Dipeptidyl peptidase IV inhibitors, a risk factor for bullous pemphigoid: Retrospective multicenter case-control study from France and Switzerland

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Dipeptidyl peptidase IV inhibitors, a risk factor for bullous pemphigoid: Retrospective multicenter case-control study from France and Switzerland

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Background: Case reports have suggested an association between dipeptidyl peptidase-4 inhibitors (DPP4is) and development of bullous pemphigoid (BP).

Objective: To evaluate the association between DPP4i treatment and development of BP.

Methods: We conducted a retrospective 1:2 case-control study, comparing case patients with diabetes and BP with age- and sex-matched control patients with diabetes issued from Swiss (Bern) and French (Marseille) dermatologic departments from January 1, 2014, to July 31, 2016.

Results: We collected 61 case patients with diabetes and BP and 122 controls. DPP4is were associated with an increased risk for development of BP (adjusted odds ratio, 2.64; 95% confidence interval, 1.19-5.85; P = .02), with vildagliptin showing the highest adjusted odds ratio (3.57 [95% confidence interval, 1.07-11.84; P = .04]). Stratified analysis showed a stronger association in males and patients age 80 years or older. DPP4i withdrawal and the initiation of first-line treatments led to clinical remission in 95% of cases.

Limitations: This was a retrospective study in tertiary referral hospitals. We focused the analysis on DPP4i intake, without analyzing the potential isolated effect of metformin.

Conclusions: DPP4is, especially vildagliptin, are associated with an increased risk for development of BP. Their use needs to be carefully evaluated, particularly in high-risk patients, such as males and those age 80 years or older.

Key words: bullous pemphigoid; case-control study; diabetes; dipeptidyl peptidase-4 inhibitor; gliptin; risk factor.

Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease that typically affects the elderly. Its cutaneous manifestations are polymorphic, ranging from pruritus with excoriated, eczematous, papular, and/or urticaria-like lesions in the nonbullous phase to vesicles and bullae in the bullous phase.[1] BP is associated with an immune response directed against

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2 molecules, the BP antigen 180 (BP180 [also called BPAG2]) and the BP antigen 230 (BP230 [also called BPAG1]).[2]

Since the publication of the first case of BP associated with sulfasalazine in 1970, a wide range of drugs (spironolactone, furosemide, chloroquine, β-blockers, and several antibiotics) have been associated with the disease.[3] Recently, several cases of BP have been reported in association with dipeptidyl peptidase-4 inhibitors (DPP4is), which are also known as gliptins.[4-13]

DPP4is are oral antihyperglycemic drugs administered to patients with type 2 diabetes as monotherapy or in combination with other oral antihyperglycemic medications or insulin. DPP4 is an enzyme that inactivates incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide). DPP4is increase levels of incretins, thereby increasing insulin secretion, decreasing glucagon secretion, and improving glycemic control. Sitagliptin was first approved in 2006 by the US Food and Drug Administration, followed by saxagliptin (in 2009), linagliptin (in 2011), and alogliptin (in 2013). Three DPP4is are currently available on the French market—sitagliptin and vildagliptin (since 2007) and saxagliptin (since 2009)—and 5 are available on the Swiss market—the 3 aforementioned DPP4is and linagliptin (since 2011) and alogliptin (since 2013)—both of which are available only on the Swiss market. They are used alone or in association with metformin in the same tablet.[4]

An increasing number of clinical reports and pharmacovigilance database analyses suggesting an association between DPP4i intake and BP have been published. Nevertheless, this has not been confirmed by a well-designed controlled study.

The main objective of our case-control study was therefore to retrospectively evaluate the association between DPP4i treatment and development of BP. The secondary end points were to determine a potential higher association for a specific DPP4i and to evaluate the disease course after DPP4i withdrawal.

CAPSULE SUMMARY

- Case reports suggest an association between dipeptidyl peptidase-4 inhibitors and development of bullous pemphigoid.
- This case-control study confirms an increased risk for development of bullous pemphigoid in patients receiving dipeptidyl peptidase-4 inhibitors.
- Dipeptidyl peptidase-4 inhibitors, especially vildagliptin, should be used cautiously in high-risk patients with diabetes (ie, males and those older than 80 years).

MATERIALS AND METHODS

The investigations were conducted as a retrospective case-control study with a 1:2 design, comparing case patients with BP and diabetes with age- and sex-matched controls with type 2 diabetes from January 1, 2014, to July 31, 2016. All study procedures adhered to the principles of the Declaration of Helsinki. The French Committee for the Protection of Persons (RO-2016/37) and the Ethics Committee of the Canton of Bern (KEK-2016/01488) approved the study. The French Advisory Committee on Information Processing in Material Research in the Field of Health and the French Commission for Information Technology and Civil Liberties also authorized this study.

Data collection for cases and controls

The study was conducted in 3 university dermatologic departments (Bern, Marseille Nord, and Marseille La Timone). By using the database of the respective histopathology departments and clinical records, we identified all patients with BP diagnosed for the first time between January 1, 2014, and July 31, 2016. The diagnosis of BP was based on the following criteria developed by the French Bullous Study Group[14]: consistent clinical features, compatible histopathology findings, positive direct immunofluorescence studies, and in some cases, positive indirect immunofluorescence microscopy studies and/or positive enzyme-linked immunosorbent assay—BP180/enzyme-linked immunosorbent assay—BP230 (MBL International, Japan). Among these patients with BP, we identified those having type 2 diabetes.

For these patients, we recorded age, sex, date of BP diagnosis, treatment of BP (with topical steroids, systemic corticosteroids, immune suppressors, or other treatments such as doxycycline or dapsone), evolution of BP (complete remission, partial remission, relapse, or death), comorbidities (including rheumatic, neurologic, cardiovascular, or digestive diseases and neoplasia), treatment with DPP4is, and other cotreatments (including diuretics, antibiotics, neuroleptics, nonsteroidal anti-inflammatory drugs, and antihypertensive drugs).

If a DPP4i was mentioned in the medical record, we examined the type of DPP4i, the chronology between BP diagnosis and onset of the DPP4i treatment, and the evolution after DPP4i withdrawal. Patients who had other autoimmune bullous

Abbreviations used:

BP: bullous pemphigoid
CI: confidence interval
DPP4i: dipeptidyl peptidase-4 inhibitor
OR: odds ratio
SD: standard deviation

diseases or did not otherwise fulfill the inclusion criteria were not included.

The control patients were obtained between January 1, 2014, and July 31, 2016, from the endocrinology departments of the same hospitals. For each case, 2 control patients with diabetes visiting the endocrinology department in the same 6-month period and matched to the case by sex and quinquennium of age were then randomly selected from all available patients satisfying the matching criteria. The patient files were reviewed for treatment of diabetes (specifically, the use of DPP4is), other cotreatments, and comorbidities. For the controls, we did not include case patients with any chronic skin diseases, including bullous dermatosis, at the time of the study.

We then compared exposure to DPP4is between case patients and controls with adjustment for potential confounders.

Statistical analysis

Descriptive data were presented as number with percentages or means with standard deviations (SDs) for categoric and continuous variables, respectively. The Mann-Whitney *U* test was used to assess possible residual differences in the distribution of age between case patients and controls. Differences between case patients and matched controls across different levels of other factors were assessed by means of univariate conditional logistic regression analysis. Factors associated with DPP4i use were also investigated by means of the Pearson χ^2 test or Fisher exact test, where required.

All factors with a *P* value less than .10 in the univariate case-control analysis and associated with DPP4i use, with a *P* value less than .10 at univariate level, were evaluated as possible confounding factors in multivariate conditional logistic regression models with backward stepwise selection algorithm. The factors retained for adjustment were neurologic and metabolic/endocrine comorbidities, as well as other dermatologic conditions unrelated to BP. The effect of DPP4i use on BP onset in diabetic patients was expressed in terms of an odds ratio (OR) along with its 95% confidence interval (CI) and *P* value. A stratified analysis by possible effect modifiers, including sex and age group, was also performed. All tests were considered statistically significant at a *P* value less than .05.

Before starting the study, we planned to recruit at least 183 patients (61 case patients and 122 controls) to detect an OR higher than 2.5 in a 1:2 matched case-control design, supposing to observe a 30% exposure to DPP4i use in the control group ($\alpha = 0.05$, $\beta = 0.20$, multiple correlation coefficients <0.2). Analyses were carried out with SPSS software (version 20.0, IBM Corp, Armonk, NY).

RESULTS

From January 2014 to July 2016, BP was diagnosed in 165 patients (61 in Bern, 47 in Marseille Nord, and 57 in Marseille La Timone). Among these, 61 had diabetes (22 in Bern, 14 in Marseille Nord, and 25 in Marseille La Timone). We collected 2 matched controls for each case patient, resulting in a total of 122 controls.

Of the case patients, 50.8% were female, and the mean age was 79.1 plus or minus 7.0 years. The main comorbidities of cases were cardiovascular (86.9%), neurologic (52.5%), and metabolic and endocrine diseases other than diabetes (39.3%) and uronephrologic diseases (39.3%) (Table I).

In our 3 investigational centers, we collected 28 patients with diabetes and BP who were taking a DPP4i. DPP4is were used more frequently in case patients with BP (45.9%) than in controls (18%), and the difference was statistically significant ($P < .001$). Of the specific DDP4is, vildagliptin was more common in case patients (23%) than in controls (4.1%). For the other cotreatments, there was no statistical difference between case patients and controls, except for the use of antihistamines ($P < .001$). There were no differences in other antidiabetic medications, including metformin, between case patients and controls ($P = .08$) (Table II).

All patients with BP were treated with high-potency topical steroids as first-line treatment. Systemic corticosteroids were used in half of them (50.8%), immunosuppressive agents in 32.8%, and other treatments such as doxycycline or dapsone in 34.4%. With treatment, 37.7% went into complete remission and 42.6% went into partial remission. Finally, there were no differences in treatment between the patients with diabetes and BP who had taken a DPP4i and the patients with diabetes and BP who had not taken a DPP4i (data not shown), an observation suggesting that presentation and initial severity of BP in these 2 groups were similar.

Table I. Demographics and comorbidities of selected cases and controls

Demographic characteristic/comorbidity	Controls		Cases		Total		
	N	%	N	%	N	%	P*
Sex							
Male	60	49.2%	30	49.2%	90	49.2%	—
Female	62	50.8%	31	50.8%	93	50.8%	
Age, y (mean, SD = 7)	79.3	7.0	78.7	7.2	79.1	7.0	.63
<75	30	24.6%	17	27.9%	47	25.7%	
75-84	62	50.8%	29	47.5%	91	49.7%	
≥85	30	24.6%	15	24.6%	45	24.6%	
Comorbidities							
Neurologic	47	38.5%	32	52.5%	79	43.2%	.06
Cardiovascular	108	88.5%	53	86.9%	161	88.0%	.75
Rheumatic	36	29.5%	11	18.0%	47	25.7%	.10
Digestive	34	27.9%	19	31.1%	53	29.0%	.65
Metabolic and endocrine†	85	69.7%	24	39.3%	109	59.6%	**<.001**
Pulmonary	27	22.1%	17	27.9%	44	24.0%	.41
Uronephrologic	45	36.9%	24	39.3%	69	37.7%	.74
Neoplasia	29	23.8%	12	19.7%	41	22.4%	.49
Dermatologic‡	5	4.1%	12	19.7%	17	9.3%	**.03**
Other	35	28.7%	23	37.7%	58	31.7%	.18

SD, Standard deviation.

*Mann-Whitney *U* test was used to assess possible residual differences in the distribution of age between cases and age- and sex-matched controls. Differences between cases and matched controls across different levels of other factors were assessed by means of univariate conditional logistic regression analysis. Boldface indicates statistical significance.

†Except for diabetes.

‡Except for BP.

DPP4is and BP

The univariate analysis of the association between DPP4i use and BP in diabetic patients yielded an OR of 3.45 (95% CI, 1.76-6.77; $P < .001$). After adjustment for possible confounding factors associated with BP onset and DPP4i use in multivariate analysis, the OR was 2.64 (95% CI, 1.19-5.85; $P = .02$) (Table III).

A more detailed analysis of DPP4i use revealed a higher association for vildagliptin, with a crude OR of 7.23 (95% CI, 2.44-21.40; $P = .001$) and an adjusted OR of 3.57 (95% CI, 1.07-11.84; $P = .04$). The study was underpowered to detect differences between other DPP4is, with linagliptin and alogliptin being only used in the Swiss cases.

Sex-stratified analysis indicated that the effect of a DPP4i on BP onset was higher in males (adjusted OR, 4.36; 95% CI, 1.38-13.83; $P = .01$) than in females (adjusted OR, 1.64; 95% CI, 0.53-5.11; $P = .39$). Age group—stratified analyses showed a stronger association for patients age 80 years or older, with an adjusted OR of 5.31 (95% CI, 1.60-17.62; $P = .006$).

Clinical course of patients with BP under treatment with a DPP4i

In our 3 centers, we collected a total of 28 patients with diabetes who developed BP under exposure to a DPP4i. The duration of DPP4i use before onset of BP ranged from 10 days to 3 years (median, 8.2 months).

Drug withdrawal was performed in 19 patients upon suspected DPP4i-associated BP. Complete (11 of 19 [58%]) or partial (7 of 19 [37%]) remission with some mild persistent disease was obtained for all patients but 1 (duration of follow up, 3-30 months; median, 16.4 months). First-line treatment was high-potency topical steroids and systemic corticosteroids in severe or refractory cases followed by a standard tapering schedule.[2,15] No further therapy was necessary in these patients after DPP4i withdrawal to obtain BP remission. For 1 patient, sitagliptin was initially stopped, leading to a partial remission, but its reintroduction combined with metformin led to a relapse of the BP. Definitive discontinuation of sitagliptin and its replacement by repaglinide resulted in a partial remission of BP with 12-month follow-up. The clinical outcome in the 9 patients in whom DPP4is were not stopped was unfavorable. There were 3 deaths of unknown causes (33%), 1 relapse (11%), 4 partial remissions (45%), and 1 complete remission (11%).

DISCUSSION

Our study demonstrates that DPP4is are associated with an increased risk for development of BP, with an adjusted OR of 2.64. Association with

Table II. DPP4i use and other cotreatments in selected cases and controls

	Controls		Cases		Total		
Treatment	**N**	**%**	**N**	**%**	**N**	**%**	***P****
DPP4i							**<.01**
None	100	82.0%	33	54.1%	133	72.7%	
Vildagliptin	5	4.1%	14	23.0%	19	10.4%	
Sitagliptin	14	11.5%	10	16.4%	24	13.1%	
Linagliptin	3	2.5%	3	4.9%	6	3.3%	
Saxagliptin	0	0.0%	1	1.6%	1	0.5%	
Cotreatment							
Diuretics	69	56.6%	28	45.9%	97	53.0%	.17
Antihypertensives/antiarrhythmic agents	101	82.8%	47	77.0%	148	80.9%	.36
Neuroleptics	46	37.7%	26	42.6%	72	39.3%	.52
Antiaggregants/anticoagulants	85	69.7%	45	73.8%	130	71.0%	.56
NSAIDs	12	9.8%	0	0.0%	12	6.6%	.14
Analgesics	22	18.0%	12	19.7%	34	18.6%	.79
Statins	71	58.2%	31	50.8%	102	55.7%	.34
Antihistamines	5	4.1%	19	31.1%	24	13.1%	**<.001**
Antidiabetics[†]	122	100.0%	51	83.6%	173	94.5%	.08
Endocrine or metabolic treatment[‡]	45	36.9%	27	44.3%	72	39.3%	.32
Proton pump inhibitors	59	48.4%	28	45.9%	87	47.5%	.75
Others	50	41.0%	23	37.7%	73	39.9%	.67

DPP4i, Dipeptidyl peptidase-4 inhibitor; *NSAID*, nonsteroidal anti-inflammatory drug.
*Boldface indicates statistical significance.
[†]Except for DPP4i.
[‡]Except for diabetes.

Table III. Univariate and multivariate analysis of the association between DPP4i use and BP in patients with diabetes, overall and in strata of sex and age group

		Controls		Cases		Univariate analysis*		Multivariate analysis[†]	
Strata	**DPP4i use**	**N**	**%**	**N**	**%**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Overall	No	100	82.0%	33	54.1%	1		1	
	Yes	22	18.0%	28	45.9%	3.45 (1.76-6.77)	**<.001**	2.64 (1.19-5.85)	**.02**
Overall (detailed)	No	100	82.0%	33	54.1%	1		1	
	Vildagliptin	5	4.1%	14	23.0%	7.23 (2.44-21.40)	**<.001**	3.57 (1.07-11.84)	**.04**
	Sitagliptin	14	11.5%	10	16.4%	1.82 (0.73-4.54)	.20	2.13 (0.77-5.89)	.15
	Linagliptin/ saxagliptin	3	2.5%	4	6.6%	5.10 (0.98-26.62)	.053	2.90 (0.47-17.74)	.25
Males	No	51	85.0%	13	43.3%	1		1	
	Yes	9	15.0%	17	56.7%	5.85 (2.13-16.08)	**.001**	4.36 (1.38-13.83)	**.01**
Females	No	49	79.0%	20	64.5%	1		1	
	Yes	13	21.0%	11	35.5%	2.00 (0.78-5.15)	.15	1.64 (0.53-5.11)	.39
Age <80 y	No	49	79.0%	18	56.2%	1		1	
	Yes	13	21.0%	14	43.8%	2.47 (1.00-6.13)	.05	1.53 (0.52-4.52)	.44
Age ≥80 y	No	51	85.0%	15	51.7%	1		1	
	Yes	9	15.0%	14	48.3%	4.50 (1.58-12.77)	**.005**	5.31 (1.60-17.62)	**.006**

Boldface indicates statistical significance.
CI, Confidence interval; *DPP4i*, dipeptidyl peptidase-4 inhibitor; *OR*, odds ratio.
*Univariate conditional logistic regression analysis.
[†]Multivariable conditional logistic regression analysis including terms for neurologic, metabolic/endocrine, and other dermatologic comorbidities.

vildagliptin was significantly higher than that with other DPP4is, with an adjusted OR of 3.57. Our findings further indicate that the rate of DPP4i intake in patients with BP is higher both in male patients and in patients older than 80 years. Finally, DPP4i withdrawal seems to have a favorable impact on the outcome of BP in patients with diabetes, as 95% of them went into remission after management

with first-line therapeutic options (ie, topical and sometimes systemic corticosteroids).

An increasing number of reports have suggested that DPP4is trigger BP. Fourteen of the 19 BP cases described (74%) appeared to be related to vildagliptin intake. The median age of the affected patients was 72.5 years, with an almost identical number of males and females.[5-13] In our study, among the 28 diabetic patients developing BP under DPP4i exposure, males were more affected (56.7%) and the median age was 80 years.

Garcia et al[5] identified 170 cases of BP in patients taking a DPP4i in the EudraVigilance database, suggesting that the intake of DPP4is was more frequently associated with development of BP when compared with that of other drugs. In the latter, a disproportionally high number of cases of vildagliptin use were found. A French case-noncase study recording all spontaneous reports of DPP4i-related BP in the National Pharmacovigilance Database between April 2008 and August 2014 also provided evidence supporting an increased risk for development of BP associated with DPP4i exposure, especially vildagliptin.[4] Our present study confirms that the association with vildagliptin is stronger than that with the other DPP4is. This cannot be explained by an overprescription of vildagliptin compared with prescription of other DPP4is. In our control group, sitagliptin was the most prescribed DPP4i, with 14 diabetic patients (11.5%), whereas only 5 patients were treated by vildagliptin (4%). Increased prescribing of sitagliptin was confirmed by an analysis of drug sales in France published by the French National Agency for Medicines and Health Products Safety in 2014. In this survey, sitagliptin was the most prescribed DPP4i and the 24th highest-earning drug in 2013, whereas vildagliptin was not ranked. A recent retrospective study suggests that DPP4i-associated BP is frequently noninflammatory or pauci-inflammatory and characterized by small blisters, mild erythema, and a limited skin distribution. The latter is potentially related to a distinct reactivity profile of autoantibodies to BP180.[16] Although in our retrospective evaluation, there was no apparent difference in clinical presentation and initial management between patients with diabetes and BP who had been treated with DPP4i and patients with diabetes and BP who had not been treated with DPP4i (data not shown), prospective studies are required to address the question of whether BP associated with the intake of a DPP4i has unique clinical and immunologic features.

The pathophysiologic mechanisms linking DPP4i intake and BP development remain unclear. DPP4is could induce BP de novo or accelerate the development of BP in susceptible individuals. Many cell types, including keratinocytes, T cells, and endothelial cells, constitutionally express DPP4. DPP4 inhibition could enhance the activity of proinflammatory chemokines, such as eotaxin, promoting eosinophil activation in the skin, tissue damage, and blister formation.[17] Thielitz et al reported that DPP4is have an antifibrogenic activity by decreasing expression of transforming growth factor-β_1 and secretion of procollagen type I.[18] All these effects could be higher for vildagliptin than other for DPP4is because of molecular differences. Furthermore, vildagliptin administration in monkeys resulted in dose-dependent and reversible skin effects, such as blister formation, peeling, and erosions.[19]

Finally and more importantly, DPP4 is a cell surface plasminogen receptor that is able to activate plasminogen, leading to plasmin formation. Plasmin is a major serine protease that is known to cleave BP180 within the juxtamembranous extracellular noncollagenous 16A domain. Hence, the inhibition of plasmin by a DPP4i may change the proper cleavage of BP180, thereby affecting its antigenicity and its function.[16]

Our study has some limitations: we focused the analysis on DPP4i intake, whereas the potential isolated effect of metformin was not analyzed. Nevertheless, after DPP4i withdrawal, metformin was either continued (in those cases in which it was initially combined with a DPP4i) or newly started in 8 of our patients with BP. Among the latter, we observed 5 complete and 3 partial remissions on follow-up. In addition, metformin intake has not been implicated thus far in the development of BP. On the basis of these observations, it is unlikely that metformin plays a triggering role, but specific studies should be designed to examine the effect of metformin on its own. Finally, we included patients with BP identified by searching our histopathology databases. It is therefore possible that we missed a number of BP cases in which either the term *pemphigoid* was not used in the corresponding histopathologic report or BP was not clinically and/or histopathologically considered.

In conclusion, our findings in a case-control study confirm that DPP4is are associated with an increased risk for development of BP in patients with diabetes. Therefore, the prescription of a DPP4i, especially vildagliptin, should potentially be limited or avoided in high-risk patients, including males and those age 80 years or older. A larger prospective study might be useful to confirm our findings.

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