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Original article

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

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Capsule summary

What is already known on this topic: Case reports suggest an association between dipeptidyl peptidase-IV inhibitors and development of bullous pemphigoid.

What this article adds to our knowledge: This case-control study confirms an increased risk of developing bullous pemphigoid in patients receiving dipeptidyl peptidase-IV inhibitors.

How this information impacts clinical practice and/or changes patient care: Dipeptidyl peptidase-IV inhibitors, especially vildagliptin, should be used cautiously in high-risk diabetic patients, ie. males and older than 80 years.

Abstract

Background: Case reports have suggested an association between dipeptidyl peptidase-IV inhibitors (DPP4i) 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 diabetic BP cases to age and sex-matched diabetic controls, issued from Swiss (Bern) and French (Marseille) dermatological departments, from January 1st 2014 to July 31st 2016.

Results: We collected 61 diabetic BP patients and 122 controls. DPP4i were associated with an increased risk of developing BP (adjusted OR=2.64; 95% CI: 1.19-5.85; p=0.02), with vildagliptin showing the highest adjusted OR (3.57; 95% CI: 1.07-11.84; p=0.04). Stratified analysis showed a stronger association in males and patients aged 80 years or older. DPP4i withdrawal and the institution 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: DPP4i, especially vildagliptin, are associated with an increased risk of developing BP. Their use needs to be carefully evaluated, particularly in high-risk patients, such as males and those aged 80 years or older.

Introduction

Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease which typically affects the elderly. Its cutaneous manifestations are polymorphic, ranging from pruritus with excoriated, eczematous, papular and/or urticaria-like lesions in the non-bullous phase, to vesicles and bullae in the bullous phase (1). BP is associated with an immune response directed against two molecules, the BP antigen 180 (BP180, BPAG2), and the BP antigen 230 (BP230, BPAG1) (2).

Since the publication of the first case of BP associated with sulfasalazine in 1970, a wide range of drugs (spironolactone, furosemide, chloroquine, beta-blockers and several antibiotics) have been associated with the disease (3). Recently, several cases of BP have been reported in association with dipeptidyl peptidase-IV inhibitors (DPP4i), also known as gliptins (7-16).

DPP4i are oral anti-hyperglycemic drugs administered to patients with type 2 diabetes in monotherapy or in combination with other oral anti-hyperglycemic medications or insulin. DPP4 is an enzyme that inactivates incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide). DPP4i increase levels of incretins, thereby increasing insulin secretion, decreasing glucagon secretion and improving glycemic control. Sitagliptin was first approved in 2006 by the U.S. Food and Drug Administration, followed by saxagliptin (2009), linagliptin (2011) and alogliptin (2013). Three DPP4i are currently available on the French market and five DPP4i on the Swiss market: sitagliptin and vildagliptin (2007), saxagliptin (2009) and, only on Swiss market, linagliptin (2011) and alogliptin (2013). They are used alone or in association with metformin in the same tablet (7).

An increasing number of clinical reports and pharmacovigilance database analyses have been published, suggesting an association between DPP4i intake and BP. 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 endpoints were to determine a potential higher association for a specific DPP4i, and to evaluate the disease course after DPP4i withdrawal.

Materials and methods

The investigations were conducted as a retrospective case-control study with 1:2 design, comparing BP diabetic cases to age and sex-matched type 2 diabetic controls, from January 1st 2014 to July 31st 2016. All study procedures adhered to the Declaration of Helsinki Principles. 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 (CCTIRS) and the French commission for information technology and civil liberties (CNIL) also authorized this study.

Data collection for cases and controls

The study was conducted in three University dermatological 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 1st 2014 and July 31st 2016. The diagnosis of BP was based on the following criteria, developed by the French bullous study group (4): consistent clinical features, compatible histopathology findings, positive direct immunofluorescence (DIF) studies and in some cases, positive indirect immunofluorescence microscopy (IIF) studies and/or positive ELISA-BP180/ELISA-BP230 (MBL International, Japan). Among these BP patients, we identified the cases having type 2 diabetes.

For these patients, we recorded: age, sex, date of BP diagnosis, treatment of BP (topical steroids, systemic corticosteroids, immune suppressors, other treatments such as doxycycline or dapsone), evolution of BP (complete remission, partial remission, relapse, death), comorbidities (rheumatic, neurological, cardio-vascular, digestive diseases, neoplasia, etc.), treatment with DPP4i, and other co-treatments (diuretics, antibiotics, neuroleptics, NSAID, antihypertensive drugs, etc.).

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 suffering from other autoimmune bullous diseases, or who did not otherwise fulfill the inclusion criteria, were not included.

The controls were obtained between January 1st 2014 and July 31st 2016 from the endocrinology departments of the same hospitals. For each case, two diabetic control patients, visiting the endocrinology department in the same 6-month period and matched to the case by gender and quinquennium of age, were then randomly selected from all available patients satisfying the matching criteria. The patient files were reviewed concerning treatment for diabetes, specifically the use of DPP4i, other co-treatments and comorbidities. For the controls, we did not include patients suffering at the time of the study from any chronic skin diseases, including bullous dermatosis.

We then compared exposure to DPP4i between cases and controls with adjustment for potential confounders.

Statistical analysis

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

All factors with p-value <0.10 in the univariate case-control analysis and associated to DPP4i use, with p-value <0.10 at univariate level, were evaluated as possible confounding factors in multivariate conditional logistic regression models with backward stepwise selection algorithm. Factors retained for adjustment were: neurological and metabolic/endocrine comorbidities, as well as other dermatological conditions unrelated with BP. The effect of DPP4i use on BP onset in diabetic patients was expressed in terms of odds ratio (OR) along with its 95% confidence interval (CI) and p-value. A stratified analysis by possible effect modifiers, including gender and age group, was also performed. All tests were considered statistically significant at p-value <0.05.

Before starting the study, we planned to recruit at least 183 patients (61 cases and 122 controls) in order to detect OR >2.5 in a 1:2 matched case-control design, supposing to observe a 30% exposure to DPP4i use in the control group, (α=0.05, β=0.20, multiple correlation coefficients <0.2). Analyses were carried out by using SPSS software v. 20.0 (Armonk, NY: IBM Corp.).

Results

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

50.8% of cases were females and the mean age was 79.1 ± 7.0 years. The main comorbidities of cases were cardio-vascular (86.9%), neurological (52.5%), metabolic and endocrine, other than diabetes (39.3%) and uronephrological diseases (39.3%) (Table 1).

In our three investigational centers, we collected 28 diabetic patients with BP on DPP4i. DPP4i were used more frequently in BP cases (45.9%) than in controls (18%) and the difference was statistically significant ($p < 0.001$). Of the specific DDP4i, vildagliptin was more common in cases (23%) compared to controls (4.1%). For the other co-treatments, there was no statistical difference between cases and controls, except for the use of antihistamines ($p < 0.001$). There were no differences in other anti-diabetic medications, including metformin, between cases and controls ($p=0.08$) (Table 2).

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

DPP4i and BP

The univariate analysis of the association between DPP4i use and BP in diabetic patients found an OR of 3.45 (95% CI: 1.76-6.77; $p < 0.001$). After adjustment for possible confounding factors associated to BP onset and DPP4i use in multivariate analysis, the OR was 2.64 (95% CI: 1.19-5.85; $p = 0.02$) (Table 3).

A more detailed analysis of DPP4i use found a higher association for vildagliptin, with a crude OR of 7.23 (95% CI: 2.44-21.40; $p = 0.001$) and an adjusted OR of 3.57 (95% CI: 1.07-11.84; $p = 0.04$). The study was underpowered to detect differences between other DPP4i, linagliptin and alogliptin being only used in the Swiss cases.

Gender-stratified analysis indicated that the effect of DPP4i on BP onset was higher in males (adjusted OR = 4.36; 95% CI: 1.38-13.83; p = 0.01) than females (adjusted OR = 1.64; 95% CI: 0.53-5.11; p = 0.39). Age group-stratified analyses showed a stronger association for patients aged 80 years or older, with an adjusted OR of 5.31 (95% CI: 1.60-17.62; p = 0.006).

Clinical course of BP patients under DPP4i

In our three centers, we collected in total 28 diabetic patients developing BP under DPP4i exposure. The duration of DPP4i use and onset of BP ranged from 10 days until 3 years (median = 8.2 months).

Drug withdrawal was performed in 19 patients on suspected DPP4i-associated BP. Complete (11/19; 58%) or partial (7/19; 37%) remission with some mild persistent disease was obtained for all patients but one (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 (5, 6). No further therapy was necessary in these patients after DPP4i withdrawal to obtain BP remission. For one 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 nine patients, in which DPP4i were not stopped, was unfavorable. There were three deaths of unknown causes (33%), one relapse (11%), four partial remissions (45%), and one complete remission (11%).

Discussion

Our study demonstrates that DPP4i are associated with an increased risk of developing BP, with an adjusted OR of 2.64. Association with vildagliptin was significantly higher compared to that with other DPP4i 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 diabetic patients, 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 DPP4i trigger BP. Fourteen (74%) out of the 19 described BP cases appeared to be related to vildagliptin intake. The median age of affected patients was 72.5 years with an almost identical number of males and females (8-16). 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.* (8) identified 170 cases of BP in patients on DPP4i in the EudraVigilance database, suggesting that the intake of DPP4i was more frequently associated with the development of BP when compared to that of other drugs. In the latter, a disproportionally high number cases using vildagliptin were found. A French case-non-case study recording all spontaneous reports of DPP4i-related BP in the National Pharmacovigilance Database between 04/2008 and 08/2014 also provided evidence for an increased risk of BP associated to DPP4i exposure, especially vildagliptin (7). Our present study confirms that the association with vildagliptin is stronger than that for the other DPP4i. This cannot be explained by an overprescription of vildagliptin compared to that of other DPP4i. 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 sitaglipitin was confirmed by an analysis of drug sales in France published by the ANSM (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 non- or pauci- inflammatory 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 (17). Although in our retrospective evaluation, there was no apparent difference in

clinical presentation and initial management between DPP4i diabetic BP patients and non-DPP4i diabetic BP patients (data not shown), prospective studies are required to address the question whether BP associated with the intake of DPP4i has unique clinical and immunological features.

The pathophysiological mechanisms linking DPP4i intake and BP development remain unclear. DPP4i 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, like eotaxin, promoting eosinophil activation in the skin, tissue damage and blister formation (18). Thielitz *et al*. reported that DPP4i have an antifibrogenic activity by decreasing TGF-β_1 expression and secretion of procollagen type I (19). All these effects could be higher for vildagliptin than other DPP4i due to molecular differences. Furthermore, vildagliptin administration in monkeys resulted in dose-dependent and reversible skin effects, such as blister formation, peeling, and erosions (20).

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 DPP4i may change the proper cleavage of BP180, affecting by this means its antigenicity and its function (17).

Our study has some limitations: we focused the analysis on DPP4i intake, while 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 DPP4i) or newly started in 8 of our BP patients. Among the latter, we observed 5 complete and three partial remissions on follow-up. In addition, metformin intake has not been implicated so far in the development of BP. Based on 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 BP patients 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 histopathological report or BP was not clinically and/or histopathologically considered.

In conclusion, our findings in a case-control study confirm that DPP4i are associated with an

277 increased risk of developing BP in diabetic patients. Therefore, the prescription of DPP4i,
278 especially vildagliptin, should potentially be limited or avoided in high-risk patients,
279 including males and those aged 80 years or older. A larger prospective study might be useful
280 to confirm our findings.

Abbreviations:

BP, Bullous pemphigoid

DPP4i, Dipeptidyl peptidase-IV inhibitors

OR, Odds ratio

CI, Confidence interval

SD, Standard deviation

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Table 1 - Demographics and comorbidities of selected cases and controls

		Controls		Cases		Total		p*
		N	%	N	%	N	%	
Gender	Male	60	49.2%	30	49.2%	90	49.2%	-
	Female	62	50.8%	31	50.8%	93	50.8%	
Age, yrs (*mean, SD*)		*79.3*	*7.0*	*78.7*	*7.2*	*79.1*	*7.0*	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	Neurological	47	38.5%	32	52.5%	79	43.2%	0.06
	Cardiovascular	108	88.5%	53	86.9%	161	88.0%	0.75
	Rheumatic	36	29.5%	11	18.0%	47	25.7%	0.10
	Digestive	34	27.9%	19	31.1%	53	29.0%	0.65
	Metabolic and endocrine**	85	69.7%	24	39.3%	109	59.6%	**<0.001**
	Pulmonary	27	22.1%	17	27.9%	44	24.0%	0.41
	Uronephrological	45	36.9%	24	39.3%	69	37.7%	0.74
	Neoplasia	29	23.8%	12	19.7%	41	22.4%	0.49
	Dermatological***	5	4.1%	12	19.7%	17	9.3%	**0.03**
	Other	35	28.7%	23	37.7%	58	31.7%	0.18

SD: standard deviation, yrs: years

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

** except for diabetes

*** except for BP

371 **Table 2**- DPP4i use and other co-treatments in selected cases and controls

372

		Controls		Cases		Total		P*
		N	%	N	%	N	%	
DPP4i	None	100	82.0%	33	54.1%	133	72.7%	**<0.001**
	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%	
Co-treatments	Diuretics	69	56.6%	28	45.9%	97	53.0%	0.17
	Antihypertensives/ antiarrhythmic agents	101	82.8%	47	77.0%	148	80.9%	0.36
	Neuroleptics	46	37.7%	26	42.6%	72	39.3%	0.52
	Antiaggregants/ anticoagulants	85	69.7%	45	73.8%	130	71.0%	0.56
	NSAIDs	12	9.8%	0	0.0%	12	6.6%	0.14
	Analgesics	22	18.0%	12	19.7%	34	18.6%	0.79
	Statins	71	58.2%	31	50.8%	102	55.7%	0.34
	Antihistamines	5	4.1%	19	31.1%	24	13.1%	**<0.001**
	Anti-diabetics**	122	100.0%	51	83.6%	173	94.5%	0.08
	Endocrine or metabolic treatment***	45	36.9%	27	44.3%	72	39.3%	0.32
	Proton pump inhibitors	59	48.4%	28	45.9%	87	47.5%	0.75
	Others	50	41.0%	23	37.7%	73	39.9%	0.67

373 ** except for DPP4i

374 *** except for diabetes

Table 3 - Univariate and multivariate analysis of the association between DPP4i use and BP in diabetic patients, overall and in strata of gender and age group

Strata	DPP4i use	Controls		Cases		Univariate analysis*		Multivariable analysis**	
		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)	**<0.001**	2.64 (1.19 - 5.85)	**0.02**
Overall (detailed)	No	100	82.0%	33	54.1%	1		1	
	Vildagliptin	5	4.1%	14	23.0%	7.23 (2.44 - 21.40)	**<0.001**	3.57 (1.07 - 11.84)	**0.04**
	Sitagliptin	14	11.5%	10	16.4%	1.82 (0.73 - 4.54)	0.20	2.13 (0.77 - 5.89)	0.15
	Linagliptin/ Saxagliptin	3	2.5%	4	6.6%	5.10 (0.98 - 26.62)	0.053	2.90 (0.47 - 17.74)	0.25
Males	No	51	85.0%	13	43.3%	1		1	
	Yes	9	15.0%	17	56.7%	5.85 (2.13 - 16.08)	**0.001**	4.36 (1.38 - 13.83)	**0.01**
Females	No	49	79.0%	20	64.5%	1		1	
	Yes	13	21.0%	11	35.5%	2.00 (0.78 - 5.15)	0.15	1.64 (0.53 - 5.11)	0.39
Age <80 yrs	No	49	79.0%	18	56.2%	1		1	
	Yes	13	21.0%	14	43.8%	2.47 (1.00 - 6.13)	0.05	1.53 (0.52 - 4.52)	0.44
Age ≥80 yrs	No	51	85.0%	15	51.7%	1		1	
	Yes	9	15.0%	14	48.3%	4.50 (1.58 - 12.77)	**0.005**	5.31 (1.60 - 17.62)	**0.006**

OR: odds ratio, CI: confidence interval, yrs: years

* Univariate conditional logistic regression analysis

** Multivariable conditional logistic regression analysis including terms for neurological, metabolic/endocrine and other dermatological comorbidities