Three Cases of Bullous Pemphigoid Associated with Dipeptidyl Peptidase-4 Inhibitors – One due to Linagliptin

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Introduction

Bullous pemphigoid (BP) is an acquired subepidermal autoimmune blistering disease in which there are humoral and cellular responses against the BP180 and BP230 antigens [1], both of which are components of hemidesmosomes. Degenerative neurological diseases, unipolar or bipolar disorder, being confined to a bed, and the chronic use of neuroleptics or spironolactone are known independent risk factors for the development of BP [2].

Dipeptidyl peptidase (DPP)-4 inhibitors enhance endogenous glucagon peptide-1 and glucose-dependent insulinotropic polypeptide secretion with food intake, which leads to insulin secretion, as well as to the reduction of glucagon secretion. Recently, several cases of DPP-4 inhibitor-associated BP have been reported. Objectives: To report 3 cases of DPP-4 inhibitor-associated BP, one of which is due to linagliptin use, as well as to review all currently published cases of DPP-4 inhibitor-associated BP. Case Reports: Three patients diagnosed with BP at our department showed a clear temporal relationship between the introduction of DPP-4 for the treatment of diabetes and the onset of BP. One case was due to linagliptin use, while the other 2 cases were due to an association with vildagliptin-metformin use. Conclusions: This is the first report of linagliptin-associated BP. Furthermore, 2 other cases of vildagliptin-associated BP are reported.

Key Words
Bullous pemphigoid · Diabetes mellitus · Drug reaction · Pemphigoid · Dipeptidyl peptidase-4 inhibitors · Linagliptin · Vildagliptin

Abstract
Background: Bullous pemphigoid (BP) is an acquired subepidermal autoimmune blistering disease in which there are humoral and cellular responses against the BP180 and BP230 antigens. Dipeptidyl peptidase (DPP)-4 inhibitors enhance endogenous glucagon peptide-1 and glucose-dependent insulinotropic polypeptide secretion with food intake, which leads to insulin secretion, as well as to the reduction of glucagon secretion. Recently, several cases of DPP-4 inhibitor-associated BP have been reported. Objectives: To report 3 cases of DPP-4 inhibitor-associated BP, one of which is due to linagliptin use, as well as to review all currently published cases of DPP-4 inhibitor-associated BP. Case Reports: Three patients diagnosed with BP at our department showed a clear temporal relationship between the introduction of DPP-4 for the treatment of diabetes and the onset of BP. One case was due to linagliptin use, while the other 2 cases were due to an association with vildagliptin-metformin use. Conclusions: This is the first report of linagliptin-associated BP. Furthermore, 2 other cases of vildagliptin-associated BP are reported.
Case Reports

Patient 1

An 82-year-old man (table 1) with arterial hypertension, dyslipidemia, hyperuricemia, and moderate chronic kidney disease presented with a pruriginous cutaneous eruption featuring small vesicles that spared the head and neck (fig. 1a). Difficulty swallowing liquids and dysphonia were also present. All of the patient’s symptoms had started within 24 h prior to admission to the emergency room. The patient was evaluated by the otolaryngology department, where the team discovered arytenoid edema with several ulcerated lesions covered with fibrin, which warranted instau-ration of a bolus of methylprednisolone (40 mg i.v. t.i.d.). Skin biopsies were taken, and the patient was discharged with dexamethasone starting at 4 mg b.i.d., and antihistamines (ebastine 10 mg/day and hydroxyzine hydrochloride 50 mg/day) were administered for 3 weeks. The lesions healed without scarring. The biopsies revealed a spongiotic dermatitis with intraepidermal vesicle formation, as well as lymphocytic and eosinophilic inflammatory infiltrates (fig. 1b). Direct immunofluorescence (DIF) and anti-basement membrane zone antibodies detected by indirect immunofluorescence (IIF) were negative at this point.

Following the treatment stop of glucocorticoids, the patient relapsed, showing typical BP bullae without mucosal lesions. The clinical diagnosis of BP [12, 13] was confirmed via histological and DIF analysis of the perilesional skin of a second set of biopsies, which showed a linear deposit of immunoglobulin G and C3 along the basement membrane zone. Enzyme-linked immunosorbent assay tests for specific BP180 and BP230 antibodies were not conducted because they are currently not available at our center.

Table 1. Reported cases of DPP-4 inhibitor-associated BP

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient No./sex/age, years</th>
<th>DPP-4 inhibitor</th>
<th>Period of DPP-4 inhibitor use before onset</th>
<th>Clinical presentation</th>
<th>Diagnosis</th>
<th>Level of causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendonça et al., 2012</td>
<td>1/M/82</td>
<td>Linagliptin</td>
<td>45 days</td>
<td>Vesicular pruriginous eruption with severe mucosal involvement</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely</td>
</tr>
<tr>
<td></td>
<td>2/F/77</td>
<td>Vildagliptin + metformin</td>
<td>Unreliable data (at least 6 months)</td>
<td>Mucosal affection at onset; afterwards, mucosal and cutaneous</td>
<td>HE + DIF + IIF</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>3/F/72</td>
<td>Vildagliptin and sitagliptin + metformin</td>
<td>3 months</td>
<td>Only cutaneous</td>
<td>HE + DIF + IIF</td>
<td>Probable</td>
</tr>
<tr>
<td>Skandalis et al. [5], 2012</td>
<td>F/78</td>
<td>Vildagliptin + metformin</td>
<td>13 months</td>
<td>Not stated in the article</td>
<td>HE + DIF + IIF</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>F/80</td>
<td>Sitagliptin + metformin</td>
<td>4 months</td>
<td>Not stated in the article</td>
<td>HE + DIF + IIF</td>
<td>Possible</td>
</tr>
<tr>
<td></td>
<td>M/72</td>
<td>Vildagliptin + metformin</td>
<td>8 months</td>
<td>Not stated in the article</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely</td>
</tr>
<tr>
<td></td>
<td>4/M/67</td>
<td>Vildagliptin + metformin</td>
<td>10 months</td>
<td>Not stated in the article</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely</td>
</tr>
<tr>
<td></td>
<td>M/75</td>
<td>Vildagliptin + metformin</td>
<td>2 months</td>
<td>Not stated in the article</td>
<td>HE + DIF + IIF</td>
<td>Possible</td>
</tr>
<tr>
<td>Pasmatzi et al. [7], 2011</td>
<td>F/59</td>
<td>Vildagliptin + metformin</td>
<td>2 months</td>
<td>Cutaneous diffuse bullous eruption on erythematous base</td>
<td>HE + DIF</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td></td>
<td>M/67</td>
<td>Vildagliptin + metformin</td>
<td>2 months</td>
<td>Cutaneous diffuse bullous eruption on erythematous base</td>
<td>HE + DIF</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td>Aouidad et al. [8], 2013</td>
<td>M/61</td>
<td>Vildagliptin + metformin</td>
<td>6 months</td>
<td>Bullous hemorrhagic lesions over an erythematous base; no mucosal involvement</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td></td>
<td>M/93</td>
<td>Sitagliptin + gliclazide</td>
<td>6 months</td>
<td>Not stated in the article</td>
<td>HE + DIF (negative IIF)</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td></td>
<td>M/76</td>
<td>Sitagliptin + metformin</td>
<td>5 months</td>
<td>Not stated in the article</td>
<td>H/E + DIF (negative IIF)</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td>Attaway et al. [9], 2014</td>
<td>M/78</td>
<td>Sitagliptin + metformin</td>
<td>12 months</td>
<td>Large bullae on normal and erythematosic skin; no mucosal involvement</td>
<td>HE + DIF</td>
<td>Probable/likely¹,²</td>
</tr>
<tr>
<td></td>
<td>F/86</td>
<td>Vildagliptin + metformin</td>
<td>1 month</td>
<td>Erythematous bullous eruption with bullae on healthy skin</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td></td>
<td>M/79</td>
<td>Vildagliptin + metformin + gliclazide</td>
<td>37 months</td>
<td>Erythematous vesicular bullous eruption</td>
<td>HE + DIF</td>
<td>Probable/likely¹</td>
</tr>
<tr>
<td></td>
<td>F/77</td>
<td>Vildagliptin + gliclazide</td>
<td>26 months</td>
<td>Pruriginous bullous eruption</td>
<td>HE + DIF + IIF</td>
<td>Probable/likely¹</td>
</tr>
</tbody>
</table>

HE = Hematoxylin-eosin staining; DIF = direct immunofluorescence; IIF = indirect immunofluorescence.
¹ The WHO-UMC system for standardized case causality assessment [6] was not used in the original article. The level of causality stated is inferred by the authors from the available information.
² The Naranjo Adverse Drug Reaction Probability Scale [11] was applied to the original report suggesting a ‘possible reaction’.
drawn after the onset of the second bout. The remaining medication, listed in Table 2, had been present at least 1 year before the onset of BP.

Treatment with 15 mg of prednisolone once daily, as well as with topical betamethasone-gentamicin cream, was enough to control the symptoms. Oral prednisolone was progressively tapered until complete withdrawal was achieved 6 months after the onset of BP. Currently, only topical treatment is being used in this patient with excellent results. At present, the patient has not experienced further exacerbations following linagliptin withdrawal.

It should be noted that this suspected adverse reaction was communicated to a pharmacovigilance authority.

Patients 2 and 3

In addition to the aforementioned patient, we reviewed all patients with BP who are currently being followed at our center, so as to identify those patients with possible [6] DPP-4 inhibitor-associated BP. Of a total of 15 patients, 2 who could benefit from drug removal were identified.

Patient 2 is a 77-year-old woman who was being treated with a combination of vildagliptin and metformin; this patient presented with typical BP symptomatology. A diagnosis of BP was confirmed by skin biopsy, IIF, and DIF. A course of prednisone (1 mg/kg/day) was initiated, and clinical control of the disease was achieved, albeit with frequent bouts. The patient was unable to precisely determine the amount of time that had elapsed between the introduction of vildagliptin and the start of BP; clinical records proved unreliable in this regard. Vildagliptin was suspended, yet the patient’s response to drug withdrawal is not available as the patient was lost to follow-up.

Patient 3 is a 72-year-old woman who was initially under treatment with a combination of vildagliptin and metformin; this patient presented with typical BP symptomatology. A diagnosis of BP was confirmed by skin biopsy, IIF, and DIF. A course of prednisone (1 mg/kg/day) was initiated, and clinical control of the disease was achieved, albeit with frequent bouts. The patient was unable to precisely determine the amount of time that had elapsed between the introduction of vildagliptin and the start of BP; clinical records proved unreliable in this regard. Vildagliptin was suspended, yet the patient’s response to drug withdrawal is not available as the patient was lost to follow-up.

As stated in the WHO-UMC system for standardized case causality assessments [6], adverse drug reactions are rarely specific; diagnostic tests are usually absent, and a drug rechallenge is not ethically justified. The problem with defining an event as an adverse drug reaction is further complicated in pluripathological patients receiving multiple drugs. In this case, it is hampered by the fact that the experienced adverse reaction was a disease that is typically found among older patients. Furthermore, labeling an event as an adverse drug reaction will almost certainly lead to the disease. Sitagliptin was discontinued 8 months after disease onset. During the 8 months in which sitagliptin use overlapped with prednisone use, the patient showed improvements. At this point, the dosage of prednisone was progressively tapered, finally reaching a plateau of 10 mg/day. Only after the stop of sitagliptin was it possible to further reduce the corticosteroid dosage down to 5 mg/day, which was enough to keep the patient asymptomatic.

The level of causality considered in this patient is ‘probable’ [6] given that the removal of sitagliptin allowed us to reduce the dose of prednisone; following this, there were no further exacerbations.

Discussion

As stated in the WHO-UMC system for standardized case causality assessments [6], adverse drug reactions are rarely specific; diagnostic tests are usually absent, and a drug rechallenge is not ethically justified. The problem with defining an event as an adverse drug reaction is further complicated in pluripathological patients receiving multiple drugs. In this case, it is hampered by the fact that the experienced adverse reaction was a disease that is typically found among older patients. Furthermore, labeling an event as an adverse drug reaction will almost certainly

### Table 2. Drugs being taken by patient 1 at the time of BP onset

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>2.5 mg/24 h</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>5 mg/24 h</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 mg/24 h</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>0.4 mg/24 h</td>
</tr>
<tr>
<td>Torasemide</td>
<td>10 mg/24 h</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>10 mg/24 h</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>300 mg/48 h</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg/24 h</td>
</tr>
</tbody>
</table>

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Linagliptin-Associated Bullous Pemphigoid
have an important impact on the general management of a patient, as it will contraindicate not only that drug, but also those that are chemically related.

Due to the plausible temporal relationship and the dramatic improvements observed following drug withdrawal, linagliptin was the most probable culprit in the development of BP in patient 1. In response, a PubMed search was performed to determine the association between the onset of BP and the drugs that were taken by the patient at around that same time (table 2). In the literature, only 1 case of amlodipine-induced BP [14] and 1 case of rosvuastatin-induced BP were described [15]. In our patient the temporal association with these drugs was not plausible. The search for clopidogrel-, tamsulosin-, ramipril-, and torasemide-induced BP gave no results. Due to ethical concerns, drug rechallenge is not indicated to prove drug etiology. According to the WHO-UMC algorithm, the level of causality of linagliptin-associated BP in our patient is ‘probable/likely’ [6].

To our knowledge, this case of DPP-4 inhibitor-associated BP is the first of its kind due to linagliptin use and the absence of metformin association. It is striking that the patient presented with oral lesions in the first episode. These lesions were not biopsied then, and they did not relapse in subsequent episodes. Only 14 cases of DPP-4 inhibitor-associated BP have been described (table 1), 10 of which were due to the association between vildagliptin and another antidiabetic, most frequently metformin [5, 7, 8, 10]. Metformin has been widely used for the treatment of diabetes, and there are no described cases of BP due to metformin. It is also striking that the majority of cases are due to vildagliptin use. It might be that vildagliptin has a greater capacity for inducing BP, or it may simply be the case that vildagliptin is more frequently prescribed than any other DPP-4 inhibitor. In fact, preclinical studies on vildagliptin have demonstrated the occurrence of necrotic lesions in cynomolgus monkeys; these lesions purportedly resulted from peripheral vasoconstriction [16]. Neither linagliptin nor sitagliptin, which was responsible for 4 cases of DPP-4 inhibitor-associated BP in the literature [5, 8, 9], showed such adverse reactions in preclinical studies [17, 18]. A review of sitagliptin-related adverse event reports from the United States Food and Drug Administration database between October 2006 and November 2008 [19] describes 2 cases of Stevens-Johnson syndrome, 2 cases of toxic epidermal necrolysis, and 22 cases of ‘bullous, desquamative, blistering, exfoliative, urticarial, or exanthematous skin reactions’. According to the referred article, no additional efforts have been made to further differentiate these skin reactions.

Large prospective case-control studies regarding BP [2] have been performed, yet DPP-4 inhibitors were not commercialized at the time; thus, the role of DPP-4 inhibitors as BP-inducing agents is not clearly demonstrated.

Conclusions

We report the first case of linagliptin-associated BP and 2 new cases of vildagliptin-associated BP, which help to further demonstrate a possible link between DPP-4 inhibitor use and the development of BP. At the present moment, it is not clear whether all DPP-4 inhibitors possess the same capacity to induce BP. A large prospective case-control study is needed to prove the association between DPP-4 inhibitors and the onset of BP.

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Statement of Ethics

Protection of humans and animals: the authors declare that no tests were carried out in humans or animals for the purpose of this study.

Confidentiality of data: the authors declare that no private patient data appear in this article.

Right to privacy and informed consent: the authors obtained informed consent from the patients and/or subjects referred to in this article.

Disclosure Statement

The authors have no conflicts of interest and no funding sources to report.

References


