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Review Article

Severe Olmesartan related enteropathy - a case report and literature review

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Abstract

Olmesartan drug-induced enteropathy was first reported 10 years ago. Its physiopathology remains largely unknown and its evocation facing diarrhea is still not systematic, especially in cases of acute and severe diarrhea episodes. In this paper, we report the case of a 71-year-old woman presenting with acute diarrhea associated with complete duodenal mucosal villous atrophy with lymphocytic infiltration. Due to disease severity organ failure will occur and admission to intensive care unit is required for renal replacement therapy. After an exhaustive diagnostic procedure, the long-prescribed Olmesartan was incriminated and discontinued. The diagnosis of coeliac disease was excluded after a negative HLA DQ2-DQ8 genotyping. Clinical and pathological evolution at 3 months was favorable after stopping Olmesartan.

The aim of this case study is to highlight the acute presentation inducing a life-threatening condition of Olmesartan related enteropathy, which is rare and still little-known among general practitioners. We also discuss the pathophysiology of this disease, as applied to the clinical case presented.

Keywords: Olmesartan, Drug-induced enteropathy, Organ failure, Acute diarrhea, Case Report

Introduction

Olmesartan (C24H26N6O3, developed around a common imidazole-based structural core) is an angiotensin II receptor antagonist, a class of drugs widely used to treat hypertension. It is used alone (10-20 mg or 40 mg tablets) or in combination with other antihypertensive treatments. The marked antihypertensive efficacy of Olmesartan may result from a unique pharmacological interaction of the drug with the AT1 receptor, resulting in a potent, long-lasting, dose-dependent blockade of angiotensin-II [1]. Olmesartan produces selective, insurmountable inhibition of the AT1 receptor and displays no AT2 receptor activity resulting in vasodilatation, decreased aldosterone and catecholamine production leading to reduced blood pressure. Olmesartan is next metabolized in the liver by the OATP1B1 and OATP1B3 transporters and excreted in the bile by MRP2 [2]. Marketed in Europe in 2003, it is only in 2012 in the United States that Olmesartan induced enteropathy was first described [3]. Enteropathy occurs in both men and women, with an average age of 68, with sex-ratio 1:1. This disease is characterized by secondary diarrhea induced by full duodenal mucosal villous atrophy with lymphocytic infiltration. Clinically, the disease leads to an important weight loss (average 18 kg), nausea with or without vomiting, abdominal pain, bloating and/or fatigue. These symptoms typically appear months or even years after Olmesartan uptake. To date over 500 cases have been described worldwide but only some severe acute kidney injuries have been reported by Roca-Argente et al. [4] and none of them were treated with dialysis therapy.

Several hypotheses have been put forward to explain this digestive toxicity, which remains unknown to this day. A particular HLA profile, a reaction mediated by cellular immunity or AT1 receptor saturation leading to AT2 receptor activation in the digestive tract are 3 non-exclusive theories that seek to explain the origin of enteropathy. In addition, reduced activity of the transporters (OATP1B1 and OATP1B3) responsible for the degradation of Olmesartan by other drugs, like statins, could increase its toxicity.

The aim of this case study is to highlight the acute presentation inducing a life-threatening condition of Olmesartan related enteropathy, which is rare and still little-known among general practitioners. We also discuss the pathophysiology of this disease, as applied to the clinical case presented. Lastly, given the serious side-effects compared with other drugs in the same class, we propose that the drug should discontinue to be reimburse in countries where this is still the case.

Case Report

A 71-year-old Caucasian woman was referred to the emergency department for 10 days of watery diarrhea unresponsive to symptomatic treatment and responsible for clinical and biological dehydration, with no other associated complaints or weight loss. Her history included hypertension treated with a combination of Olmesartan (40 mg) and hydrochlorothiazide (25 mg) 1x/day for over 5 years, epilepsy treated with depakine and phenobarbital, and hypercholesterolemia treated with simvastatin (40 mg) 1x/d. She had no addictions or allergies. She had been vaccinated against COVID-19 2 months previously (AstraZeneca) and reported a change of statin 4 months prior to admission (formerly Rosuvastatin). The full clinical examination on arrival did not reveal anything, including abdominal examination.

Admission biology showed acute renal failure (KDIGO 2 with creatinine 3.76 mg/dL, urea 120 mg/dL), hypokalemia 3 mmol/L, no inflammatory syndrome (CRP 26 mg/dL), a falsely normal albumin due to dehydration (37 g/L) and no vitamin deficiency. Blood count, liver, and thyroid function tests (TSH, T3, and T4) were normal. The initial complementary investigations included a negative bacteriological card with coprocultures, a parasitological examination of the stools and urinary cytobacteriology, a blank abdominal CT scan revealing no cause and a complete endoscopic examination (gastro-duodenoscopy and ileo-colonoscopy) showing no macroscopic abnormalities. The initial laboratory work-up included a negative celiac serologies (anti-transglutaminase IgA, anti-gliadin IgG) without total IgA deficiency and serologies for cytomegalovirus, Epstein-Barr virus, hepatitis A, B and C viruses and human immunodeficiency virus, all of which were negative. Pathological examination of gastro-duodenal biopsies revealed marked duodenal villous atrophy with significant intraepithelial lymphocytosis (>100 lymphocytes/100 enterocytes) and chronic *Helicobacter pylori* gastritis. There were no ileocolic microscopic abnormalities. The workup was completed by a negative autoimmune workup (anti-nuclear, anti-neutrophil cytoplasmic antibodies, anti-*Saccharomyces cerevisiae*, anti-enterocytes antibodies), fecal calprotectin at 177 µg/g, i.e. an intermediate level, 72-hour stool collection showing no steatorrhea, VIP assay (30 ng/L, norm: <101), gastrin (32 pg/mL, norm <100) and chromogranin A (101.6 µg/L, norm <101.9) negative. A subcutaneous biopsy showing no amyloidosis, a negative tuberculin intradermal reaction and a negative HLA DQ2/DQ8 typing were also performed.

Despite copious intravenous hydration (3L/24H), renal function deteriorated (ARF KDIGO 3 - creatinine 5.56 mg/dL), necessitating intensive care unit treatment with continuous veno-venous hemofiltration (CVVH), vasopressor (Levophed) and inotropic (Dobutamine) support. In this context, Olmesartan treatment was discontinued. On rereading the anatomopathology of the duodenal swabs, celiac disease was suspected, prompting the introduction of a gluten-free diet which improved the diarrhea until it ceased, with normalization of renal function, allowing the patient to return home. At 3 months post-hospitalization, the patient no longer complained of diarrhea and even noted a tendency towards constipation. Follow-up duodenal biopsies showed duodenal mucosa within normal limits, with no villous atrophy. Excluding the diagnosis of seronegative celiac disease due to the absence of compatible HLA, the patient was offered the possibility of reintroducing gluten; for the time being, she prefers to continue on a gluten-free diet.

Discussion

Chronic enteropathies characterized by villous atrophy and negative coeliac serology represent a group of heterogeneous conditions (including autoimmune enteropathy, seronegative celiac disease and Olmesartan induced enteropathy, see **Appendix 1**) often with a poor prognosis, and for which diagnostic challenges are common [5]. Autoimmune enteropathy needs IgA/IgG positive enterocyte antibodies (indirect immunofluorescence on human/monkey jejunum) to be confirmed while Olmesartan induced enteropathy and coeliac disease are similar clinically and anatomopathologically. Both pathologies present chronic diarrhea with associated long-term weight loss and are characterized by subtotal or total villous atrophy with an increase in intra-epithelial lymphocytes on anatomopathological analysis of duodenal biopsies [3,6]. We may also encounter more acute forms, with no weight loss at the onset of diarrhea, which may delay the diagnosis, as was the case with our patient. In the presence of a clinico-pathological picture suggestive of celiac disease with negative serology and in the presence of Olmesartan, the possibility of Olmesartan induced enteropathy should be systematically evoked. We present a comparative table of both pathologies to help clinicians make difference between them and make the right diagnosis (**Appendix 2**).

In our case, celiac serology and anti-enterocyte antibodies were negatives, and the anatomopathologist confirmed villous atrophy and noted the absence of arguments for infectious pathology (Whipple, giardiasis), neoplastic or inflammatory pathology, collagen sprue, or common variable immune deficiency (CVID), without making a specific diagnosis. During the drug review, Olmesartan treatment was highlighted and already suspended due to hypotension in the context of hypovolemic shock. An HLA DQ2-DQ8 genotyping test was requested, so as not to exclude seronegative celiac disease [4], given the severity of the pathology and the gluten-rich daily diet. On review of the listed etiologies of villous-atrophy (**Appendix 1**) and taking into account the diagnostic work-up carried out, the diagnosis of enteropathy attributed to Olmesartan was retained.

Although the underlying pathophysiological mechanism remains unknown, three theories seem to have emerged. One proposes that a particular HLA profile (DQ2/DQ8) may increase the risk of dysimmunity under Olmesartan, based on a higher HLA-DQ2/DQ8 prevalence in patients developing enteropathy under Olmesartan than the general population (60-80% according to case studies vs. 30%) [3,7]. The patient did not carry a particular HLA typing and therefore had no genetic predisposition to this type of reaction.

Another hypothesis proposes a cellular immunity-mediated reaction, given the often-long delay between the start of Olmesartan treatment and the appearance of the first symptoms; 3.1 years on average and as long as 7 years [3,7]. However, no single triggering factor has yet been identified to explain the sudden intolerance to treatment. In our case, vaccination against COVID-19 two months before with Astrazeneca vaccine (non-replicating chimpanzee

recombinant DNA encoding SARS-CoV-2 glycoprotein S) was noted. The link between vaccination and autoimmunity is highly debated in the literature and has only been demonstrated in very rare cases.

Finally, given the existence of two types of angiotensin receptor expressed in the digestive tract (AT(1), involved in digestive homeostasis, and AT(2), inducing cell apoptosis), and the greater affinity of Olmesartan for AT(1), it is hypothesized that the drug saturates AT(1), allowing circulating angiotensin to bind more strongly to AT(2), leading to apoptosis of intestinal cells and consequent villous atrophy [8].

We also noted a change in lipid-lowering treatment with statins 4 months before the first symptoms. Olmesartan is metabolized in the liver by the OATP1B1 and OATP1B3 transporters and excreted in the bile by MRP2 [2]. Statins, including Rosuvastatin and Simvastatin, are known inhibitors of the OATP1B1 and OATP1B3 transporters, resulting in a decrease in the uptake of substrates of these transporters, with a consequent increase in their blood concentration and a potential increase in their side effects. This could explain the development of enteropathy in some patients on long-standing Olmesartan therapy to whom statin therapy is added. However, the inhibitory profile of the statins is different, and it is interesting to note that Rosuvastatin is a more potent inhibitor of OATP1B1 and especially OATP1B3 than simvastatin [9,10], which rules out the hypothesis of a change of statin causing the intolerance to Olmesartan in our patient. The existence of a polymorphism of the *SLCO1B1* gene, encoding OATP1B1, also showed that *SLCO1B1*15/*15* subjects tended to have higher levels of circulating Olmesartan than *SLCO1B1*1b/*1b* subjects in the presence of concomitant statin treatment [11]. These induced changes in Olmesartan pharmacokinetics have so far been poorly studied in cases of Olmesartan induced enteropathy reported in the literature and prevent us from concluding that there is a causal clinical impact.

More recently, enteropathy with other angiotensin receptor antagonists has been described, but remains much less frequent. Thus, among 248 cases reported in 2018 [12], 94% were attributed to Olmesartan (233 cases), against 5 cases with Telmisartan, 4 cases with Irbesartan, 3 cases with Valsartan and 2 cases with Losartan. Given the increased risk of enteropathy and hospitalization with Olmesartan, and its lack of proven superior efficacy compared to other drugs in the same class, France's Haute Autorité de Santé issued an unfavorable opinion on the reimbursement of Olmesartan in 2015 [13], as did other countries.

Conclusion

This clinical case highlights a severe enteropathy with organ failure on Olmesartan, in the absence of genetic predisposition. To date over 500 cases have been described worldwide but only some severe acute kidney injuries have been reported and a little of them were treated with dialysis therapy. The aim of this case study is to highlight the acute presentation inducing a life-threatening condition of Olmesartan related enteropathy, which is rare and still little-known among general practitioners. To date, the pathophysiology of this enteropathy remains unknown, although several theories exist: an HLA DQ2/DQ8 profile, a cellular immunity-mediated reaction or a AT1 receptor saturation leading to AT2 receptor activation in the digestive. In addition, we raise the question of a possible drug interaction on the transporters (OATP1B1 and OATP1B3) responsible for the degradation of Olmesartan, causing an increase in its digestive toxicity.

To conclude, it reminds us of the importance of evoking this diagnosis in the face of acute onset diarrhea, even in the absence of weight loss, and puts emphasis on the important collaboration required between pathologists and clinicians to reduce the diagnostic delay. Lastly, given the serious side-effects compared with other drugs in the same class, we propose that the drug should discontinue to be reimburse in countries where this is still the case.

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Author's Contributions

Dr Rémi Gason designed the paper. All the authors contributed to the writing and review. All authors read and approved the final version.

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