Olmesartan-induced enteropathy treated with budesonide

S. Kempenaers[1], J. Bogaert[2], M. De Maeyer[2], P. Van Hauthem[2], M. Ramael[3,4], P. Schoeters[2]

(1) Faculty of Medicine, University of Leuven, 3000 Leuven, Belgium ; (2) Department of Gastroenterology, AZ Herentals, 2200 Herentals, Belgium ; (3) Department of Pathology, AZ Herentals, 2200 Herentals, Belgium ; (4) Department of Cytology and Histology, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium.

Abstract

Olmesartan, an angiotensin receptor blocker, is a widely spread antihypertensive drug. Seronegative villous atrophy of the small intestine due to olmesartan use was first described in 2012. We present a new case of olmesartan-induced enteropathy and compare it to recent literature. This case might suggest a use of budesonide for treatment. (Acta gastroenterol. belg., **2019**, 82, **319-321**).

Key words : seronegative villous atrophy, olmesartan-induced, olmesartan-associated, sprue-like, enteropathy.

Introduction

Olmesartan medoxomil, a nonpeptide angiotensin II receptor antagonist developed in 1995 by Sankyo (1) and first approved in 2002 by the Food and Drug Administration (FDA) (2), is a widely used antihypertensive drug. The angiotensin receptor blockers are especially useful in patients treated for hypertension with an intolerance to angiotensin-converting enzyme inhibitors and one of the following conditions: left ventricular hypertrophy, microalbuminuria, renal dysfunction, previous myocardial infarction, heart failure, end-stage renal disease, metabolic syndrome and diabetes mellitus (3). Olmesartan has a good safety profile with only very few patients reporting adverse effects like dizziness, vertigo or oedema (4). Furthermore, it seems to be more cost-effective than other angiotensin receptor blockers (5).

Villous atrophy of the small intestine is a histological manifestation most commonly associated with celiac disease. The diagnosis is apparent when the triad is completed with the classical presentation of diarrhoea and weight-loss (6). However, when serological testing for anti-transglutaminase IgA antibody is negative and there is no resolution of diarrhoea under a strict gluten-free diet, a case of villous atrophy not attributable to celiac disease is present. A recent UK-based prospective study (7) found 39% of such cases attributable to an infection, 25% to an inflammatory/immune-mediated disorder and 9% to drugs. 26% of cases remained unexplained.

Olmesartan as a cause of villous atrophy was first described by Rubio-Tapia in 2012 (8). In 2013, the FDA approved changes to the labels of these drugs to include this concern (9). Since then, a limited number of similar cases have been reported worldwide and only a few review studies were conducted.

In this article, we present you a new case of olmesartan-induced enteropathy.

Case report

A 57-year old man with a history of gout, arterial hypertension and abuse of nicotine and ethyl presented at our gastroenterology department with vomiting and diarrhoea for at least 6 months causing a major weight loss of 30 kg. Physical examination was unremarkable. Blood exam revealed normochromic normocytic anaemia, leukopenia, inflammatory parameters (high CRP and ferritin), folic acid deficiency and hypoalbuminemia. A stool sample was negative for Salmonella, Campylobacter, Aeromonas, Yersinia, Shigella, Clostridium toxin and parasites. On upper endoscopy, a marked atrophy of the duodenum was noted and biopsies showed subtotal villous atrophy, an oedematous lamina propria with a dense infiltrate and an increase in intraepithelial lymphocytes (Figure 1a). Colonoscopy findings were normal. An additional blood sample was taken and anti-transglutaminase IgA antibody was negative. The presumptive diagnosis of serology-negative celiac disease was made and the patient was treated with a gluten-free diet.

Three weeks later, the patient presented again at our department with further diarrhoea and weight loss with fatigue and weakness despite a strict gluten-free diet. New biopsies showed an unchanged histopathological image. The patient was hospitalized for further investigations. Current medications were olmesartan 20 mg, calcium/cholecalciferal 500/400 mg/IE, folic acid 0,4 mg and pantoprazole 40 mg daily. After careful review of the literature, we assumed that the enteropathy might be secondary to the use of olmesartan, which the patient had been taking for over 4 years. Olmesartan was stopped and the patient was put on total parenteral nutrition. There was an amelioration of symptoms, but no full recovery was noted. On the 11th day of hospitalisation, we started budesonide 9 mg daily. Full recovery was made and the patient was discharged on the 18th day. Budesonide was

Correspondence to : Patrick Schoeters, M.D., .Department of Gastroenterology , AZ Herentals, Nederrij 133, B-2200 Herentals, Belgium
E-mail : patrick.schoeters@azherentals.be

Submission date : 27/04/2017
Acceptance date : 13/09/2017

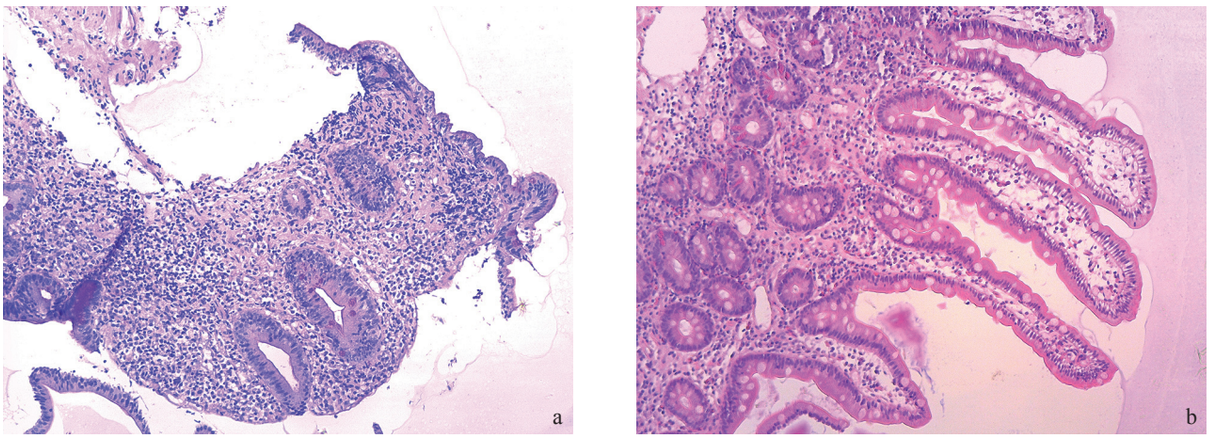

Figure 1. — Histological images before (a) and 6 months after (b) cessation of olmesartan therapy. (a) shows villous atrophy (magnification 100x, periodic acid-Schiff stain) while (b) shows partial recovery of duodenal villi (magnification 100x, haematoxylin-eosin stain).

continued in a withdrawal scheme for 15 weeks. We saw the patient 2 weeks and 9 weeks after hospitalisation. Stools normalised and weight gain was noted. 6 months after the start of budesonide treatment we performed a follow-up upper endoscopy. Histopathological analysis showed partial recovery of duodenal villi (Figure 1b).

Discussion

Olmesartan-induced enteropathy is a novel and rare finding with only a limited number of case reports, clinical trials and reviews available. Although, a French nationwide observational cohort study showed that olmesartan is associated with an increased risk of hospitalisation for intestinal malabsorption and coeliac disease in comparison with angiotensin-converting enzyme inhibitors and other angiotensin receptor blockers (10).

As compared to a review study by Ianiro G. in 2014 on 54 cases (11), the case we presented here has rather typical findings of olmesartan-induced enteropathy. Our patient had been treated with olmesartan for some years when this occurred. Typical findings on presentation were diarrhoea and weight loss. Less typical but still common findings were fatigue and vomiting. Common blood test findings were normochromic normocytic anaemia and hypoalbuminemia. Anti-transglutaminase IgA antibody was negative in our case as in all cases reported. Histopathological examination showed subtotal villous atrophy, which was also a finding reported in almost all cases. Misdiagnosis with coeliac disease and administration of a gluten-free diet without improvement of symptoms happened in almost eighty percent of all cases. Cessation of olmesartan resulted in the resolution of diarrhoea in all cases and the majority reported weight gain after cessation. Like the other cases reported, our patient did respond to steroid treatment.

Although the underlying mechanisms of olmesartan-induced enteropathy are still uncertain, some theories have been proposed like a pro-apoptotic effect through the AT2 receptor on intestinal epithelial cells or a cell-mediated immune response through induced gene expression of transforming growth factor (TGF)-beta by olmesartan (11,12). As a proven very potent glucocorticoid with a favourable safety profile in the treatment of Crohn's disease (13), it is plausible to assume that budesonide has a positive effect on the healing of olmesartan-induced enteropathy due to its immunosuppressive and anti-inflammatory effects. This might explain the accelerated cessation of symptoms, like diarrhoea and weakness, we noted after starting budesonide.

In conclusion, when confronted with a case of seronegative villous atrophy not resolving under a gluten-free diet, the gastroenterologist should broaden his differential diagnosis to drug-induced enteropathy. Special attention should be given to olmesartan use, as more and more cases of olmesartan-induced enteropathy are being reported worldwide and the seriousness of the diarrhoea and weight loss prompts urgent discontinuation of olmesartan. Furthermore, this particular case might suggest the use of budesonide treatment to accelerate recovery of olmesartan-induced enteropathy.

References

1. MIZUNO M., SADA T., IKEDA M., FUKUDA N., MIYAMOTO M., YANAGISAWA H., *et al.* Pharmacology of CS-866, a novel nonpeptide angiotensin II receptor antagonist. *Eur J Pharmacol*., 1995, **285(2)** : 181-8.
2. FDA. Drug Approval Package for Benicar (Olmesartan Medoxomil) Tablets: U.S. Department of Health and Human Services; 2002 [Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-286_Benicar.cfm.
3. MANCIA G., FAGARD R., NARKIEWICZ K., REDON J., ZANCHETTI A., BOHM M, *et al.* 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press,* 2014, **23(1)** : 3-16.
4. KUMBLA D.K., KUMAR S., REDDY Y.V., TRAILOKYA A., NAIK M. Win over study : Efficacy and safety of olmesartan in Indian hypertensive patients: results of an open label, non-comparative, multi-centric, post marketing observational study. *Indian Heart J*., 2014, **66(3)** : 340-4.
5. KOURLABA G., GIALAMA F., TSIOUFIS K., MANIADAKIS N. A literature review to evaluate the clinical and economic value of olmesartan for the treatment of hypertensive patients. *Int J Cardiol*., 2016, **221** : 60-74.

6. ELLI L., BRANCHI F., TOMBA C., VILLALTA D., NORSA L., FERRETTI F., *et al.* Diagnosis of gluten related disorders: Celiac disease, wheat allergy and non-celiac gluten sensitivity. *World J Gastroenterol*., 2015, **21(23)** : 7110-9.
7. AZIZ I., PEERALLY M.F., BARNES J.H., KANDASAMY V., WHITELEY J.C., PARTRIDGE D., *et al.* The clinical and phenotypical assessment of seronegative villous atrophy; a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000-2015). *Gut*, 2016.
8. Rubio-Tapia A., Herman M.L., Ludvigsson J.F., Kelly D.G., Mangan T.F., Wu T.T., *et al.* Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*., 2012, **87(8)** : 732-8.
9. FDA. FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil : U.S. Department of Health and Human Services; 2013 [Available from: http://www.fda.gov/Drugs/DrugSafety/ucm359477.htm.
10. BASSON M., MEZZAROBBA M., WEILL A., RICORDEAU P., ALLEMAND H., ALLA F., *et al.* Severe intestinal malabsorption associated with olmesartan : a French nationwide observational cohort study. *Gut*, 2016, **65(10)** : 1664-9.
11. IANIRO G., BIBBO S., MONTALTO M., RICCI R., GASBARRINI A., CAMMAROTA G. Systematic review : Sprue-like enteropathy associated with olmesartan. *Aliment Pharmacol Ther*., 2014, **40(1)** : 16-23.
12. TRAN T.H., LI H. Olmesartan and drug-induced enteropathy. *P t.,* 2014, **39(1)** : 47-50.
13. CAMPIERI M., FERGUSON A., DOE W., PERSSON T., NILSSON L.-G. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. *Gut*, 1997, **41(2)** : 209-14.