Drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient taking sitagliptin

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Received 10 May 2012; received in revised form 4 July 2012; accepted 6 July 2012

Abstract

Sitagliptin is a recent oral antidiabetic drug for type 2 diabetes patients. This report is the first case of a severe drug reaction with eosinophilia and systemic symptoms (DRESS), which resolved with systemic corticosteroids. However, vigilance is necessary during the prescription of these compounds.

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Keywords: Sitagliptin; Drug reaction

1. Introduction

Sitagliptin (Januvia®, Merck & Co., Inc., Whitehouse Station, NJ, USA) has recently been licensed as either monotherapy or combination therapy with metformin, a sulphonylurea or a glitazone, or as add-on treatment to insulin for glycaemic control in patients with type 2 diabetes mellitus (T2DM). It is an orally active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme, which improves glycaemic control in patients with T2DM by enhancing levels of active incretin hormones. Common reported clinical adverse events with sitagliptin are nasopharyngitis, upper respiratory infections, headache, gastrointestinal symptoms and musculoskeletal pain [1]. However, there have also been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These drug reactions include anaphylaxis, angioedema, exfoliative rashes, toxic epidermal necrolysis (Stevens–Johnson syndrome and erythema multiforme) and hypersensitivity vasculitis [2–4]. The present report is of a case of a severe drug reaction with eosinophilia and systemic symptoms (DRESS).

2. Case report

A 66-year-old woman with T2DM had been treated with sitagliptin 100 mg/day for 3 weeks when she developed a generalized skin eruption. Her medical history included obesity and hypertension. She had also been taking metformin, insulin, glimepiride and telmisartan for more than 6 months. The skin reaction started as a non-pruriginous rash on her face and hands. High fever (temperature 40°C) appeared on the first day of the skin reaction. Ten days later, physical examination at the emergency department revealed erythroderma, with oedema of the face and extremities (Figs. 1 and 2), purpura and pustules on the inner thighs, and oropharyngeal erosions. The patient had a high fever and enlarged cervical lymph nodes. Blood pressure was initially low, but well tolerated (systolic blood pressure 80 mmHg). She presented no signs of either dehydration or hypovolaemic shock.
The patient’s initial laboratory investigations are detailed in Table 1. No viral (human herpesvirus 6, cytomegalovirus, Epstein-Barr virus) reactivation was found, and blood cultures were negative. Clinical and biological findings led to the diagnosis of DRESS with skin and kidney involvement. It was suspected that sitagliptin was responsible for the reaction, and all oral antidiabetic drugs were withdrawn. Because of the patient’s severe acute renal failure, systemic corticosteroids (prednisone 1 mg/kg/day) were introduced. After 4 days of treatment, the patient’s eosinophil count rose to $17.4 \times 10^9/L$ and, after 2 weeks of treatment, the eruption resolved and the laboratory data progressively normalized. Insulin for uncontrolled diabetes and antihypertensive therapy with telmisartan were reintroduced with no recurrence of the skin reaction. However, because of the potentially fatal outcome of DRESS, sitagliptin was not reintroduced. Other oral antidiabetic drugs (metformin and gliclizide) were no longer needed.

### 3. Discussion

DRESS is a severe adverse drug-induced reaction with a mortality rate of approximately 10%. It consists of a severe skin eruption, fever (> 38°C), haematological abnormalities (eosinophilia or atypical lymphocytes) and internal organ involvement. The other noteworthy features are a delayed onset, usually 2–6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms despite discontinuation of the culprit drug. The main culprit drugs are anticonvulsant therapies (mainly carbamazepine), allopurinol and sulphasalazine, although around 50 drugs can induce DRESS [5,6].

In our present case, sitagliptin was the most likely drug as the patient had the typical clinical presentation: skin rash, high-grade fever, and peripheral lymphadenopathy associated with hypereosinophilia and renal failure, with a delay of 3 weeks between first drug use and appearance of the skin reaction. Our case was defined as a “probable” (final score 4–5) to “definite” case (final score > 5), according to the RegiSCAR scoring system [5,6]. However, liver involvement, the most frequently reported internal organ involvement, was not found in our case. Liver involvement is determined by either elevated liver function tests or the presence of hepatomegaly. The involvement of other organs is rarely reported, such as the kidney involvement in our present case. However, no other cause of renal failure, such as dehydration, hypotension or induced by telmisartan, could be found. High doses of oral corticosteroids allowed recovery.

### Table 1
Laboratory test results 7 days after the beginning of the skin reaction.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient’s values</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes, $10^9/L$</td>
<td>19.4</td>
<td>4–10</td>
</tr>
<tr>
<td>Neutrophils, $10^9/L$</td>
<td>17.5</td>
<td>2–7.5</td>
</tr>
<tr>
<td>Eosinophils, $10^9/L$</td>
<td>0.58</td>
<td>0.04–0.8</td>
</tr>
<tr>
<td>Lymphocytes, $10^9/L$</td>
<td>1.4</td>
<td>1.5–4</td>
</tr>
<tr>
<td>Haemoglobin, g/dL</td>
<td>10.7</td>
<td>11.8–14.8</td>
</tr>
<tr>
<td>Platelets, $10^9/L$</td>
<td>288</td>
<td>150–400</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>30</td>
<td>15–45</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>12</td>
<td>15–40</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase, U/L</td>
<td>20</td>
<td>10–45</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/mL</td>
<td>592</td>
<td>120–220</td>
</tr>
<tr>
<td>Ureaemia, mmol/L</td>
<td>17.7</td>
<td>2.5–7.5</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>285</td>
<td>50–100</td>
</tr>
<tr>
<td>Natraemia, mmol/L</td>
<td>129</td>
<td>135–143</td>
</tr>
<tr>
<td>Triglyceridaemia, mmol/L</td>
<td>1.95</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Ferritinaemia, mg/L</td>
<td>396</td>
<td>15–150</td>
</tr>
</tbody>
</table>
4. Conclusion

Sitagliptin is a new oral antidiabetic drug with limited efficacy. Although rare, DRESS is a life-threatening reaction and needs to be borne in mind when starting patients on sitagliptin.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


