Abstract

Aim. – Unlike other dipeptidyl peptidase 4 (DPP-4) inhibitors, the excretion of linagliptin is mainly through a biliary route. Despite this fact, liver injury with linagliptin has thus far not been reported in the literature. However, this report describes the first case of probable linagliptin-induced liver toxicity.

Methods. – The clinical history, diagnosis, investigations and drug treatment of the patient are reviewed here.

Results. – A 58-year-old Japanese woman presented with fatigue, nausea, jaundice and marked elevations of hepatic enzymes 4 weeks after starting linagliptin 5 mg/day as monotherapy. No other medications were taken, and imaging studies revealed no other obvious causes of hepatic injury. Tests for viral serology and antinuclear antigen were negative. Symptoms disappeared and the levels of hepatic parameters (serum aminotransferases and biliary enzymes) slowly recovered after discontinuation of linagliptin. The slow recovery process may have been due to the very long half-life of the drug. The patient’s Naranjo scale score was 6 and RUCAM score was 7.

Conclusion. – Although linagliptin currently carries no liver warnings, it may be necessary to monitor hepatic function in some patients upon administration of this drug until further evidence is obtained.

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Keywords: DPP-4 inhibitors; Linagliptin; Drug-induced liver toxicity

1. Introduction

Dipeptidyl peptidase 4 (DPP-4) inhibitors are promising new therapeutic options for the treatment of type 2 diabetes mellitus (T2DM). They block the degradation of incretin by DPP-4 and present with a wide range of physiological effects associated with improved glycaemic control, including the stimulation of glucose-dependent insulin secretion and suppression of glucagon secretion. However, a number of adverse events have been anticipated with DPP-4 inhibitors, including pancreatitis, thyroid cancer and infections [1,2].

Linagliptin is one of the newest DPP-4 inhibitors on the market and is currently available in the European Union (EU), the USA and Japan. It has a number of unique characteristics (such as non-linear pharmacokinetics). Also, unlike other DPP-4 inhibitors, it is excreted through a non-renal route, which means that linagliptin may be beneficial to those with impaired renal function [3,4]. However, linagliptin is mostly excreted through a biliary route [5], which could be a disadvantage in the presence of liver impairment. Nevertheless, it was recently reported that linagliptin had no negative effects on hepatic parameters in those with liver dysfunction [6]. Increases in serum aminotransferase activities have been reported in clinical trials performed in Japan and are indicated in the package insert for this drug [7]. Yet, there have been no case reports in the literature describing the clinical presentation and features of a patient with linagliptin-induced hepatic toxicity.

The present report is of a case in which linagliptin was most probably responsible for the development of severe hepatic injury in a 58-year-old Japanese female patient.

2. Case report

The patient was a 58-year-old woman with T2DM, who was diagnosed with T2DM and hypertension in 2007, and was visiting the outpatients division of the Department of Internal Medicine at Higashi Totsuka Memorial Hospital in Yokohama. Her glycaemic control was within a reasonable range (HbA1c: 7–7.5%). She was neither a smoker nor alcohol drinker, and had...
Table 1 Laboratory findings from initiation of linagliptin 5 mg/day monotherapy (27 March) until discontinuation (1 May).

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<tr>
<td>T-Bil (0.3–1.2 mg/dL)</td>
<td>0.35</td>
<td>1.35</td>
<td>1.83</td>
<td>2.1</td>
<td>1.89</td>
<td>0.71</td>
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<tr>
<td>ALP (100–340 IU/L)</td>
<td>542</td>
<td>722</td>
<td>647</td>
<td>725</td>
<td>705</td>
<td>495</td>
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<tr>
<td>AST (8–40 IU/L)</td>
<td>23</td>
<td>476</td>
<td>471</td>
<td>281</td>
<td>133</td>
<td>61</td>
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<tr>
<td>ALT (0–35 IU/L)</td>
<td>23</td>
<td>1006</td>
<td>984</td>
<td>604</td>
<td>371</td>
<td>61</td>
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<tr>
<td>GGT (0–35 IU/L)</td>
<td>23</td>
<td>136</td>
<td>195</td>
<td>211</td>
<td>206</td>
<td>69</td>
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<tr>
<td>LDH (115–245 IU/L)</td>
<td>357</td>
<td>526</td>
<td>526</td>
<td>388</td>
<td>318</td>
<td>394</td>
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<tr>
<td>BUN (8–23 mg/dL)</td>
<td>16.1</td>
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<td>CRE (0.46–8.0 mg/dL)</td>
<td>0.5</td>
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<td>UA (2.6–7.0 mEq/L)</td>
<td>4.2</td>
<td>5.3</td>
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<td>Na (136–147 mEq/L)</td>
<td>140</td>
<td>141</td>
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<td>K (3.5–5.9 mEq/L)</td>
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<td>Cl (98–108 mEq/L)</td>
<td>102</td>
<td>105</td>
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<tr>
<td>HbA1c (4.7–602% NGSP)</td>
<td>8.8</td>
<td>8.3</td>
<td>7.6</td>
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<tr>
<td>Casual BS (70–109 mg/dL)</td>
<td>284</td>
<td>243</td>
<td>206</td>
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<td>261</td>
<td>126</td>
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<td>IgG (870–1700 mg/dL)</td>
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<td>1021</td>
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<td>HBS–Ag</td>
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<td>HCV–Ab</td>
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<td>ANA (0–0.05 mg/dL)</td>
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<td>8.2</td>
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</table>

Hepatic and other parameters were followed until 3 July 2013; values in parentheses are the normal ranges used at our hospital; T-Bil: total bilirubin; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; CRE: creatinine; UA: uric acid; Na: sodium; K: potassium; Cl: chloride; BS: blood sugar; IgG: immunoglobulin G; HBS–Ag: surface antigen for hepatitis B virus; HCV–Ab: antibodies against hepatitis C virus; ANA: antinuclear antigen.

no history of other clinically significant disorder and no clinical evidence of macrovascular disease, neuropathy, retinopathy, chronic kidney disease or liver dysfunction.

The patient had discontinued her treatment for approximately 5 months, but had returned to hospital on the 27th March 2013 to restart the therapy. In the 5 months prior to that date, she had taken no medications whatsoever. On examination, her height was 159.5 cm, her weight was 64 kg and her blood pressure (systolic/diastolic) was 137/74 mmHg. Serum liver enzymes, such as alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT) and total bilirubin (T-Bil), were all within normal ranges (Table 1). Renal function as assessed by blood urea nitrogen (BUN), creatinine (CRE) and uric acid (UA) was also within the normal range. At this time, linagliptin 5 mg/day as monotherapy was initiated, and no other drugs were prescribed.

Approximately 4 weeks after starting linagliptin (1 May 2013), she visited the outpatients department complaining of nausea, fatigue and jaundice. A blood analysis revealed marked elevations in hepatic enzymes (AST, ALT, ALP, GGT and serum T-Bil), although renal function was still within the normal range (Table 1).

No changes in lifestyle (such as, travel abroad, or taking other drugs or dietary supplements) were reported by the patient. Admission to hospital and further examinations were suggested, but the patient declined. Tests for viral serology, such as surface antigen for hepatitis B virus (HBV–Ag), antibodies against hepatitis C virus (HCV–Ab) and antinuclear antigen (ANA) were all negative (Table 1). Ultrasonographic evaluation showed no clinically significant liver disorders, such as abnormalities of the intrahepatic or extrahepatic biliary ducts, nor was the presence of stones detected (data not shown). However, slight fatty changes were noted in the liver (data not shown). The newly initiated linagliptin monotherapy was strongly suspected as being responsible for the patient’s condition. For this reason, its administration was immediately discontinued.

A week after stopping linagliptin (8th May 2013), the patient’s nausea disappeared and slight reductions in transaminase levels were observed. However, biliary parameters (serum T-Bil, ALP and GGT levels) had increased (Table 1). Transaminase levels further decreased (albeit very slowly) from this time onwards and were almost normal 8 weeks after linagliptin discontinuation (3rd July 2013; Table 1). Levels of biliary parameters increased for 3 weeks after stopping linagliptin (21st May 2013), then, began to decrease thereafter and were within the normal range 8 weeks after discontinuation (3rd July 2013). The patient’s Naranjo scale score [8] was 6 and her CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method) scale score [9,10] was 7.

3. Discussion

The present report is of a probable case of acute hepatic injury induced by linagliptin. The patient’s Naranjo probability scale [8] score of 6 was consistent with a possible adverse drug reaction, and the more specific clinical CIOMS/RUCAM score [9,10] score of 7 was consistent with probable drug-induced hepatotoxicity. Other causes of liver damage, such as HBV or HCV infection, autoimmune hepatitis, or the consumption of alcohol and concomitant hepatotoxic drugs were excluded. The patient was taking only linagliptin at the time. Also important were the observed disappearance of symptoms and reduction in hepatic parameters, albeit rather slowly, after discontinuation of the drug (Table 1).

Among DPP-4 inhibitors, linagliptin has a number of unique characteristics, including its exclusively biliary excretion route [5] and very long half-life (> 100 h) [3,4]. These unique features
may have contributed to the liver injury in this patient (with the slow recovery time most likely due to the very long half-life). Thus, given these considerations, it is plausible that liver injury in this case was most probably related to linagliptin.

As described in Introduction, linagliptin has been studied in patients with hepatic dysfunction, and short-term exposures (7 days) had no effect on hepatic parameters [6]. Furthermore, there has been a report that DPP-4 is expressed in the liver and, in fact, DPP-4 has been implicated in the pathogenesis of several chronic liver diseases [11]. For these reasons, DPP-4 inhibition has been proposed as beneficial in chronic liver diseases. On the other hand, it has been reported that oral medications with significant hepatic metabolism are at higher risk of hepatic adverse events [12].

The discrepancies among these reports (that DPP-4 inhibitors are safe and beneficial to the liver vs possibly hepatotoxic, as in the present report) [6,11,12] remain to be elucidated. One potential explanation is that the exposure of linagliptin in the study by Graefe-Mody et al. [6] was too short-term (7 days) and that the patients’ medical histories may have been very different from that of the present patient. Also, at least two case reports of potential sitagliptin-induced liver toxicity can be found in the literature [13,14]. This suggests that liver toxicity might be a class effect of DPP-4 inhibitors. If this is so, then it is of major importance to investigate the mechanism of how DPP-4 inhibitors might cause liver toxicity.

4. Conclusion

This case of probable linagliptin-induced liver injury is thus far unique. However, as the drug is excreted mostly through a biliary route, adverse effects on the liver may be more likely compared with other DPP-4 inhibitors. Given these facts, although linagliptin does not carry any liver warnings at this time, it appears to be necessary to monitor liver function in some patients upon administration of this drug.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.09.009.

References