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Short Report

Five cases of sprue-like enteropathy in patients treated by olmesartan

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ABSTRACT

We describe five cases of sprue-like enteropathy during treatment with olmesartan, an angiotensin II receptor antagonist indicated for the treatment of hypertension. Patients presented severe diarrhoea, significant weight loss or dehydration, with or without intestinal villous atrophy. Clinical signs ceased upon drug discontinuation in all cases; olmesartan was reintroduced in two cases and rechallenge was positive in both. These add to the previously reported cases that led to a label change for olmesartan in the United States. However, all cases were observed in a small gastroenterology unit, which suggests that this adverse effect may not be rare. A preliminary search for the other angiotensin II receptor antagonists in the French pharmacovigilance system found severe diarrhoea and colitis, but no case with villous atrophy. Therefore, in the presence of severe diarrhoea, olmesartan or other angiotensin II receptor antagonists should be discontinued, even if the treatment has been taken for several months or years.

1. Introduction

Olmesartan is an angiotensin II receptor antagonist (ARA) indicated for the treatment of hypertension [1]. It was launched in Europe and the United States in 2002 and subsequently in Japan in 2004. Thereafter, fixed-dose combinations of olmesartan with other anti-hypertensive agents (hydrochlorothiazide, amlodipine) were made available. We describe here five cases of sprue-like enteropathy during treatment with olmesartan.

Case 1: in December 2010, an 83-year-old man was hospitalised for on-going sudden profuse diarrhoea (20 stools per day) that had started one month previously, weight loss of 5 kg, dehydration, and renal failure. A partial villous atrophy was found (grade IIIa according to modified Marsh classification [2], Fig. 1). Colonoscopy showed erosive ileitis; other etiological investigations were normal (Table S1). The patient had a history of hypertension, atrial fibrillation, coronary angioplasty and carotid stenosis, and was treated by more than 10 drugs. Outcome was favourable after discontinuation of all drugs. Later, olmesartan was reintroduced and the same day the patient was re-hospitalised for profuse diarrhoea. Olmesartan was definitely discontinued and a gluten-free diet initiated. The 6 follow-up biopsies performed two months after the second hospitalisation showed an intraepithelial lymphocytosis but no villous atrophy (Fig. 1). When gluten was reintroduced, diarrhoea did not reoccur.

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Case 2: in September 2011, a diabetic and hypertensive 82-year-old woman with multinodular goitre was hospitalised for persistent diarrhoea that had started 7 months previously, weight loss of 6 kg, and lack of response to antidiarrhoeals. Other than steatorrhea of 9 g/24 h, investigations performed were normal (Table S1). No villous atrophy was observed in biopsies. There was no response to a gluten-free test diet and to treatment with racecadotril and pancreatic enzymes. As diarrhoea was persistent, long-term olmesartan and nebivolol antihypertensive treatment was discontinued. Diarrhoea ceased within less than 5 days after drug discontinuation and did not reoccur after 2 years of follow up.

Case 3: in October 2011, a 79-year-old man with a previous history of phlebitis, hypertension, and obesity was hospitalised for asthenia, severe dehydration, renal failure, watery diarrhoea, and weight loss of 2 kg. Colonoscopy did not find microscopic colitis. Stool culture and stool *Clostridium difficile* toxin assays were negative. After discontinuation of all drugs except lercanidipine, diarrhoea ceased within 5 days. Two weeks later, olmesartan was reintroduced and the patient was re-hospitalised for profuse diarrhoea and renal failure (serum creatinine of 288 μmol/L). The gastro-colonoscopy showed a bulbar ulcer, subtotal villous atrophy

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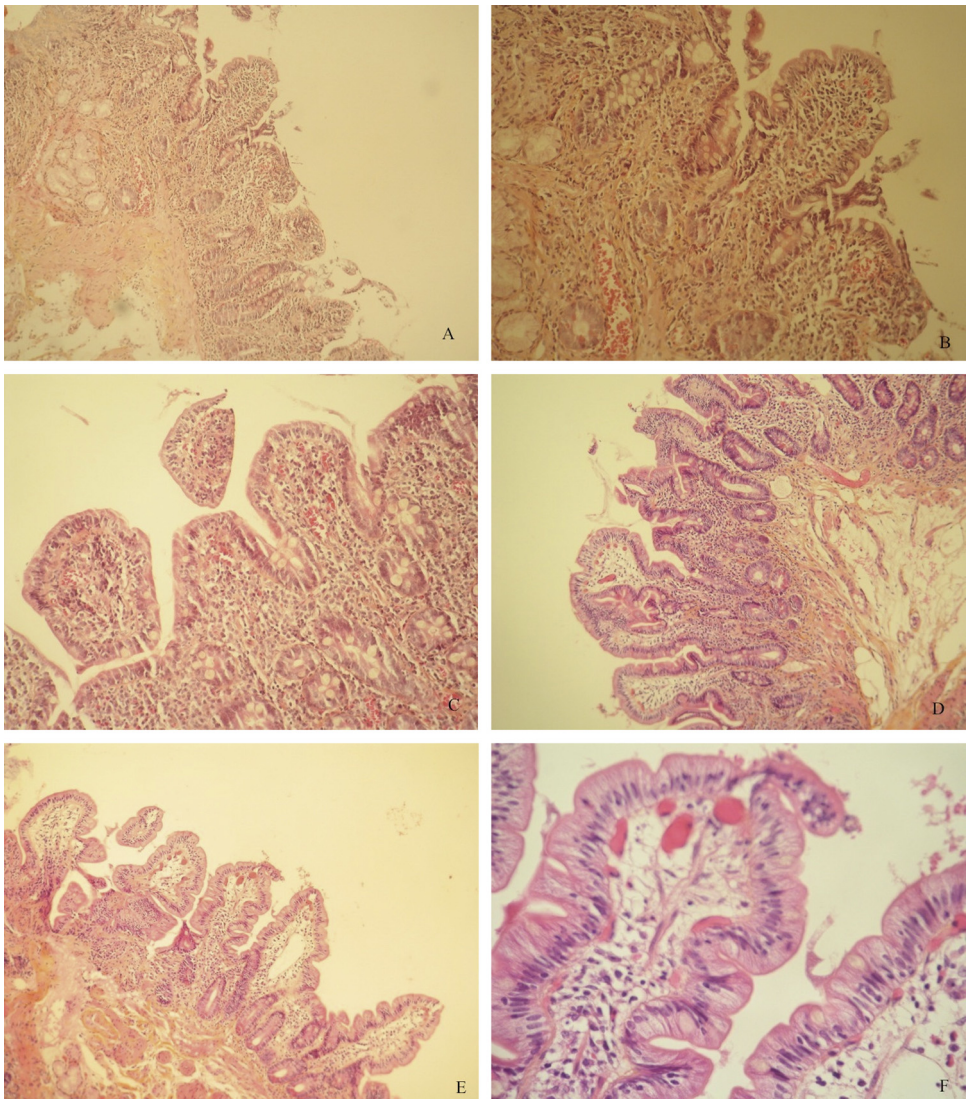

Fig. 1. Histological features of case #1. Duodenum 100× (A), 200× (B and C): partial villous atrophy (modified Marsh IIIa grade) with a villous to crypt ratio of 1, a slight increase of caliciform cells number; duodenum 100× (D and E), 400× (F): well developed villous relief, slight intraepithelial lymphocytosis.

(grade IIIb [2], Fig. 2), and two polyps; other endoscopic and histological findings were normal (Table S1). Diarrhoea ceased after polyp ablation, discontinuation of olmesartan, and initiation of a gluten-free diet. Two months later, gastroscopy showed neither ulcer, nor villous atrophy (Fig. 2). During the following months, hospitalisation for diarrhoea, hypokalaemia and renal failure was again required for this patient, who had resumed olmesartan. After definitive discontinuation of olmesartan and continuation of gluten-free diet, diarrhoea did not reoccur.

Case 4: in July 2012, an 87-year-old woman was hospitalised for profuse diarrhoea, that started 15 days previously, asthenia, dehydration, metabolic acidosis (alkaline reserve 15 mmol/L) and hypokalaemia (2.6 mmol/L). Gastroscopy showed a subtotal villous atrophy (grade IIIb [2], Fig. 3); all other etiological investigations were normal (Table S1). After discontinuation of all drugs taken for hypertension, hyperuricaemia, and arthrosis, she recovered within 24 h. Three months after hospital discharge, the patient was completely clinically recovered. Most previous treatments but not olmesartan were reintroduced thereafter without reoccurrence of diarrhoea.

Case 5: in January 2013, a 78-year-old man with previous history of hypertension, hyperuricaemia, and hypercholesterolaemia was hospitalised for mucoid diarrhoea (3–6 daily stools) and weight loss of 3 kg. Gastroscopy showed partial duodenal atrophy (grade IIIa [2], Fig. 4) with intraepithelial lymphocytosis over 30 for 100 enterocytes. Colonoscopy (10 biopsies) found non-specific congestive colitis; all other etiological investigations were normal (Table S1). Outcome was favourable only after discontinuation of the fixed-drug combination containing olmesartan. Diarrhoea did not reoccur 3 months after olmesartan discontinuation.

2. Discussion

The five cases of severe sprue-like enteropathy described here add to the series of 22 cases reported by Rubio-Tapia et al. [3] and to two recent case reports which achieved clinical improvement without any intervention other than olmesartan withdrawal [4,5]. In these three publications, patients were aged from 47 to 81 years, had severe chronic diarrhoea and/or weight loss, and an unexplained enteropathy while being treated by olmesartan for several months or years prior to the onset of signs. Variable degrees of mucosal inflammation and villous involvement graded according to the modified Marsh classification was noted, with total villous atrophy in 15 patients [3], partial villous atrophy in 7 patients [3], and