Emergence of inflammatory bowel disease during treatment with sitagliptin

Díaz-Acedo R[1], Serrano-Giménez R[1], Hernando-Jiménez V[2], Fobelo-Lozano MJ[1]
1 Servicio Farmacia
2 Servicio Endocrinología y Nutrición
Hospital de Valme. Sevilla (España)

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SUMMARY
We present one clinical case of diagnosed inflammatory bowel disease, as a probable adverse reaction to sitagliptin. Sitagliptin is a dipeptidylpeptidase (DPP)-4 inhibitor authorised for the type II diabetes mellitus treatment in adult patients who do not achieve good blood glucose control and if other therapeutic alternatives are not correctly tolerated. In addition to the DPP-4 role in the gastric hormones release and glucose homeostasis, the DPP-4 involvement in the inflammatory response is known. However, the relationship between inflammatory bowel disease (IBD) and inhibition of PPD-4 is controversial. On the one hand, the T lymphocytes of patients with this pathology seem to express high levels of the enzyme DPP-4, so their inhibition could be associated with a decrease in the activity of IBD. On the other hand, in a cohort study of patients treated with oral antidiabetics an increased risk of IBD was observed and there are different published cases of IBD occurrence during the use of sitagliptin.

Key Words: **Sitagliptin, Crohn's disease, adverse effect.**

Debut de enfermedad inflamatoria intestinal durante el tratamiento con sitagliptina

RESUMEN
Presentamos un caso de debut de enfermedad inflamatoria intestinal (EII) como probable reacción adversa a la administración de sitagliptina. Sitagliptina es un inhibidor de la dipeptidilpeptidasa 4 (DPP-4) autorizado para el tratamiento de la diabetes mellitus tipo II en pacientes adultos que no consiguen buen control de la glucemia, o si el resto de alternativas terapéuticas no son bien toleradas.
Además del papel de la DPP-4 en la liberación de hormonas gástricas y en la homeostasis de la glucosa, se sabe que esta enzima también está implicada en la respuesta inflamatoria. Sin embargo, la relación entre la EII y la inhibición de la DPP-4 es controvertida. Por un lado, los linfocitos T de los pacientes con esta patología parecen expresar altos niveles de la enzima DPP-4, por lo que su inhibición se podría asociar a un descenso en la actividad de la EII. Por otro lado, en un estudio de cohortes de pacientes tratados con antidiabéticos orales se observó un aumento del riesgo de EII y existen diferentes casos publicados de aparición de IBD durante el uso de sitagliptina.

Palabras clave: **Sitagliptina, enfermedad de Crohn, reacción adversa.**

INTRODUCTION

Sitagliptin is a dipeptidylpeptidase-4 (DPP-4) inhibitor authorised for the type II diabetes mellitus treatment in adult patients who do not achieve good blood glucose control or if other therapeutic alternatives are not correctly tolerated.

DPP-4 is an enzyme responsible for degrading incretines, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)[1]. In addition to this role, the DPP-4 involvement in inflammatory response and immune activity is known[2]. However, regarding to the relationship between inflammatory bowel disease (IBD) and DPP-4 inhibition, there is controversy. On the one hand, some studies claim that an improvement in activity[3] and a decrease in the incidence[4] of this disease occur in subjects treated with those drugs. On the other hand, the appearance of cases of IBD during the treatment with DPP-4 inhibitors[5-6] has been published too.

We present a debut of Crohn's disease (CD) in a patient treated with sitagliptin.

CASE REPORT

Female, 75-year-old, with a personal history of type II diabetes mellitus and autoimmune thyroiditis, both newly diagnosed. She underwent treatment with metformin and sulfonylureas. Both were removed due to poor tolerance and sitagliptin 50 mg per day was initiated. Two months after the onset, the patient was admitted to hospital for fever and abdominal pain, diagnosed with myelodysplastic syndrome with multiline dysplasia. During admission, computerized axial tomography (CT) images of terminal ileum with significant diffuse thickening were described. One month later, she was admitted again with abdominal pain, fever, besides diarrhea and loss of 10 kg of weight were noted. Coprocultures and *Clostridium Difficile* toxin detection resulted negative. Thereupon, a new CT is performed resulting in ileitis-compatible images. In the Entero-Magnetic resonance imaging (Entero-MRI) a collection of predominantly aerial content was noted (it was not observed in

Reyes Serrano Giménez ◆ Hospital de Valme -Servicio de Farmacia (planta sótano) ◆ Carretera de Cádiz, s/n ◆ 41014 Sevilla (España)
reysergim@gmail.com

previous CT scans); it was compatible with an abscess secondary to an ileum deep ulceration.

A diagnosis of active stenosing and penetrating IBD, possibly CD, was made. It was started a corticosteroids treatment, with significant clinical improvement after onset. During this second admission, the Endocrine Service suspended sitagliptin and replaced it with insulin therapy, which was maintained after hospital discharge. Forty-five days later, the patient reentererd because of clinical worsening (intra-abdominal abscess). Due to active disease, associated with hematological disease, a surgical treatment was proposed, but it was rejected because of extensive involvement. After clinical stabilization, due to prolonged antibiotic treatment and corticorrefractoriness, a biological treatment with vedolizumab was started in agreement with Hematology. From a digestive point of view, abdominal pain and digestive intolerance persisted, both to oral supplements and to different enteral nutrition formulas. From the hematological point of view, she presented multifactorial anemia and neutropenia. Three vedolizumab induction dose were administered. The patient presented bacteremia on two occasions, and deceased two months later.

DISCUSSION

DPP-4 is a T lymphocyte surface antigen involved in the activation, maturation and homeostasis of T lymphocytes, so this enzyme inhibition could be related to immune system alterations. DPP-4/CD26 has been described as a migration and maturation mediator of T lymphocytes; as a consequence, there are studies supporting the negative effect of this inhibition and others defending the protective effect in immune-related diseases.

Regarding to the first, they claim that lower than normal TCD4 lymphocytes levels were noted in mice with a deficiency in this enzyme or treated with DPP-4 inhibitors[2]. On the other hand, a sitagliptin compared to placebo randomized study in humans was published[7]; an increase in DPP-4/CD26 expression in the T lymphocytes of patients treated with sitagliptin was detected at the beginning of the treatment, but it was not maintained after the 28th day of follow-up. So, it was not found other significant differences that demonstrated the sitagliptin immunomodulatory action.

On the other hand, in patients with some autoimmune diseases, alterations in DPP-4 levels have also been found[8]. In fact, reduced levels of the enzyme were observed in serum samples from patients with active CD compared to healthy patients' samples. Similarly, a reduction in the expression of the enzyme in intestinal tissue was found in diseased individuals. Even though no relationship was established between levels of DPP-4 and disease activity[8].

The immune system-related adverse reactions described in the sitagliptin data sheet[1] are interstitial lung disease, acute pancreatitis, cutaneous vasculitis or bullous pemphigoid. Although the development of other autoimmune diseases such as rheumatoid arthritis (RA) or IBD are not included in the typical DPP-4 adverse reactions, a case of sitagliptin-induced RA has been published in a type II diabetes mellitus patient, with clinical onset of the RA after three months of treatment with DPP-4 inhibitors[9].

Focusing on IBD, two studies have recently been published. In one of them, a higher prevalence of CD and Hashimoto's thyroiditis has been observed in a group of patients treated with DPP-4 inhibitors compared to another group not receiving them[5]. The other one is a cohort study by Abrahami et al.[6] which includes patients over 18 years of age, who had never been treated with insulin and who started treatment with DPP-4 inhibitors; they included 30,488 patients with DPP-4 inhibitors treatment, with median treatment duration of 1.6 years. The use of these drugs was associated with a 75% increased risk of IBD (53.4 *vs.* 34.5 per 100.000 patients/year. Hazard Ratio (HR) 1.75, confidence interval 1.22-2.49). In addition, secondary analyses showed an increased risk of developing IBD in patients who maintained treatment with DPP-4 inhibitors for a longer period.

In the South Health Management Area of Seville, there are currently a total of 2.391 patients undergoing treatment with sitagliptin. The patient in our case had not previously been treated with insulin, although she had been treated with metformin and sulfonylureas and three months after the onset of sitagliptin she was diagnosed with CD. The suspected adverse drug reaction was notified to the Andalusian Centre of Pharmacovigilance.

Conversely, DPP-4 inhibition has been associated in some studies with an colitis improvement in mice; consequently it has been attributed a therapeutic potential in IBD to DPP-4 inhibitors[3]. In addition, a cohort study in type II diabetes mellitus patients has also been published and its results indicated a lower incidence in the appearance of RA and systemic lupus erythematosus in the group treated with DPP-4 inhibitors[4].

As a conclusion, DPP-4 inhibitors effect on the immune system is a controversial and recently discussed topic. Therefore, and because the onset or worsening of this kind of diseases is a relevant event, it must be necessary to monitor the start or aggravation of symptoms suggestive of IBD or RA among others.

Conflicts of interest: The authors declare that they have no conflict of interest.

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