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ORIGINAL ARTICLE

Dipeptidyl peptidase-4 inhibitors-associated bullous pemphigoid: A retrospective study of 168 pemphigoid and 9,304 diabetes mellitus patients

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Keywords
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ABSTRACT

Aims/Introduction: Bullous pemphigoid (BP) might be drug-induced. The present study evaluated the relationship between BP and dipeptidyl peptidase-4 inhibitors (DPP4Is).

Materials and Methods: We recruited patients diagnosed with BP at Ogaki Municipal Hospital from 1 December 2009 through 31 December 2017. We retrospectively collected data from medical records and divided patients into two groups based on whether they received DPP4Is. Additionally, we determined the incidence of BP in patients who were first prescribed DPP4Is at our hospital during the study period.

Results: Of 168 patients diagnosed with BP, 133 (79.1%) were positive for anti-BP180NC16a antibody. A total of 32 (19.0%) patients had been prescribed a DPP4I, 21 of whom (65.6%) were positive for anti-BP180NC16a antibody; this rate was lower than that in patients not receiving a DPP4I (82.3%; $P = 0.0360$). A total of 16 patients with type 2 diabetes mellitus had not been prescribed a DPP4I; only one (6.3%) was positive for anti-BP180NC16a antibody ($P = 0.0339$). During the study period, 9,304 patients were prescribed DPP4Is, eight of whom developed BP; six (75.0%) had non-inflammatory BP, and five of the six (83.3%) were negative for anti-BP180NC16a antibody.

Conclusions: The positive rate of anti-BP180NC16a antibody was lower in BP patients with DPP4I than without DPP4I, regardless of type 2 diabetes mellitus. The antibody titer was low in both the overall and type 2 diabetes mellitus populations. The prevalence of BP in 9,304 patients receiving DPP4Is was 0.0859%, which is higher than that in the general population. As DPP4Is are common diabetes treatments, we must be aware of the risk of BP.

INTRODUCTION

Bullous pemphigoid (BP) is the most common autoimmune subepidermal bullous disease affecting the skin and mucosa. It mainly affects elderly people, and is characterized by pruritus with localized or generalized bullous lesions on the trunk, lower limbs and face. The pathogenesis of BP involves the presence of circulating antibodies (mainly immunoglobulin G) against hemidesmosomal proteins (antigens BP180 and BP230) of basal keratinocytes. The binding of autoantibodies leads to the activation of the complement cascade, recruitment of inflammatory cells and release of proteolytic enzymes that can damage the dermoepidermal junction[1]. Also, it has been reported that the development of BP might be associated with the administration of various drugs, such as antibiotics, antihypertensive agents, anti-inflammatory agents, diuretics, tumor necrosis factor-α inhibitors, antirheumatic drugs, vaccines and so on[2,3]. The first dipeptidyl peptidase-4 inhibitor (DPP4I) was sold as a diabetes drug in Japan in December 2009. Since then, the use of DPP4Is

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has increased, and they are most commonly prescribed in Japan. Although DPP4Is have few side-effects, recent reports showed that some patients receiving DPP4Is developed BP. However, the association between BP and DPP4Is has not been fully elucidated, and we therefore carried out the present retrospective cohort study to analyze their relationship.

METHODS

Participants and measurements

This was a retrospective, observational study to analyze the relationship between the use of DPP4Is and the onset of BP in Japanese patients. We recruited participants from patients diagnosed with BP at Ogaki Municipal Hospital, Ogaki, Gifu, Japan, from 1 December 2009 to 31 December 2017, and analyzed their medical records.

Bullous pemphigoid was diagnosed by a dermatologist in our hospital with reference to skin rash, clinical course, and blood and pathological examination. We collected the following data, recorded on the day of BP diagnosis: age at BP onset, sex, the presence of type 2 diabetes mellitus, glycated hemoglobin level and whether or not DPP4Is were taken before BP onset. We defined the presence of type 2 diabetes mellitus by the use of antidiabetic drugs or a glycated hemoglobin level >6.5%. We also examined data on the anti-BP180NC16a antibody, which has been reported as useful for the diagnosis and evaluation of BP. Anti-180NC16a antibody titer positivity was defined as ≥9 U/mL[4]. We also assessed BP severity by determining whether steroids were administered systemically and whether patients were hospitalized. Although we hoped to evaluate the presence of erythema in all cases to distinguish between inflammatory and non-inflammatory BP, this was impossible, because the medical records were often inadequate.

We divided the study participants into two groups based on whether or not they received DPP4Is. However, as this categorization method influenced the calculation of type 2 diabetes mellitus prevalence, because all patients taking DPP4Is had type 2 diabetes mellitus, we separately divided only type 2 diabetes mellitus patients into two groups based on whether or not they received DPP4Is.

We also examined the number of patients who were prescribed DPP4Is between 1 December 2009 and 31 December 2017. Furthermore, we analyzed the characteristics of the patients in this group who were diagnosed with BP. We collected the following data on the patients who had received DPP4Is: age at BP onset, presence of erythema, the period from initial DPP4I administration to BP onset, the type of DPP4I, anti-BP180NC16a antibody positivity, administration of systemic steroids, need for hospitalization and clinical course.

Finally, in patients who currently visit our hospital and who used DPP4Is before BP onset, we analyzed the titers of antibodies directing the full length of BP180 and HLA-DQB1*03:01, both of which are considered to be associated with DPP4I-induced BP[5,6]. The antibodies directing the full length of BP180 titer positivity were defined as ≥4.64 U/mL. This study was carried out in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of Ogaki Municipal Hospital and Hokkaido University Hospital.

Statistical analysis

Statistical analyses were carried out using JMP (SAS Institute Japan Ltd., Roppongi, Minato-ku, Tokyo, Japan) 12 and the results are expressed as mean ± standard deviation, average and percentages. The bilateral *F*-test was used for the equal variance test. The *t*-test and χ^2-test were used to compare the DPP4I and non-DPP4I groups.

RESULTS

A total of 168 patients were included in this analysis (65 men and 103 women). The average age at diagnosis of BP was 79.7 years. Of these patients, 48 (28.5%) had type 2 diabetes mellitus and 32 (19.0%) used DPP4Is. There was no significant difference between the DPP4I and non-DPP4I groups in terms of age, sex, hospitalization rate and rate of systematic steroid administration, as shown in Table 1. The prevalence of diabetes and glycated hemoglobin levels differed between the two groups, because all patients with DPP4I had type 2 diabetes mellitus. There was no significant difference in any of the above parameters when the analysis was restricted to patients with type 2 diabetes mellitus, as shown in Table 2.

Anti-BP180NC16a antibody positivity was noted in 133 patients (79.1%) in the overall sample, 21 patients (65.6%) in the DPP4I group and 110 patients (82.3%) in the non-DPP4I group. The mean antibody titers in the positive cases were 206.7 ± 238.5 in the DPP4I group and 551.1 ± 1323.6 in the non-DPP4I group. Both the antibody-positive rate and the antibody titer were significantly lower in the DPP4I group than the non-DPP4I group ($P = 0.0360$, $P = 0.0136$, respectively; Table 3). There was no cut-off value for the antibody titer, because the dispersion was large. In the patients with type 2 diabetes mellitus, 15 (93.7%) of those in the non-DPP4I group were anti-BP180NC16a antibody-positive, with a mean titer of 871.1 ± 2146.0; in contrast, in the DPP4I group the positive rate was significantly lower ($P = 0.0339$) and the mean titer was lower, but not significantly so ($P = 0.2677$; Table 4).

Table 1 | Patient characteristics

	DPP4I group	Non-DPP4I group	*P*-value
Total (%)	32 (19.1)	136 (80.9)	–
Age, years (SD)	78.8 (9.4)	79.9 (12.1)	0.6507
Sex, male (%)	15 (46.8)	50 (36.7)	0.2907
Hospitalization (%)	7 (21.8)	34 (25.0)	0.7112
Systematic steroid use (%)	22 (68.75)	103 (75.7)	0.4152
T2DM (%)	32 (100)	16 (11.7)	<0.0001
HbA1c, % (SD)	7.01 (0.94)	5.56 (1.17)	<0.0001

Glycated hemoglobin (HbA1c) was not measured in three patients in the dipeptidyl peptidase-4 inhibitor (DPP4I) group and in 19 patients in the non-DPP4I group. SD, standard deviation; T2DM, type 2 diabetes mellitus.

Table 2 | Characteristics of patients with type 2 diabetes mellitus

	DPP4I group	Non-DPP4I group	*P*-value
Total (%)	32 (66.6)	16 (33.3)	–
Age, years (SD)	78.87 (9.4)	79.87 (9.8)	0.7399
Sex, male (%)	15 (46.8)	8 (50.0)	0.8381
Hospitalization (%)	7 (21.8)	1 (6.25)	0.1709
Systematic steroid use (%)	22 (68.7)	14 (87.5)	0.1573
HbA1c, % (SD)	7.01 (0.94)	6.74 (1.17)	0.4212

DPP4I, dipeptidyl peptidase-4 inhibitor; HbA1c, glycated hemoglobin; SD, standard deviation.

Table 3 | Relationship between anti-BP180 antibody and dipeptidyl peptidase-4 inhibitor treatment

	DPP4I group (n = 32)	Non-DPP4I group (n = 136)	*P*-value
Anti-BP180 antibody-positive (%)	21 (65.6)	112 (82.3)	0.0360
Anti BP180 antibody titer (SD)	206.7 (238.5)	551.1 (1,323.6)	0.0136

DPP4I, dipeptidyl peptidase-4 inhibitor; SD, standard deviation.

DPP4Is were administered to 9,304 patients at our hospital during the study period. The specific drugs used were as follows: sitagliptin, 5,071; alogliptin, 1,899; linagliptin, 1,307; and vildagliptin, 1,027. BP occurred in eight of the 9,304 patients; sitagliptin was being taken by three of these patients, alogliptin by one, linagliptin by one and vildagliptin by three. The incident rate of BP among all patients taking DPP4Is at our hospital was 0.0859%. Stratified by specific drugs, BP occurred in three of 5,071 patients taking sitagliptin (0.059%), one of 1,899 taking alogliptin (0.052%), one of 1,307 taking linagliptin (0.076%) and three of 1,027 taking vildagliptin (0.292%). Table 5 shows the characteristics of the eight patients who developed BP. The average number of months between the start of DPP4I administration and the diagnosis of BP was 48.37 (8–19 months). Two patients had inflammatory-type BP with erythema; both were positive for anti-BP180NC16a antibody. In contrast, only one of six patients with non-inflammatory-type BP without erythema was antibody-positive. Five of the eight BP patients received a systemic steroid as initial treatment, and one required hospitalization. All of the patients continued taking DPP4Is after BP diagnosis, and they have been stable in skin condition; three have continued to receive systemic steroids, whereas five have not.

A total of 12 patients who currently visit our hospital used DPP4Is before BP onset; their characteristics are shown in Table 6. While age, erythema and anti-BP180NC16a antibody titers were assessed at the time of BP diagnosis, the antibodies directing full-length BP180 and HLA-DQB1*0301 protein were examined after treatment initiation. As a result, two patients were positive for the NC16a domain and negative for the antibodies directing full-length BP180. Although four patients were negative for anti-BP180NC16a antibody (30.0%), they were positive for the full-length BP180 antibodies. Additionally, these four patients had non-inflammatory BP without erythema, and three of the four (75.0%) had HLA-DQB1*0301. The other eight patients who took DPP4Is before BP onset were positive for the anti-BP180NC16a antibody and had inflammatory BP with erythema. Five out of these eight patients (62.5%) had HLA-DQB1*0301.

Table 4 | Relationship between anti-BP180 antibody and dipeptidyl peptidase-4 inhibitor treatment in patients with type 2 diabetes mellitus

	DPP4I group (n = 32)	Non-DPP4I group (n = 16)	*P*-value
Anti-BP180 antibody-positive (%)	21 (65.6)	15 (93.75)	0.0339
Anti BP180 antibody titer (SD)	206.7 (238.5)	871.1 (2146.0)	0.2677

DPP4I, dipeptidyl peptidase-4 inhibitor; SD, standard deviation.

DISCUSSION

The 110-kD transmembrane protein DPP4, also known as CD 26, is expressed on the cell membrane surface of immune cells, such as T cells[7]. DPP4 blocks incretin, which is responsible for insulin secretion from β-cells of the pancreas and thus affects circulating blood glucose. DPP4Is are compounds that block DPP4, promoting insulin secretion as a result[8]. DPP4Is are well-known antihyperglycemic agents, but these drugs also block CD26, expressed on lymphocytes, and might therefore affect the immune system. It has been reported that suppression of DPP4 causes migration of eosinophils to the skin in rats and inhibition of fibrosis by skin fibroblasts[9,10].

Epidermal–dermal adherence is achieved in part by hemidesmosomes and related molecules present at the junction between the basement membrane and epidermal cells. BP180 is one of the transmembrane proteins involved in this binding, and a past study reported that the autoantibodies to BP180 were found in the blood of BP patients. Furthermore, immunoglobulin G against the NC16a region of BP180 was found in 80–90% of BP patients[11]. This NC16a region or BP180 is considered to play important roles in blister formation, because the NC16a domain contains a major pathogenic epitope[12], and epidermolysis can be induced when this antibody is administered in animal experiments[13,14].

In humans, anti-BP180Nc6a antibody has been applied clinically for the diagnosis and evaluation of BP[15]. In the present study, the positive rate of BP180NC16a autoantibodies was 79.1% in the overall sample, which is similar to past reports[11]. The positive rate of these antibodies was lower in the DPP4I group than that of the non-DPP4I group (65.6% vs 82.3%, P = 0.0360), which was consistent with a previous study[5]. The antibody titer was also lower in the DPP4I group than in the

Table 5 | Characteristics of patients who developed bullous pemphigoid after dipeptidyl peptidase-4 inhibitors were prescribed at Ogaki Municipal Hospital

Case	Sex	Age	Erythema	Type of DPP4I	Anti-BP180Nc16a antibody		No. months from DPP4I start to BP onset	Steroid systematic administration	Hospitalization	Current status
					Presence	Titer				
1	M	62	+	Linagliptin	Positive	28.9	39	+	−	Systemic steroid administration was discontinued at 38 weeks. The patient died 6 months after BP onset, but there was no relapse before death without drug therapy.
2	M	75	+	Sitagliptin	Positive	276.3	56	+	+	The patient died 15 months after BP onset. Skin condition was stable while taking 12 mg prednisone and 100 mg mizoribine.
3	M	78	−	Alogliptin	Negative	−	12	−	−	Skin condition was stable with 200 mg minocycline without systemic steroid use.
4	M	63	−	Vildagliptin	Negative	−	8	+	−	Systemic steroid administration was discontinued at 27 weeks. No relapse after BP onset without drug therapy.
5	F	81	−	Vildagliptin	Negative	−	45	+	−	Skin condition was stable while taking 0.5 mg dexamethasone and topical steroid.
6	M	83	−	Sitagliptin	Negative	−	78	−	−	In remission without drug therapy.
7	M	73	−	Sitagliptin	Negative	−	79	−	−	Skin condition was stable with 100 mg minocycline and topical steroid without systemic steroid use.
8	F	54	−	Vildagliptin	Positive	52.5	70	+	−	Skin condition was stable while taking 5 mg prednisone.

All cases continued dipeptidyl peptidase-4 inhibitor (DPP4I) after diagnosed bullous pemphigoid (BP). F, female; M, male.

Table 6 | Characteristics of currently followed bullous pemphigoid patients who used dipeptidyl peptidase-4 inhibitor before diagnosis

No.	Sex	Age	Erythema	Antibodies directing BP180		HLA-DQB1 03:01
				Nc16a domain	Full-length	
1	M	73	–	–	6.86	+
2	F	88	–	–	7.42	+
3	F	84	–	–	15.04	+
4	M	92	–	–	16.26	–
5	M	61	+	642	–	+
6	F	86	+	517.3	25.56	+
7	F	84	+	337.4	12.5	+
8	M	80	+	130.2	15.51	–
9	F	76	+	110	9.59	–
10	F	75	+	79.6	–	–
11	F	83	+	69.7	7.52	+
12	F	54	+	52.5	1.03	+

F, female; M, male.

non-DDP4I group (206.7 ± 238.5 vs 551.1 ± 1323.6, $P = 0.0136$). In terms of the anti-BP180Nc6a antibody-positive rate, the pattern of the results was similar when the analysis was restricted to type 2 diabetes mellitus patients: the DPP4I group had a lower positive rate than the non-DPP4I group (65.6% vs 93.7%, $P = 0.0339$). However, although titers in type 2 diabetes mellitus patients were lower in the DPP4I group than in the non-DPP4I group, the difference was not significant (206.7 ± 238.5 vs 871.1 ± 2146.0, $P = 0.2677$). This lack of significance might be due to the very low number of type 2 diabetes mellitus patients in the present study. Though it is unknown why BP patients who had taken DPP4Is were more likely to be negative for anti-BP180NC16a antibody and have lower titers than patients who had not taken DPP4Is, these findings suggest that DPP4Is might induce BP by a mechanism that does not involve this antibody.

The anti-BP180Nc6a antibody was reported to be associated with the severity of BP[16], and DPP4I-induced BP tended to be milder than BP not associated with DPP4I[11]. Despite these reports, in the present study there were no significant differences in the rates of either hospitalization or systemic steroid administration between the DPP4I and non-DPP4I groups. However, it is possible that a significant difference might be observed if the number of cases was increased. Further research is required to clarify this issue.

As in past reports[17], at our hospital the period between initial DPP4I administration and the onset of BP varied considerably, from 8 to 79 months. A past study also reported that patients with DPP4I-related BP tended to have the non-inflammatory type and were negative for anti-BP180NC16a antibody[5,6]. The present study confirmed this pattern; as shown in Table 5, of the eight patients who were prescribed DPP4Is and who subsequently developed BP, six (75.0%) had the non-inflammatory type and five (62.5%) were negative for anti-BP180NC16a antibody. Furthermore, while five of the six (83.3%) patients with non-inflammatory BP were negative for anti-BP180NC16a antibody, both patients with the inflammatory type were antibody-positive. Based on these results, we postulated a strong relationship between erythema and anti-BP180NC16a antibody. We also hypothesize that DPP4Is were not related to BP onset in patients with inflammatory-type BP or those who were positive for anti-BP180NC16a antibodies. Of note, it was reported that DPP4Is-associated BP was often relieved when the DPP4I was discontinued[18]. We were not able to evaluate whether stopping DPP4I affected BP, because the eight patients who began DPP4I therapy in our hospital continued this therapy after BP diagnosis and were stable in skin condition. In December 2017, four of the eight patients were receiving systemic steroid administration. Though the state of BP was regulated with continuing DPP4I in the present study, this result did not show that continuing DPP4I after diagnosis of BP had no problem. We need to recruit more patients to elucidate how discontinuation of DPP4I impacts BP. Therefore, it is important at this time to keep in mind that DPP4I is likely to be involved in BP onset and to consider which is more beneficial of stopping or continuing DPP4I for each case.

A previous clinical study reported that the odds ratio of exposure to DPP4Is during BP onset was 67.5% (47.1–96.9), suggesting a relationship between DPP4Is and BP onset[18]. Although it has been reported that the spontaneous incidence rate of BP is 21–66 per 1 million people (0.0021–0.0066%)[19], BP was more common in our study, occurring in 0.0859% of the patients who received DPP4Is. Furthermore, there was a possibility of non-captured cases. The odds of exposure to each DPP4 differed in the previous report mentioned above, namely 225.3% (148.9–340.9) for vildagliptin, 17.0% (8.9–32.5) for sitagliptin and 16.5% (2.3–119.1) for saxagliptin[18]. Although we could not evaluate this point in detail in the present study due to the small number of patients, BP onset occurred most frequently in patients who received vildagliptin, even though this DPP4I was least commonly prescribed. These results suggest that BP might be more likely to develop in conjunction with vildagliptin than with other DPP4Is. Although this is presumably because vildagliptin has the lowest DPP4I selectivity among the DPP4Is, thus more strongly inhibiting the action of the DPP8 and DPP9 isozymes than other DPP4Is[20], this is only a hypothesis at this point, as the functions of DPP8 and DPP9 are unknown.

Several studies have reported an association between human leukocyte antigen (HLA) types and drug-induced reactions[21,22]. HLA-DQB1*03:01, which is also thought to be associated with mucous membrane pemphigoid, was reported as a risk factor for non-inflammatory DPP4-induced BP in Japan[23,24]. Although the prevalence of this HLA type was found to be just 18% in all Japanese and 31% in those with type 2 diabetes mellitus who were receiving a DPP4I, it occurred in 86% of patients with non-inflammatory DPP4-induced BP[6]. In a previous study, patients with DPP4I-induced BP were found to

have negative of anti-BP180NC16a antibody, but even in individuals where this antibody was absent, the antibodies directing full-length BP180 were present[25]. In the present study, four patients had non-inflammatory-type BP and were negative for anti-BP180NC16a antibody. A comparison of patients with inflammatory- and non-inflammatory-type BP in the present study strongly suggested that erythema (inflammatory type) tends to be anti-BP180NC16a antibody-negative. Both inflammatory- and non-inflammatory-type BP have a higher prevalence of HLA-DQB1*03:01 than the Japanese general population. Accurate evaluation was difficult, because there was no control group, but HLA-DQB1*03:01 involvement is suspected in cases of BP associated with DPP4Is. Clarification of these results will require examination of additional cases in the future.

The limitations of the present study are as follows. First, it was carried out at a single hospital, so it is possible that BP-related morbidity and the prevalence of HLA-DQB1*03:01 were higher in this sample than in the general population. Second, we could not follow all patients who were prescribed DPP4Is, because many transferred their care to other hospitals and therefore we were unable to accurately determine the incidence of BP in this population. Third, BP was diagnosed by a dermatologist who might have been influenced by the presence or absence of anti-BP180NC16a antibody. As a result, BP patients without this antibody might have been overlooked, whereas those without BP, but who were antibody-positive, might have been incorrectly diagnosed with BP. Fourth, we could not examine the prevalence of BP as a control group, because some patients with diabetes had received the treatment for diabetes in other institution. Therefore, we used the prevalence of BP in the general population as a reference value. This result might not completely show the comparison with our data. It is important to take each of these points into consideration when forming conclusions based on the study results.

The present study comprehensively analyzed numerous cases of BP, a low-incidence disease. It showed that the positive rate of anti-BP180NC16a antibody was lower in BP patients who were taking DPP4Is than in those who were not, regardless of the presence of type 2 diabetes mellitus. Furthermore, the titer of this antibody was low in both the overall population and in patients with type 2 diabetes mellitus. DPP4-induced BP tended to be non-inflammatory, and negative for the NC16a domain, but positive for the full length of the antibodies directing BP180, and HLA-DQB1*03:01 was common. After DPP4I administration, BP developed in eight of 9,304 patients. The incidence rate of 0.0859% was higher than identified in a previous study, and among the DPP4Is, vildagliptin conferred the highest risk of BP. Though some of these results were reported in the past, many are confirmed here. We consider that it is highly important to identify the features of DPP4I-induced BP. Although DPP4Is are effective drugs for the treatment of diabetes, care should be taken regarding the development of BP.

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DISCLOSURE

The authors declare no conflict of interest.

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