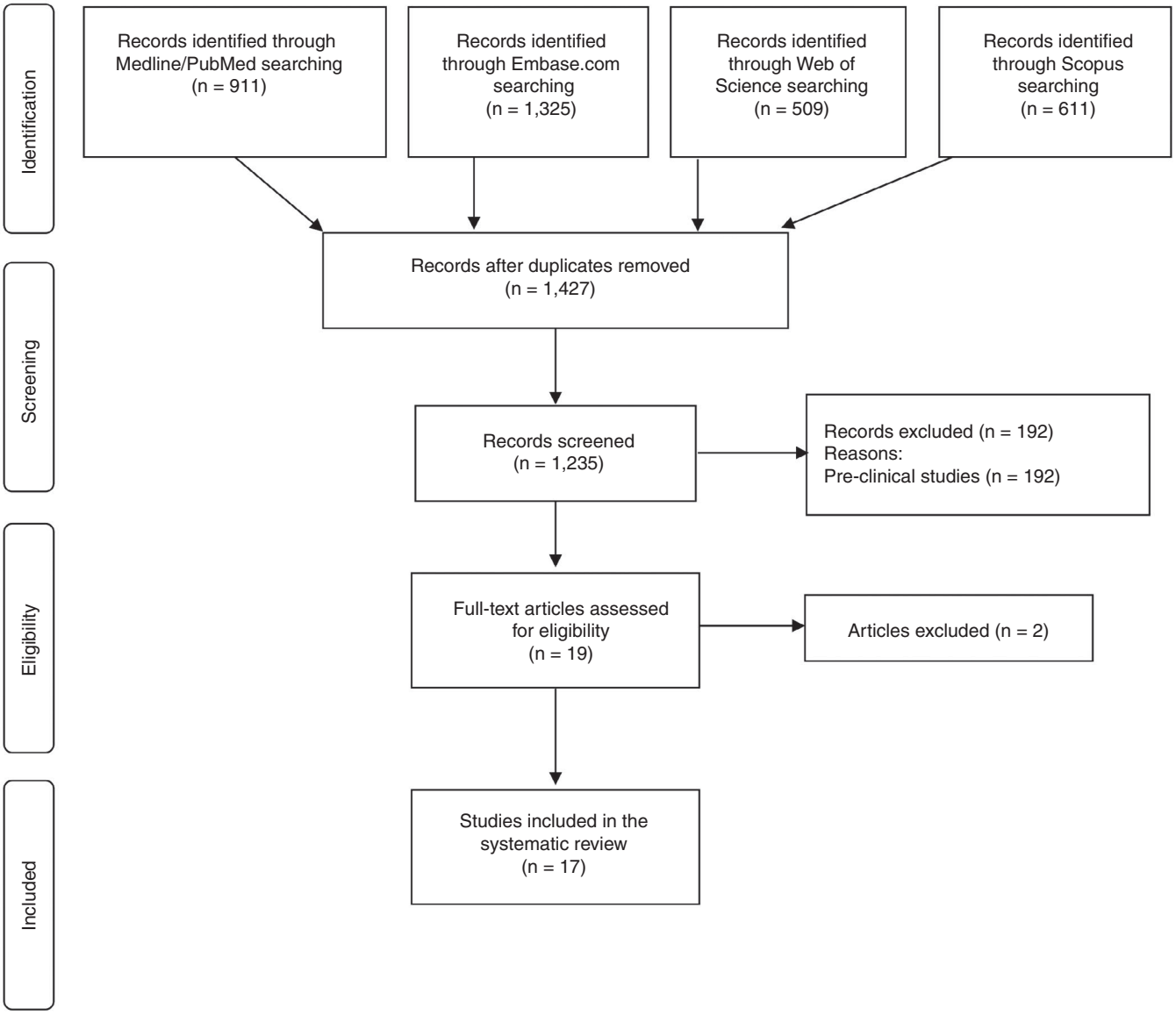

FIGURE 1 PRISMA article selection flow diagram

Table 3 summarises the histological and serological data of the treated patients. Among the cases studied, serological testing for coeliac disease or autoimmune enteropathy was negative, if performed. In the three cases were no serology and no histological confirmation of SLE was documented, the clinical symptoms of SLE were reversible by withdrawal of the ARB. Varying degrees of villous atrophy were evident when duodenal biopsy was performed, and mucosal inflammation was a common finding during endoscopy.

Symptomatic treatment (including antibiotics and corticosteroids) and dietary modifications failed to significantly improve enteropathy symptoms in the treated patients (Table 3). Diarrhoea and/or other gastrointestinal symptoms improved significantly or resolved in all the 22 cases following the withdrawal of ARB treatment. Amelioration of symptoms was often rapid, and weight gain was commonly reported. When follow-up biopsy was performed, the duodenal histology after ARB withdrawal showed changes ranging from a slight improvement in mucosal architecture at 3 and 6 months after withdrawal to marked regression of villous atrophy commonly at 3 months follow-up, and in some cases after longer follow-up durations (6-12 months).

4 | DISCUSSION

Olmesartan-related SLE is a rare event, but well established as a distinct nosological entity.[3,7] However, whether olmesartan-associated SLE is drug specific or a class effect in susceptible individuals remains a controversial issue. As a contribution to this question, we performed a systematic search of the available literature and retrieved 17 individual case reports of severe malabsorption associated with ARBs other than olmesartan (candesartan, eprosartan, irbesartan, losartan, telmisartan and valsartan)

TABLE 2 Demographic and clinical data of patients

Study	Sex/age (y)	ARB dose (mg/day)/ treatment duration	Time between ARB intake and onset of symptoms	Weight loss (kg)	GI symptoms and related conditions	Clinical response to dietary modifications	Clinical response to ARB withdrawal	Time between ARB withdrawal and clinical recovery	Concomitant diseases/other information	Hospitalisation due to SLE symptoms
Candesartan										
Mondet 2016[16]	M/81	NR/9 y	1 y	NR	Chronic diarrhoea	NR	Recovery	Few days	Symptomatic treatment	Yes
Eprosartan										
Maier 2015[17]	F/83	600/10 y	>9 y	NR	Diarrhoea	NR	Recovery	NR	Symptom onset reported after uptitration of ARB dose	NR
Irbesartan										
Cammarota 2014[18]	F/80	NR/6 mo	NR	NR	Diarrhoea and weight loss	NR	Recovery	NR	NR	NR
Marthey 2014[19]	F/54	NR/2 y	10 mo	39%	Diarrhoea abdominal pain, acute renal failure	NR	Recovery	NR	NR	Yes
Zanelli 2017[20]	M/78	NR/3 y	NR	NR	Chronic watery diarrhoea, nausea, loss of appetite, weight loss	NR	Recovery	NR	NR	NR
Zanelli 2017[20]	F/54	NR/13 y	NR	10	Chronic watery diarrhoea	NR	Recovery	NR	NR	NR
Losartan										
Ghosh 2016[22]	M/63	25/NR	NR	NR	Chronic diarrhoea	NR	Partial recovery	1 mo	Myelofibrosis	NR
Mazhar 2017[25]	M/67	100/>3 y	NR	9	Chronic diarrhoea	NR	Recovery	2 wks	Unresponsive to anti-motility agents, ciprofloxacin, metronidazole	Yes
Montoro De Francisco 2018[15]	F/77	100/10 y	10 y	NR	Chronic non-bloody diarrhoea worsening after 6 y, abdominal pain/bloating, weight loss	Unresponsive to a GF diet	Recovery	2 wks	Unresponsive to antibiotic and corticosteroid treatment	Yes
Montoro De Francisco 2018[15]	F/81	100/3 y	3 y	NR	Chronic non-bloody diarrhoea, worsening after 1 y, abdominal pain/bloating, weight loss	Unresponsive to a GF diet	Recovery	4 wks	Unresponsive to antibiotic and corticosteroid treatment	Yes

(Continues)

TABLE 2 (Continued)

Study	Sex/age (y)	ARB dose (mg/day)/ treatment duration	Time between ARB intake and onset of symptoms	Weight loss (kg)	GI symptoms and related conditions	Clinical response to dietary modifications	Clinical response to ARB withdrawal	Time between ARB withdrawal and clinical recovery	Concomitant diseases/other information	Hospitalisation due to SLE symptoms
Negro 2015[21]	M/67	50/3 y	>2 y	11	Chronic non-bloody diarrhoea	NR	Recovery	1 wk	–	Yes
Sawant 2017[23]	M/42	–/NR	NR	NR	Diarrhoea, persistent abdominal pain, bloating, weight loss	NR	Recovery	Short time lapse	Cystic fibrosis, pancreatic insufficiency, lung transplantation	NR
Van Gils 2017[24]	M/56	50/2 y	21 mo	14	Frequent fatty diarrhoea, nausea	Unresponsive to a GF diet	Recovery	Short time lapse	Budesonide administered for >2 mo; weight gain	NR
Telmisartan										
Alzueta 2020[29]	F/80	40/5 y	>3 y	3	Non-bloody diarrhoea, abdominal pain	NR	Recovery	1 mo	Diabetes mellitus, dyslipidaemia, aortic stenosis, asthmatic bronchitis, osteoporosis, history of breast cancer	Association of ARB intake and enteropathy: *possible* (Naranjo scale); *probable* (Karch Lasagna and WHO–UMC criteria)
Cyrany 2014[26]	F/71	40/2 mo	NR	NR	Diarrhoea and weight loss leading to hospitalisation with renal failure	Not done	Recovery	Short time lapse	–	Yes
Mandavdhare 2017[27]	F/45	40/1 y	4 mo	10	Chronic diarrhoea	NR	Recovery	Short time lapse	Hypothyroidism, chronic kidney disease (improved following ARB cessation)	NR
Negro 2017[28]	M/52	40/3 y	30 mo	7	Chronic non-bloody diarrhoea, abdominal discomfort, fatigue, nausea, loss of appetite	Not done	Recovery	1 wk	Post-adrenalectomy for adenoma. Weight gain after 5 mo	Yes
Valsartan										
del Val 2018[31]	M/77	80/3 y	1 y	9	Chronic diarrhoea, abdominal discomfort	NR	Recovery	Few wks	Diabetes mellitus, chronic ischaemia	NR

(Continues)

TABLE 2 (Continued)

Study	Sex/age (y)	ARB dose (mg/day)/ treatment duration	Time between ARB intake and onset of symptoms	Weight loss (kg)	GI symptoms and related conditions	Clinical response to dietary modifications	Clinical response to ARB withdrawal	Time between ARB withdrawal and clinical recovery	Concomitant diseases/other information	Hospitalisation due to SLE symptoms
Herman 2015[30]	F/71	NR/NR	NR	27	Abdominal pain, nausea, vomiting and diarrhoea, muscle wasting, minimal adipose tissue	Unresponsive to a GF diet; negative gluten challenge after ARB withdrawal	Recovery	Several wks	Rheumatoid arthritis, hypothyroiditis, psoriasis, lower extremity oedema. Unresponsive to antibiotic treatment	NR
Zanelli 2017[20]	M/85	NR/3 y	NR	NR	Chronic watery diarrhoea, dehydration, weight loss	NR	Recovery	NR	NR	NR
Zanelli 2017[20]	F/83	NR/10 y	NR	NR	Chronic non-bloody diarrhoea, loss of appetite, weight loss, physical decay	NR	Recovery	NR	NR	NR

Abbreviations: ARB, angiotensin receptor blockers; F, female; GF, gluten-free; GI, gastrointestinal; M, male; mo, months; NR, not reported; SLE, sprue-like enteropathy; wks, weeks; y, years.

TABLE 3 Histological and serological data of patients

Study	Sex/age (y)	Coeliac disease serology[a]	HLA-DQ2/ HLA-DQ8 genotyping	Duodenal histology at diagnosis	Colon histology	Endoscopic findings	Laboratory findings	Workup for infective/ parasitic/ autoimmune aetiology	Histology after withdrawal
Candesartan									
Mondet 2016[16]	M/81	Negative	NR	Inflammation without VA; appearance of VA after 8 y	Colonic mucosal atrophy, crypt atrophy, oedema, stromal fibrosis after 8 y	Diverticulitis on colonoscopy; gastroduodenal endoscopy normal	Colonic exudative inflammation, hypoalbuminaemia	Negative infective workup	Marked regression of atrophy 3 mo after withdrawal
Eprosartan									
Maier 2015[17]	F/83	Negative	NR	Severe VA with IELs and eosinophilic granulocytes	NR	NR	NR	Negative for AIE	Partial improvement in mucosal architecture at 3 and 6 mo
Irbesartan									
Cammarota 2014[18]	F/80	Negative	Negative/ negative	Complete VA	NR	NR	NR	Negative infectious and autoimmune workups	Recovery of duodenal villi at 3 mo
Marthey 2014[19]	F/54	Negative	Negative/ negative	Complete VA	NR	NR	NR	Anti-enterocyte antibodies negative	NR
Zanelli 2017[20]	M/78	Negative	NR	Not performed	Collagenous colitis, increased IELs	NR	Mild renal failure	NR	NR
Zanelli 2017[20]	F/54	Negative	NR	Not performed	Mild chronic non-specific colitis	NR	NR	NR	NR
Losartan									
Ghosh 2016[22]	M/63	Negative	NR	Focused VA, increased IELs, shortening of crypts	NR	NR	No occult blood	Negative parasitic workup	NR
Mazhar 2017[25]	M/67	NR	NR	Marked VA and increased IELs	NR	NR		Negative infectious, inflammatory, absorptive, autoimmune workup	Complete resolution of VA at 3 mo

(Continues)

TABLE 3 (Continued)

Study	Sex/age (y)	Coeliac disease serology[a]	HLA-DQ2/ HLA-DQ8 genotyping	Duodenal histology at diagnosis	Colon histology	Endoscopic findings	Laboratory findings	Workup for infective/ parasitic/ autoimmune aetiology	Histology after withdrawal
Montoro De Francisco 2018[15]	F/77	NR	NR	NR	Microscopic colitis	NR	Negative allergological studies for food	NR	NR
Montoro De Francisco 2018[15]	F/81	NR	NR	NR	Microscopic colitis	NR	Negative allergological studies for food	NR	NR
Negro 2015[21]	M/67	Negative	Negative/ negative	Total VA and inflammation of the lamina propria	NR	NR	Anaemia, hypoalbuminaemia, low Fe, K, Ca, P, total/ HDL cholesterol, triglycerides; no occult blood	Negative infective, parasitic workups	Partial and complete restoration of villous architecture at 3 and 11 mo respectively
Sawant 2017[23]	M/42	Negative	NR	Partial VA	NR	NR	NR	Negative infective, parasitic workups	Histological improvement following ARB withdrawal
Van Gils 2017[24]	M/56	Negative	Positive/ positive	Subtotal VA with IELs	NR	NR	NR	Anti-enterocyte antibodies negative	Rapid recovery of villi at 5 mo follow-up despite the cessation of budesonide therapy and the gluten-free diet.
Telmisartan									
Alzueta 2020[29]	F/80	Not performed	NR	Not performed	NR	NR	NR	NR	NR
Cyrany 2014[26]	F/71	Negative	NR	Severe VA with IELs, severe inflammatory infiltration, subepithelial collagen deposits in gastric samples	Subepithelial hyaline band	Duodenoscopy normal; focally erythematous colonic mucosa with exudate	NR	Negative infectious workup	Histology of ileum and colon normalised within 7 mo
Mandavdhare 2017[27]	F/45	Negative	NR	Subtotal VA, increased IELs, crypt hyperplasia	NR	Typical scalloping and grooving with nodularity	Anaemia, elevated leukocytes, hypoalbuminaemia, normal liver function	Negative infectious and parasitic workup	Normal duodenal folds within 4 mo

(Continues)

TABLE 3 (Continued)

Study	Sex/age (y)	Coeliac disease serology[a]	HLA-DQ2/ HLA-DQ8 genotyping	Duodenal histology at diagnosis	Colon histology	Endoscopic findings	Laboratory findings	Workup for infective/ parasitic/ autoimmune aetiology	Histology after withdrawal
Negro 2017[28]	M/52	Negative	Negative/ negative	Subtotal VA and inflammation of the lamina propria	Moderate inflammatory infiltrate with eosinophilia	NR	No significant laboratory abnormalities; no occult blood	Negative infectious, parasitic workups	Progressive duodenal recovery apparent at 3 mo
Valsartan									
del Val 2018[31]	M/77	Negative	NR	Partial VA, increased IELs, crypt hyperplasia	Diverticulosis, tubulovillous polyps (resected), microscopic colitis excluded	Complete gastric metaplasia	Anaemia, elevated CRP	Negative infectious and inflammatory workups	VA resolved by 6 mo but increased IELs and crypt hyperplasia were still found
Herman 2015[30]	F/71	Negative	positive/ positive	Complete VA, IELs and crypt hyperplasia	Diffuse small bowel dilatation, mesenteric adenopathy, biliary dilatation	Scalloping, blunted villi, classic sprue-like appearance of the mucosa	Blood and stool tests predictive of severe malabsorption, normalisation of anaemia, transaminase and macro/micro nutrients in follow-up after ARB withdrawal	Negative infectious workup	Normalisation of villous architecture apparent at 1 y follow-up
Zanelli 2017[20]	M/85	Negative	NR	Mild VA, increased IELs	Acute eosinophilic colitis	NR	Metabolic acidosis, hypokalaemia, severe renal failure	NR	NR
Zanelli 2017[20]	F/83	Negative	NR	NR	Collagenous colitis, increased IELs	NR	Hypokalaemia, hyponatraemia, anaemia	NR	NR

Abbreviations: AIE, autoimmune enteropathy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; F, female; HDL, high-density lipoprotein; IELs, intraepithelial lymphocytosis; IgA, immunoglobulin A; M, male; mo, months; NR, not reported; VA, villous atrophy; y, years.

[a]Tissue transglutaminase antibodies and/or endomysial antibodies.

in 21 patients. All 21 patients included in the analysis presented with severe intestinal symptoms following the intake of one of the ARBs. In 10 patients, significant weight loss in addition to severe diarrhoea was reported. All had other unspecific abdominal symptoms. The clinical picture was similar to the one reported in association with olmesartan. Sprue-like intestinal abnormalities were found adequately documented in biopsy samples from 14 of the 21 patients. The histological changes include severe and complete villous atrophy, focal villous atrophy, small intestinal inflammation characterised by increased intraepithelial lymphocytosis (IEL), and shortening and hyperplasia of crypts. In a single case,[26] apart from duodenal villous atrophy, collagenous bands were described in the gastric biopsy samples, which sometimes is also found in sprue-like olmesartan-associated enteropathy. The onset of clinical intestinal manifestations after ARB treatment initiation was highly variable, ranging from 2 months to several years (up to 10 years). Most patients used the recommended dose of ARBs, but was not reported in some patients exposed to candesartan (n = 1), irbesartan (n = 4), losartan (n = 1) and valsartan (n = 2).

The association of enteropathy with other potentially harmful drugs was excluded in all cases of SLE associated with different ARBs, as was pre-existing coeliac disease ruled out by negative transglutaminase antibodies in all 17 of the 21 patients who underwent serological testing. The HLA-DQ2/HLA-DQ8 genotype for susceptibility to coeliac disease was reported in two of six patients tested which is, however, not dissimilar to that in the general population.

The strongest evidence for the causal relationship between ARB treatment and SLE is provided by the recovery/resolution of clinical symptoms following ARB withdrawal in all patients studied. Incomplete clinical recovery in a few patients is most likely due to short follow-up periods. It is worth mentioning that complete clinical recovery occurred rapidly within 2-4 weeks after termination of ARB treatment. Histological examinations at follow-up were reported in 11 of 21 cases, showing that rapid resolution occurred in all cases and was usually observed 3 months after ARB withdrawal. In addition, Zanelli et al. reported six cases of collagenous-like colitis (including acute eosinophilic colitis in two cases) associated SLE induced by ARBs other than olmesartan.[20] In all cases, the SLE, as well as the associated condition of collagenous colitis, was reversible on withdrawal of the ARB. In none of these cases was additional therapy required. These observations provide evidence that the clinical and histological characteristics of SLE associated with olmesartan and other ARBs are comparable.

SLE with ARBs other than olmesartan has also been described in the context of previous olmesartan case reports. In a Mayo Clinic case series on the association of SLE and olmesartan intake (n = 35), many patients were susceptible to coeliac disease according to HLA-DQ2 genotype, and three patients who presented with clinical symptoms similar to olmesartan-associated SLE were on other ARBs (ie irbesartan, valsartan and telmisartan).[32] In another case report of a patient who developed SLE during olmesartan treatment, intestinal symptoms continued even after olmesartan had been replaced with a different ARB.[33] It is notable that, in this patient, clinical recovery was seen only after discontinuation of the alternate ARB,[33] which lends support to the argument that SLE is a class effect.

Although only a small number of SLE cases with ARBs other than olmesartan have been reported to date, the available evidence suggests a class effect. A further indication for this comes from a retrospective study in patients with abdominal pain who underwent upper gastrointestinal endoscopy with duodenal biopsies. In this cohort, no statistically significant differences were found for any single histopathological abnormality between olmesartan and users of other ARBs.[34] In this context, it needs to be stressed that the incidence of any type of ARB-induced SLE is rare. In an endoscopic database, no association with SLE was found for olmesartan or other ARBs.[35] Furthermore, the absence of an increased risk of severe villous atrophy (Marsh grade 3) in patients with a prior record of ARB use was reported from a retrospective Swedish case-control study based on nationwide, including histopathology, registries.[36] It should be noted that olmesartan is not available in Sweden, and its use was not examined in the study.

The pathogenetic mechanisms of SLE related to ARB treatment remain uncertain. No dose dependency suggestive of a toxic drug effect was reported for olmesartan or for other ARBs. To make the picture even more complicated, patients with ARB-related SLE sometimes have involvement of the colonic mucosa with features of microscopic/collagenous colitis, quite distinct from the classical symptoms of coeliac disease. In contrast, some patients with olmesartan-related SLE present with the HLA-DQ2/8 genotype,[32] which indicates susceptibility to coeliac disease and increased vulnerability to immune-mediated damage. In the case reports described here, two of the six patients on an ARB who underwent genetic testing had an HLA genotype indicating susceptibility to coeliac disease. From these observations, it can be speculated that genetic susceptibility may be a facilitator of ARB-associated SLE, but it is certainly not a sine qua non. However, this does not exclude the possible coexistence of both conditions in individual patients. In the case reports reviewed here, coeliac disease as a confounder for ARB-associated SLE was excluded not only due to lack of specific markers but also the fact that clinical and histological recovery was achieved only after ARB cessation and not after specific dietary intervention.

Initial clinical reports on olmesartan-related SLE prompted several retrospective population-based studies to assess its relevance, mainly by measuring the risk of hospitalisation with a diagnosis of coeliac disease or a diagnosis of unspecified malabsorption in patients initiating treatment with ARBs. These studies had conflicting results: a French study[4] and a US study[5] highlighted an increased risk of severe intestinal malabsorption in patients treated with olmesartan in comparison with other ARBs while a pooled analysis of two large cohorts of patients obtained from Italian and German databases[6] and a study conducted in South Korea[37] did not confirm such previous findings. All these studies agreed on the very low frequency of severe SLE in patients treated with ARBs. The significance of findings from these studies is debatable, as relative risk calculations were based on a small number of cases and partially lacked adjustment for potential confounders.

5 | CONCLUSION

The evidence from the clinical cases presented in this review suggests that SLE is not restricted to olmesartan alone but can also occur with other ARBs, and thus it should be considered a class effect. The paucity of data for SLE related to 'other' ARBs is likely to be due to the rare incidence of severe enteropathy cases with this class of drugs in general. The fact that more cases are reported with olmesartan may be consequent to the likely bias associated with 'first come, first served' (or 'notoriety effect').[38]

In clinical practice, physicians should be aware of the rare but possible cause of SLE induced by ARBs. This will facilitate the diagnosis of ARB-induced SLE without delay and the subsequent implementation of proper treatment. Withdrawal of the ARB usually achieves a rapid resolution of clinical symptoms and reversal of intestinal damage.

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AUTHORSHIP

Guarantor of the article: Peter Malfertheiner.

Author contributions: PM undertook the study concept and design and was involved in the acquisition, analysis and interpretation of the data, drafted and critically revised the manuscript for important intellectual content and approved the final draft. CF performed the bibliographic research and approved the final draft.

ETHICAL CONSIDERATIONS

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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