Original Research

Bullous Pemphigoid Associated with Dipeptidyl Peptidase 4 Inhibitors for the Treatment of Type 2 Diabetes: A Multicenter Study in Istanbul

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Abstract

Objectives: Recent studies have revealed an association between dipeptidyl peptidase 4 inhibitors (DPP4i) and development of bullous pemphigoid (BP). The main aim of our study is to evaluate the association between DPP4i treatment and BP development. The secondary endpoints were to evaluate clinical characteristics and biochemical parameters of the DPP4i associated BP cases and determine the differences of DPP4i associated BP disease than non-DPP4i associated BP cases.

Methods: We designed a retrospective case-control study, comparing type 2 diabetic 58 BP cases to 75 type 2 diabetic controls. Data were collected from three dermatological departments in Istanbul/Turkey, from November 1, 2008, to January 1, 2019. Medical records of each patient's demographic, clinical characteristics, drugs used, and laboratory data were reviewed.

Results: There was no statistical difference in age and gender between the patient and control group. The most common prescribed oral antidiabetic for both groups was metformin. The most commonly prescribed DPP4i was vildagliptin. Fourteen (24.1%) out of 58 diabetic patients with BP were using vildagliptin, 12 (20.7%) out of 58 diabetic BP patients were using linagliptin, 6 (10.3%) out of 58 diabetic BP patients were using sitagliptin, and 1 (1.7%) out of 58 diabetic BP patients were using saxagliptin. There was no significant difference between the two groups regarding the DPP4 is use (using DPPi at the time of diagnosis and not). Both groups had similar clinical characteristics, localizations, disease severity, comorbidities, treatment responses, and biochemical parameters. BP patients using DPP4i had statistically less mucosal involvement than BP patients not using DPP4i (p=0.044).

Conclusion: Even though there was no difference between two groups, when BP develops in diabetic patients, DPP4 is should be questioned and with cooperation with clinician's consideration of change may be planned.

Keywords: Bullous pemphigoid, diabetes, dipeptidyl peptidase 4 inhibitors

Please cite this article as "Ugurer E, Ozkur E, Kivanc Altunay I, Cil Sen E, Koku Aksu AE, Ozcan I, et al. Bullous Pemphigoid Associated with Dipeptidyl Peptidase 4 Inhibitors for the Treatment of Type 2 Diabetes: A Multicenter Study in Istanbul. Med Bull Sisli Etfal Hosp 2022;56(3):375–380".

Bullous pemphigoid (BP), the most common autoimmune bullous disease, typically presents with tense, pruritic blisters, and erosions, which generally affect the elderly population.[1] It is an autoimmune reaction directed against hemidesmosome proteins (BPA1 and BPA2) at the dermo-epidermal junction.[2]

Dipeptidyl peptidase 4 inhibitors (DPP4i) are relatively a newly-introduced group of oral antidiabetic drugs for patients with type 2 diabetes.[3] DPP4i inhibits the degradation of incretins, decreasing glucagon secretion, increasing insulin release, and decreasing blood glucose levels.[4] Sitagliptin was the first DPP4i approved by the US Food and Drug Administration in 2006, followed by saxagliptin in 2009, linagliptin in 2011, and alogliptin in 2013. In Turkey, sitagliptin was the first approved by the end of 2008, followed by vildagliptin by 2010 and saxagliptin by 2011. The first cases of DPP4i induced BP cases occurred in 2011[5] and gradually increasing numbers of patients have been reported in the literature since then. [6-8] In a recent meta-analysis of 13 case-control studies, one cohort, and one randomized clinical trial, the authors found a significant association of the development of BP with the use of DPP4i.[9] Consistent with these studies, case-control studies in Switzerland,[10] Israel,[11] Finland,[11] South Korea,[12] and France[13] have shown that the treatment with DPP4i associated with an increased risk of BP development. DPP4i are increasingly being positioned in treatment because of their favorable characteristics. They are associated with fewer side effects; they are weight-neutral they do not naturally cause hypoglycemia, and do not increase cardiovascular risk.[14]

The main aim of our case-control study was to evaluate the association between oral antidiabetic and the development of BP. The secondary endpoints were to evaluate clinical characteristics of the DPP4i associated BP cases and determine the differences of DPP4i associated BP cases than non-DPP4i associated BP cases. This is the first study from Turkey analyzing BP cases associated with DPP4i.

Methods

The study was designed as a retrospective case-control study comparing BP cases with type 2 diabetes to type 2 diabetic controls without BP, from November 1, 2008, to January 1, 2019. The study included three dermatology centers and was conducted in University of Health Science, Sisli Hamidiye Etfal Training and Research Hospital, University of Health Science, Istanbul Training and Research Hospital, Istanbul Medeniyet University Faculty of Medicine, Prof. Dr. Süleyman Yalcin City Hospital dermatology departments. Using the database of the clinical records and pa-

tient files, we identified all patients with newly diagnosed BP with type 2 diabetes in the study period.

BP was diagnosed as a blistering disease of the skin with suggestive clinical features with typical histopathology of BP, including a subepidermal blister with inflammatory-cell infiltrate in the superficial dermis, often containing eosinophils, alongside immunopathological features: Linear deposits of IgG and/or C3 along the basement membrane zone by direct immunofluorescence. For these patients, age, sex, date of BP diagnosis, treatment of BP, course of the disease, comorbidities, biochemical parameters, prescribed use of DPP4i, and other oral medications were recorded. Disease severity was categorized as mild, moderate, and severe according to body surface area according to BP scoring system.[15] The mild disease involves less than 10 % of the affected body surface area, the moderate disease involves 10-30% of the affected body surface area, and severe disease involves more than 30% of the affected body surface area. The controls were obtained from the endocrinology department of the University of Health Science, Sisli Hamidiye Etfal Training and Research Hospital in the same study period. The medical files of type 2 diabetic controls without BP were reviewed, and the treatment for diabetes, specifically the use of DPP4i, and other co-treatments were recorded. Patients with any other chronic skin diseases were excluded from the study for both groups. The study was approved by the University of Health Science, Sisli Hamidiye Etfal Training and Research Hospital ethics committee (approval date and code: 15.10.2019, 1343)

Statistical Analysis

Statistical Package for the Social Sciences for Windows version 15.0 (SPSS, Chicago, IL, USA) was performed for statistical analysis. Descriptive statistics and categorical variables were given as numbers and percentages, mean, standard deviation, minimum, maximum, and median for numerical variables. For intergroup comparison of independent numerical variables, the Mann-Whitney U test was used when the normal distribution condition was not met. The ratio of the categorical variables between groups was compared with Chi-square analysis. The determining factors were examined with Logistic Regression Analysis. The statistical alpha significance level was accepted as $p<0.05$.

Results

A total of 58 BP cases with type 2 diabetes were included in the study. We included a total of 75 type 2 diabetic controls. There was no statistical difference in age and gender between the two groups. Demographic features of study participants are shown in Table 1. The mean age of BP

Table 1. Demographic features of study participants

Study group	Patient group		Control group		p
	n	%	n	%	
Age (yrs) Mean±SD (Min-max)	74.4±9.4 (48-92)		74.3±6.0 (64-90)		0.932
Age Group					
0-69 years	16	27.6	18	24.0	0.065
70-79 years	26	44.8	47	62.7	
80 years and older	16	27.6	10	13.3	
Sex					
Male	20	34.5	26	34.7	0.982
Female	38	65.5	49	65.3	
Diabetes duration (month) Mean±SD (Min-max)	128.8±90.8 (4-360)		159.8±86.1 (36-410)		0.027
HBA1C(%) Mean±SD (Min-max)	7.32±1.61 (3.8-13.8)		7.06±1.24 (5.2-11)		0.240
Oral Antidiabetics at the time of diagnosis					
Metformin	40	69.0	64	85.3	0.023
Gliclazid	15	25.9	18	24.0	0.805
Vildagliptin	14	24.1	9	12.0	0.066
Linagliptin	12	20.7	17	22.7	0.784
Sitagliptin	6	10.3	9	12.0	0.765
Akarbose	6	10.3	5	6.7	0.532
Nateglinid	2	3.4	3	4.0	1.000
Repaglinid	1	1.7	1	1.3	1.000
Saxagliptin	1	1.7	3	4.0	0.632
Pioglitazon	0	0.0	2	2.7	0.504
Dapagliflozin	0	0.0	6	8.0	0.035
Glimepride	0	0.0	1	1.3	1.000
Empaglifozin	0	0.0	2	2.7	0.504

Table 2. Characteristics of patient group with BP

Patient characteristics	n	%
DPP4i use at the time of diagnosis of BP	34	58.6
Comorbidities		
Hypertension	46	79.3
Others	27	46.6
Coronary artery disease	20	34.5
Cerebrovascular disease	9	15.5
Dementia	6	10.3
Parkinson	1	1.17
Disease severity		
Mild (BSA<10%)	12	20.7
Moderate (BSA 10-30%)	27	46.6
Severe (BSA>30%)	19	32.7
Mucosal involvement	16	27.6
Localization		
Disease severity	21	36.2
Face	6	10.3
Oral Mucosa	10	17.2
Trunk	54	93.1
Extremities	50	86.2
Genitalia	5	8.6
Hand/Foot	25	43.1
Urticarial plaque	26	44.8
Prurigo Papules	16	27.6
Pruritus	48	82.8
Ferritin (ng/mL) Mean±SD (Min-max)	83.9±77.3 (11-390.9)	
CRP (mg/L) Mean±SD (Min-max)	10.0±20.2 (0.13-112)	
Sedimentasyon rate (mm/hour) Mean±SD (Min-max)	34.0±26.3 (2-96)	
Eozinofil count (cells/microL) Mean±SD (Min-max)	961.8±1267.0 (0-6300)	
Treatments for BP		
Topical CS	46	79.3
Oral CS	23	39.7
Doxicycline/Tetracycline	6	10.3
Niacin	4	6.9
Complete remission		
No	17	29.8
Yes	40	70.2

BP: Bullous pemphigoid; DPP4i: Dipeptidyl peptidase 4 inhibitors; BSA: Body surface area; CRP: C-reactive protein; CS: Corticosteroids.

cases was 74.4±9.4 years, while the mean age of controls was 74.3±6.0 (p=0.932). The mean diabetes duration of cases was 128.8±90.8 months, while the mean duration of controls was 159.8±86.1 months (p=0.027). The most common prescribed oral antidiabetic for both groups was metformin. The most commonly prescribed DPP4i was vildagliptin. Fourteen (24.1%) out of 58 diabetic patients with BP were using vildagliptin, 12 (20.7%) out of 58 diabetic BP patients were using linagliptin, six (10.3%) out of 58 diabetic BP patients were using sitagliptin, and one (1.7%) out of 58 diabetic BP patients were using saxagliptin. There was no significant difference between the two groups regarding the DPP4i use (using DPPi at the time of diagnosis and not).

The characteristics of BP patients are shown in Table 2. The most common localizations were trunk (93.1%) and extremities (86.2%). Mucosal involvement was observed in 27.6% of all BP patients. Disease severity was moderate (46.6%) in most cases. The most commonly prescribed treatment for BP was oral and topical corticosteroids. With the first-line treatments, 70% of patients achieved complete remission. Thirty-three (56.8%) diabetic patients with BP were on DP-P4i treatment. As shown in Table 3; 14 (41.2%) diabetic BP patients were using vildagliptin, 12 (35.3%) diabetic BP patients were using linagliptin, six (17.6%) diabetic BP patients were using sitagliptin, and one (2.9%) diabetic BP patients

Table 3. Characteristics of patients with DPP4i associated BP and those with non-DPP4i associated BP

	DPP4I use at the time of diagnosis				p
	Yes		No		
	n	%	n	%	
Comorbidities					
Hypertension	27	79.4	19	79.2	1.000
Coronary artery disease	11	32.4	9	37.5	0.685
Cerebrovascular disease	3	8.8	6	25.0	1.000
Dementia	3	8.8	3	12.5	0.142
Parkinson	1	2.9	0	0.0	1.000
Others*	21	61.8	6	25.0	0.006
Disease severity					
Mild (BSA<10%)	5	14.7	7	29.2	0.336
Moderate (BSA 10-30%)	16	47.1	11	45.8	
Severe ((BSA>30%)	13	38.2	6	25.0	
Mucosal involvement	6	17.6	10	41.7	0.044
Localization					
Scalp	11	32.4	10	41.7	0.684
Face	3	8.8	3	12.5	0.291
Oral Mucosa	4	11.8	6	25.0	1.000
Trunk	30	88.4	24	100	0.134
Extremities	29	85.3	21	87.5	1.000
Genitalia	4	11.8	1	4.2	0.392
Hand/Foot	13	38.2	12	50.0	0.427
Urticarial plaque	17	50.0	9	37.5	0.346
Prurigo Papules	9	26.5	7	29.2	0.821
Pruritus	28	82.4	20	83.3	1.000
Ferritin(ng/mL) Mean±SD (Min-max)	61.8±50.4 (55.9)		108.1±94.3 (92.2)		0.053
CRP(mg/L) Mean±SD (Min-Max)	10.1±18.6 (2.45)		9.9±22.4 (3.28)		0.834
Sedimentasyon rate(mm/hour) Mean±SD (Min-max)	32.2±22.6 (22)		36.5±31.2 (24)		0.868
Eozinofil count(cells/microL) Mean±SD (Min-max)	830.1±1069.5 (390)		1147.5±1509.6 (410)		0.594
Oral Antidiabetics at the time of diagnosis					
Metformin	21	61.8	19	79.2	0.158
Vildagliptin	14	41.2	0	0.0	<0.001
Linagliptin	12	35.3	0	0.0	0.001
Gliclazid	7	20.6	8	33.3	0.275
Sitagliptin	6	17.6	0	0.0	0.037
Acarbose	3	8.8	3	12.5	0.684
Nateglinid	2	5.9	0	0.0	0.506
Repaglinid	1	2.9	0	0.0	1.000
Saxagliptin	1	2.9	0	0.0	1.000

*Others: Malignancy, hypothyroidism, chronic obstructive pulmonary disease, psoriasis. BP: Bullous pemphigoid; DPP4I: Dipeptidyl peptidase 4 inhibitors; BSA: Body surface area; CRP: C-reactive protein

were using saxagliptin when compared with those with non-DPP4i associated BP (p<0.001, p=0.001, and p=0.037, respectively). In Table 3, we compared the patients with BP according to the use of DPPi. Both groups (using DPPi at the time of diagnosis and not) had similar clinical characteristics, localizations, disease severity, comorbidities, treatment responses, and biochemical parameters such as C-reactive protein, sedimentation rate, eosinophil count, ferritin (p>0.05 for all comparisons). Only the difference was in the mucosal involvement. BP patients using DPP4i had statistically less mucosal involvement than BP patients not using DPP4i (p=0.044).

Discussion

Our study demonstrates that 14 (24.1%) out of 58 diabetic patients with BP appeared to be related with vildagliptin use, 12 (20.7%) out of 58 diabetic BP patients appeared to be associated with linagliptin use, six (10.3%) out of 58 diabetic BP patients appeared to be related with sitagliptin use, and one (1.7%) out of 58 diabetic BP patients appeared to be related with saxagliptin use. However, clinical characteristics, localizations, disease severity, comorbidities, treatment responses, and biochemical parameters had not been affected by DPP4i use. Only the difference was in the mucosal involvement.

In this study, mucosal involvement was less frequent in DPPi associated BP cases. The previous data about mucosal involvement of DPPi associated BP cases have some conflicting results. The clinical characteristics of DPP4i associated BP have been conducted in two Japanese studies. Both of the studies found that DPPi associated cases had more frequent mucosal involvement.[16,17] They even concluded that a minor mucosal lesion is one of the features of DPP4i associated BP.

On the other hand, Garcia-Diez et al.[18] reported that skin involvement dominated over mucosal involvement, and lesions healed without residual scarring in DPP4i induced BP. Most European studies have reported that there are no significant clinical and immunological differences between DPP4i-BP and non-DPP4i-BP, opposing to Japanese studies.[13,19] Future studies may reveal why different clinical and immunological features are observed in different regions.

We found a statistically higher percentage of patients using DPP4i (vildagliptin, sitagliptin, and linagliptin) in BP patients than BP patients not using DPP4i in the patient group. However, there was no significant difference between the patient and control group. The strong relation of DPP4i use with BP onset was first reported in 2016 in the French Pharmacovigilance Database. Exceptionally, higher odds ratios (OR) in the development of BP were reported for vildagliptin (22.53), sitagliptin (17.0), and saxagliptin (16.5) than for furosemide (3.3), which was formerly known to be a major BP-inducing drug.[20] Later in 2018, a Japanese pharmacovigilance database study, showed a higher risk for BP particularly among patients treated with vildagliptin (OR: 105.33), followed by teneligliptin (OR: 58.52) and linagliptin (OR: 28.94).[21] In a recent meta-analysis in 2020, the use of DPP4i was also significantly associated with BP with a relatively low OR than Japanese pharmacovigilance database study (pooled OR, 1.92; 95% CI, 1.55-2.38), whereas no significant associations of BP with metformin and other antidiabetics were found.[9] We also found no significant association of BP with other antidiabetics.

At present, the pathogenesis of DPP4i associated BP remains mostly obscure, but it may be reasonable to expect that the inhibition of DPP4, which is also known as CD26 that located on T-cells may explain why the immune system is affected. A previous study in a murine model by Forssmann et al.[22] reported that DPP4 inhibition induces eosinophilic infiltration into the skin. Since infiltration into the skin by eosinophils is a typical histopathologic pattern of BP, a dysfunction of eosinophils due to DPP4i is important. DPP4 is a cell-surface plasminogen receptor that converts plasminogen to plasmin.[23] Plasmin can cause cleavage of BP180 into 120 kD and 97 kD ectodomains.[24,25] Therefore, DPP4 inhibition may affect the development of epitopes for DPP4i-BP autoantibodies.

Limitations

The main limitation of our study is the retrospective data. The median time to BP development after the introduction of DPP4i is not mentioned. The small number of DPP4i associated patients among both cases and controls may limit the generalization of these results to other populations. However, our study comprises the largest clinically characterized subgroup of patients with BP who were exposed to DPP4i in Turkey as a multi-center study from three clinics.

Conclusion

Our results in a case-control study confirm that DPP4i are associated with less mucosal involvement in diabetic BP patients. Even though there was no difference between two groups, when BP develops in diabetic patients, DPP4 should be questioned and with cooperation with endocrinologists consideration of change may be planned.

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