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Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid

Ágnes Kinyó

Abstract

Bullous pemphigoid (BP) is the most common type of autoimmune bullous diseases; drug-induced bullous pemphigoid is a rare variant of it. In the last decade, there is an increasing prevalence of BP, especially dipeptidyl peptidase-4 inhibitor-associated BP (DPP-4i-BP), with the higher prevalence of BP in diabetic patients. Recently, several clinical phenotypes of BP were detected, but there is a tendency in BP cases related to DPP-4 inhibitors to show an atypical noninflammatory form with less distributed skin symptoms, mild erythema, decreased eosinophilic infiltration in the periblister area, and normal or slightly elevated peripheral eosinophil count. Anti-NC16A BP180 autoantibodies are less frequently detected by ELISA, but they response to other epitopes of BP180. Clinical outcome is similar such as in classical non-DPP-4 BP patients, regardless of withdrawal of DPP-4 inhibitors.

Keywords: bullous pemphigoid, noninflammatory, dipeptidyl peptidase-4 inhibitor, gliptins, eosinophil

1. Introduction

Bullous pemphigoid (BP) is a rare autoimmune blistering disease of elderly patients, but in the last decades, it shows increasing incidence [1–8]. Higher prevalence of BP may be according to the increasing global life expectancy of the population, increasing incidence of predisposing neurological diseases, growing numbers of provoking drugs, and improving awareness of newly recognized atypical clinical phenotypes and better diagnostic methods [1]. The role of culprit drugs such as neuroleptics, diuretics, and antidiabetics is reported in several studies [1, 2, 9]. BP is typically present in elderly with a higher predominance in female patients [4, 7]. The classical clinical features of BP are generalized bullous skin eruptions with surrounding erythema and itching; peripheral eosinophilia is also common. Mucosal involvement was observed in 10–30% of patients [2]. Atypical clinical variants may be present up to 20% in BP, including the more common prurigo-like or urticarial type, eczema-like type, dyshidrosiform type, erosive type, and erythema annulare centrifugum-like phenotype [1, 7]. The diagnosis is based on the histological findings, including direct and indirect immunofluorescence microscopy and anti-BP180/BP230 enzyme-linked immunosorbent assays (ELISA) [2]. The gold standard for the treatment of the disease according to guidelines is corticosteroid, in topical or systemic administration and in severe cases with adjuvant immunosuppressive medications, such as azathioprine, methotrexate, or mycophenolate mofetil [2]. In the case of drug-induced BP, the most important therapeutic step is the withdrawal of the culprit drug [9].

2. Bullous pemphigoid and diabetes

BP is a chronic, relapsing disease in patients with several comorbidities and significant morbidity. Investigating the prevalence of diabetes mellitus (DM) in BP, a higher frequency of DM has been found in the last decade [10, 11]. In accordance to several case reports [12–18], case series, case-control studies, pharmacovigilance reports, and retrospective investigations [19–37], the growing number of DM in BP patients is in association with the increasing use of an antidiabetic drug, the dipeptidyl peptidase-4 inhibitor (DPP-4i). DPP-4i, also called gliptins, was approved in 2006 to treat type 2 DM. Sitagliptin, vildagliptin, linagliptin, saxagliptin, and alogliptin have been approved by FDA or EMA; anagliptin, trelagliptin, omarigliptin, and teneligliptin have approval only in Japan. Gliptins are used in monotherapy or in combination with metformin. However, there is a clear evidence of provoking role of DPP-4 inhibitors in BP; the pathomechanism of it is still not understood.

3. Demographics of DPP-4 inhibitor-related BP

DPP-4 inhibitor intake was associated with a threefold increased risk for BP [27, 31, 38]. According to the former investigations [14, 23, 26, 27, 29, 31, 38, 39], vildagliptin has the strongest association with BP; the risk was tenfold (ranged between 7.23 and 11.8) in a systemic review and meta-analysis by Kridin et al. [38]. A higher, sixfold risk was also observed with linagliptin [27, 38]. Higher risk of DPP-4i-BP was also found with sitagliptin by Lee et al. [40], and they also found in a larger sample size (patients with DPP-4i-BP n = 260) that the risks associated with specific DPP-4 inhibitors were lower than the previous studies [27, 38], 1.81 for vildagliptin, 1.64 for linagliptin, and 1.7 for sitagliptin. However, a significant association was detected with vildagliptin, linagliptin, and sitagliptin in age- and sex-matched controlled population; the association with saxagliptin in BP was not significant [27, 31]. Saxagliptin, anagliptin- and alogliptin-induced BP were presented only in a few sporadic cases [29, 31, 32, 40, 41]. DPP-4 inhibitors are often given in combination with metformin; the two recent publications reported that the association of BP and gliptins is independent of metformin exposure [27, 30]. Despite the BP is more common in females, a multicenter investigation and EudraVigilance data showed that DPP-4 inhibitor-associated BP tends to be more common in men [14, 23], similarly to Kridin et al. [27] and Lee et al. [40] and in contrast to Varpuluoma et al., who found a higher risk for BP in women taking DPP-4 inhibitors [30]. The mean age of DPP-4i-related BP patients ranged between 76.6 and 79.1 years [23, 27, 39]. Kridin et al. presented the strongest association in patients younger than 70 years [27], while Benzaquen et al. found stronger association in patients older than 80 years [23], while Lee et al. observed 1.76-fold risk in patients younger than 75 years and 1.5-fold risk in patients older than 75 years [40]. The mean latency period between the initiation of gliptin and the appearance of BP is ranging from 6 to 26.4 months [23, 27, 29, 30, 33]. That means DPP-4 inhibitors can be suspected in the pathogenesis of BP if the drug has been initiated at least 6 months, but it also has to be considered if the drug intake last for more than 2 years prior to the onset of BP.

4. Clinical features of DPP-4 inhibitors-related noninflammatory BP

The classical clinical picture of BP is generalized as bullous skin lesions, tense blisters with severe urticarial erythema. Recent publications characterized a noninflammatory form of BP with limited distribution, smaller blisters, and scant erythema

Figure 1.
DPP-4i-related bullous pemphigoid. Mild skin involvement localized to the upper part of the trunk with small blisters and erosions without erythema in a male patient.

Figure 2.
DPP-4i-related bullous pemphigoid in a female patient with small, round erosions without erythema on the upper extremities.

(**Figures 1** and **2**) [37, 42, 43]. These noninflammatory phenotypes do not react with the NC16A domain of BP, show better clinical outcome, and has a higher prevalence in DPP-4 inhibitor taking patients [22, 32, 34–37, 42, 43]. Noninflammatory BP can

also be found in non-DPP-4-related cases but in a significantly lower manner. Higher frequency of mucosal involvement was reported in gliptin-associated BP in two studies (Kridin et al., 22.2%, n = 36, and Chijiwa et al., 78%, n = 9) [27, 33], but this observation was not supported by Plaquevent (n = 108) [31]. Interestingly, in gliptin-associated mucous membrane pemphigoid (MMP) there is a significantly lower buccal and more common cutaneous involvement [44]. Previous studies demonstrated that eosinophil count is in correlation with the severity of BP [45–47] and with BPDAI score [46]. Comparing the Bullous Pemphigoid Disease Area Index (BPDAI) [48], BPDAI scores for urticaria/erythema (U/E) were significantly lower in noninflammatory phenotypes [33, 36, 42, 43], and lower BPDAI U/E was in correlation with decreased eosinophil count in the perilesional skin [33, 42]. Significantly decreased peripheral eosinophil count was detected in patients of Kridin et al. [27].

5. Immunological characterization of DPP-4 inhibitor-related BP

In BP, there are two targets for autoantibodies, the hemidesmosomal BP180 and BP230 and the juxtamembranous extracellular non-collagenous 16A (NC16A), both of them can be easily detected by commercially available ELISA tests [2, 49, 50]. The domain of BP180 (also called COL17) is a major target epitope in 80–90% of cases [49]. In several investigations, noninflammatory BP patients did not show reactivity against the NC16A domain of BP180, but they were positive for full-length BP180 and its ectodomain midportion with ELISA [34, 36, 42]. The midportion of BP180 is more likely to be recognized than the NC16A domain in DPP-4i-associated noninflammatory BP patients; they are presented with localized symptoms and mild erythema [32, 35, 36, 42, 51]. Although there was a positive reaction to anti-NC16A in DPP-4i-BP cases, but they were mainly presented with prominent erythema and inflammation, concurring with classical phenotype of BP [31, 35, 42]. Kawaguchi et al. showed that the rate of ELISA positivity and antibody titers for anti-BP180 NC16A was significantly lower in DPP-4i-BP than the non-DPP-4 group [22], and this lower titer was also observed by García-Díez et al. [52]. Kawaguchi has also emphasized that patients with DPP-4i-BP tended to have noninflammatory phenotype of BP and presented with negative ELISA for BP180 NC16A domain [22]. Some studies reported noninflammatory DPP-4-induced BP patients who were negative for anti-NC16A domain initially but responded to the full-length BP180 and became positive for NC16A during the course of the disease. This epitope spreading was observed in several cases, after the prolonged use of DPP-4 inhibitors after the onset of BP [17, 37, 52]. Other investigations also demonstrated that multiple epitopes of BP180 are targeted in DPP-4i-BP (midportion, C terminus, and LAD1) [35, 52], and it may suggest that epitope spreading is more common in DPP-4i-BP than in classical BP cases [35]. García-Díez et al. suggested the major role of the midportion of BP180 in DPP-4i-BP, while other BP180 regions are involved later by epitope spreading [52]. Indirect IF positivity was also detected in DPP-4i-BP patients [13, 27, 34], and anti-BP230 autoantibodies were present [34, 35], but the sensitivity of the test was only 38%, which is lower than usually reported [51].

6. Clinical outcome

Based on several investigations, withdrawal of the DPP-4 inhibitors was the first therapeutic step in most cases in the treatment of the disease [23, 34]. Regarding to these data, discontinuation of DPP-4i treatment seems to have a favorable

impact on the clinical outcome of BP [23, 27, 34], but Plaquevent et al. have found that there is no difference in outcome in patients who have further got the gliptin treatment after the diagnosis of BP [31]. Regardless of DPP-4 inhibitor withdrawal, standard treatment protocol was applied in most cases, topical potent corticosteroid treatment in localized form and gold standard systemic corticosteroid treatment with adjuvant immunosuppressive therapy, such as azathioprine, mycophenolate mofetil, or methotrexate in severe cases [27, 31]. Relapse rates were similar in DPP-4i-BP patients such it was previously reported [31].

7. Conclusions

Dipeptidyl peptidase-4 inhibitors (also called gliptins) are widely used drug in the treatment of type 2 diabetes mellitus. There is an increased risk of BP in patients during DPP-4 inhibitor treatment. The exact pathomechanism of DPP-4i-associated BP is still unclear. Dipeptidyl peptidase 4 (also called CD26) is a 110 kDa transmembrane glycoprotein, which is expressed on the surface of several cells, such as T cells [53, 54]. DPP-4 has antihyperglycemic effect and enzymatic activity; it plays a major role in glucose metabolism by blocking incretin [54]. DPP-4 is a plasminogen receptor that activates plasminogen resulted in plasmin formation [55, 56]. Plasmin, a serine protease, which has a high level in lesional skin and in blister fluid in BP [57], cleaves BP180 within the NC16A domain [58]. Cleavage of BP180 in the NC16A region can induce neoepitopes with altered anti-genicities [42, 59]. The antifibrotic effect of DPP-4 inhibitors in the skin also supports the role of DPP-4 in collagen metabolism [56]. DPP-4 is involved in immune cell activation, and its inhibition can modify the immune response, which may increase the activation of eosinophil recruitment into the dermis, which is considered to be essential in blister formation in BP [60]. In contrary to these findings, in patients with gliptin-associated noninflammatory BP, both peripheral and perilesional skin eosinophil counts are significantly lower than in classical BP [27, 33], so the exact pathognostic role of eosinophils in DPP-4-related BP needs further investigations. It is also not elucidated why vildagliptin has the strongest association with BP, but it is known that vildagliptin has the lowest selectivity among gliptins with strong inhibition of DDP8 and DPP9 isozymes [22, 61]. Some results suggest that DPP-4 inhibitor has immunomodifier effect mainly in

	DPP4i-related BP	Classical type BP
Distribution	Limited	Generalized
Bullous eruption	Smaller blisters	Tense bullas
Erythema	Absent or sparse	Pronounced
Perilesional eosinophilic infiltration	Absent or mild	Pronounced
Serum eosinophil count	Normal or slightly elevated	Elevated

Table 1.
Comparison of clinical features in DPP-4i-related and classical type bullous pemphigoid.

genetically susceptible individuals, and they have detected that HLA-DQB1*03:01 allele has higher prevalence in DPP-4i-BP patients [22, 62].

In conclusion, DPP-4 inhibitor-related BP tends to be presented with noninflammatory phenotype of BP, with limited extension, smaller blisters, scant perilesional erythema and eosinophilic infiltration, and normal or slightly elevated peripheral eosinophil count (**Table 1**). Anti-NC16A BP180 positivity is less common, and ELISA titers are slightly elevated, similarly to anti-BP230, but positivity for full-length BP180 or other epitopes of BP180 may be detected. Response to therapy is similar such as in classical non-DPP-4i-BP patients, regardless of withdrawal of DPP-4 inhibitors.

Conflict of interest

There is no conflict of interest.

Acronyms and abbreviations

BP	bullous pemphigoid
BPDAI	bullous pemphigoid disease area index
COL17	collagen XVII
DM	diabetes mellitus
DPP-4	dipeptidyl peptidase-4
DPP-4i-BP	dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid
ELISA	enzyme-linked immunosorbent assays
EMA	European Medicines Agency
FDA	Food and Drug Administration
NC16A	non-collagenous 16A
MMP	mucous membrane pemphigoid
BPDAI	BP disease area index

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References

[1] Kridin K, Ludwig RJ. The growing incidence of bullous Pemphigoid: Overview and potential explanations. Frontiers in Medicine (Lausanne). 2018;**5**:220. DOI: 10.3389/fmed.2018.00220

[2] Bernard P, Antonicelli F. Bullous pemphigoid: A review of its diagnosis, associations and treatment. American Journal of Clinical Dermatology. 2017;**18**:513-528. DOI: 10.1007/s40257-017-0264-2

[3] Schmidt E, Spindler V, Eming R, Amagai M, Antonicelli F, Baines JF, et al. Meeting report of the pathogenesis of pemphigus and Pemphigoid meeting in Munich, September 2016. The Journal of Investigative Dermatology. 2017;**137**:1199-1203. DOI: 10.1016/j.jid.2017.01.028

[4] Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJP, West J. Bullous pemphigoid and pemphigus vulgaris—Incidence and mortality in the UK: Population based cohort study. BMJ. 2008;**337**:160-163. DOI: 10.1136/bmj.a180

[5] Hübner F, Recke A, Zillikens D, Linder R, Schmidt E. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. The Journal of Investigative Dermatology. 2016;**136**:2495-2498. DOI: 10.1016/j.jid.2016.07.013

[6] Bernard P, Vaillant L, Labeille B, Bedane C, Arbeille B, Denoeux JP, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous diseases French study group. Archives of Dermatology. 1995;**131**:48-52

[7] Joly P, Baricault S, Sparsa A, Bernard P, Bédane C, Duvert-Lehembre S, et al. Incidence and mortality of bullous pemphigoid in France. The Journal of Investigative Dermatology. 2012;**132**:1998-2004. DOI: 10.1038/jid.2012.35

[8] Försti AK, Jokelainen J, Timonen M, Tasanen K. Increasing incidence of bullous pemphigoid in Northern Finland: A retrospective database study in Oulu University Hospital. The British Journal of Dermatology. 2014;**171**:1223-1226. DOI: 10.1111/bjd.13189

[9] Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: A review of the literature. Journal of the European Academy of Dermatology and Venereology. 2014;**28**:1133-1140. DOI: 10.1111/jdv.12366

[10] Fania L, Di Zenzo G, Didona B, Pilla MA, Sobrino L, Panebianco A, et al. Increased prevalence of diabetes mellitus in bullous pemphigoid patients during the last decade. Journal of the European Academy of Dermatology and Venereology. 2018;**32**:e153-e154. DOI: 10.1111/jdv.14649

[11] Gravani A, Gaitanis G, Tsironi T, Tigas S, Bassukas ID. Changing prevalence of diabetes mellitus in bullous pemphigoid: It is the dipeptidyl peptidase-4 inhibitors. Journal of the European Academy of Dermatology and Venereology. 2018;**32**:e438-e439. DOI: 10.1111/jdv.14957

[12] Aouidad I, Fite C, Marinho E, Deschamps L, Crickx B, Descamps V. A case report of bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. JAMA Dermatology. 2013;**149**:243-245. DOI: 10.1001/jamadermatol.2013.1073

[13] Attaway A, Mersfelder TL, Vaishnav S, Baker JK. Bullous pemphigoid associated with dipeptidyl peptidase IV inhibitors. A case report and review of literature. Journal of Dermatological Case

Reports. 2014;**8**:24-28. DOI: 10.3315/jdcr.2014.1166

[14] García M, Aranburu MA, Palacios-Zabalza I, Lertxundi U, Aguirre C. Dipeptidyl peptidase-IV inhibitors induced bullous pemphigoid: A case report and analysis of cases reported in the European pharmacovigilance database. Journal of Clinical Pharmacy and Therapeutics. 2016;**41**:368-370. DOI: 10.1111/jcpt.12397

[15] Harada M, Yoneda A, Haruyama S, Yabuki K, Honma Y, Hiura M, et al. Bullous Pemphigoid associated with the dipeptidyl peptidase-4 inhibitor sitagliptin in a patient with liver cirrhosis complicated with rapidly progressive hepatocellular carcinoma. Internal Medicine. 2017;**56**:2471-2474. DOI: 10.2169/internalmedicine.8703-16

[16] Maki N, Nishie W, Takazawa M, Kakurai M, Yamada T, Umemoto N, et al. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid in a patient with acquired reactive perforating collagenosis. The Journal of Dermatology. 2018;**45**:600-602. DOI: 10.1111/1346-8138.14254

[17] Takama H, Yoshida M, Izumi K, Yanagishita T, Muto J, Ohshima Y, et al. Dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid: Recurrence with epitope spreading. Acta Dermato-Venereologica. 2018;**98**: 983-984. DOI: 10.2340/00015555-3010

[18] Oya K, Fujii M, Taguchi S, Nishie W, Izumi K, Shimizu H. Localized bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitor treatment. European Journal of Dermatology. 2018;**28**:250-251. DOI: 10.1684/ejd.2018.3230

[19] Pasmatzi E, Monastirli A, Habeos J, Georgiou S, Tsambaos D. Dipeptidyl peptidase-4 inhibitors cause bullous pemphigoid in diabetic patients: Report of two cases. Diabetes Care. 2011;**34**:e133. DOI: 10.2337/dc11-0804

[20] Mendonça FM, Martín-Gutierrez FJ, Ríos-Martín JJ, Camacho-Martinez F. Three cases of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors—One due to Linagliptin. Dermatology. 2016;**232**:249-253. DOI: 10.1159/000443330

[21] Haber R, Fayad AM, Stephan F, Obeid G, Tomb R. Bullous pemphigoid associated with linagliptin treatment. JAMA Dermatology. 2016;**152**:224-226. DOI: 10.1001/jamadermatol.2015.2939

[22] Kawaguchi Y, Shimauchi R, Nishibori N, Kawashima K, Oshitani S, Fujiya A, et al. Dipeptidyl peptidase-4 inhibitors-associated bullous pemphigoid: A retrospective study of 168 pemphigoid and 9,304 diabetes mellitus patients. Journal of Diabetes Investigation. 2018. DOI: 10.1111/jdi.12877. [Epub ahead of print]

[23] Benzaquen M, Borradori L, Berbis P, Cazzaniga S, Valero R, Richard MA, et al. Dipeptidyl peptidase IV inhibitors, a risk factor for bullous pemphigoid: Retrospective multicenter case-control study from France and Switzerland. Journal of the American Academy of Dermatology. 2018;**78**:1090-1096. DOI: 10.1016/j.jaad.2017.12.038

[24] Béné J, Jacobsoone A, Coupe P, Auffret M, Babai S, Hillaire-Buys D, et al. Bullous pemphigoid induced by vildagliptin: A report of three cases. Fundamental & Clinical Pharmacology. 2015;**29**:112-114. DOI: 10.1111/bjd.14601

[25] Skandalis K, Spirova M, Gaitanis G, Tsartsarakis A, Bassukas ID. Drug-induced bullous pemphigoid in diabetes mellitus patients receiving dipeptidyl peptidase-IV inhibitors plus metformin. Journal of the European Academy of Dermatology and Venereology. 2012;**26**:249-253. DOI: 10.1111/j.1468-3083.2011.04062.x

[26] Schaffer C, Buclin T, Jornayvaz FR, Cazzaniga S, Borradori L, Gilliet M,

et al. Use of Dipeptidyl-peptidase IV inhibitors and bullous pemphigoid. Dermatology. 2017;**233**:401-403. DOI: 10.1159/000480498

[27] Kridin K, Bergman R. Association of bullous pemphigoid with dipeptidyl-peptidase 4 inhibitors in patients with diabetes: Estimating the risk of the new agents and characterizing the patients. JAMA Dermatology. 2018;**154**:1152-1158. DOI: 10.1001/jamadermatol.2018.2352

[28] Arai M, Shirakawa J, Konishi H, Sagawa N, Terauchi Y. Bullous pemphigoid and dipeptidyl peptidase 4 inhibitors: A disproportionality analysis based on the Japanese adverse drug event report database. Diabetes Care. 2018;**41**:e130-e132. DOI: 10.2337/dc18-0210

[29] Béné J, Moulis G, Bennani I, Auffret M, Coupe P, Babai S, et al. French Association of Regional PharmacoVigilance Centres: Bullous pemphigoid and dipeptidyl peptidase IV inhibitors: A case-noncase study in the French Pharmacovigilance database. The British Journal of Dermatology. 2016;**175**:296-301. DOI: 10.1111/fcp.12083

[30] Varpuluoma O, Försti AK, Jokelainen J, Turpeinen M, Timonen M, Tasanen K, et al. Oral diabetes medications other than dipeptidyl peptidase 4 inhibitors are not associated with bullous pemphigoid: A Finnish nationwide case-control study. Journal of the American Academy of Dermatology. 2018;**79**:1034-1038. DOI: 10.1016/j.jaad.2018.05.030

[31] Plaquevent M, Tétart F, Fardet L, et al. Higher frequency of dipeptidyl peptidase IV inhibitor intake in bullous pemphigoid patients than in the French general population. The Journal of Investigative Dermatology. 2018;**18**:32923-3. DOI: 10.1016/j.jid.2018

[32] Yoshiji S, Murakami T, Harashima SI, Ko R, Kashima R, Yabe D, et al. Bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors: A report of five cases. Journal of Diabetes Investigation. 2018;**9**:445-447. DOI: 10.1111/jdi.12695

[33] Chijiwa C, Takeoka S, Kamata M, Tateishi M, Fukaya S, Hayashi K, et al. Decrease in eosinophils infiltrating into the skin of patients with dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid. The Journal of Dermatology. 2018;**45**:596-599. DOI: 10.1111/1346-8138.14245

[34] García-Díez I, Ivars-Lleó M, López-Aventín D, Ishii N, Hashimoto T, Iranzo P, et al. Bullous pemphigoid induced by dipeptidyl peptidase-4 inhibitors. Eight cases with clinical and immunological characterization. International Journal of Dermatology. 2018;**57**:810-816. DOI: 10.1111/ijd.14005

[35] Fania L, Salemme A, Provini A, Pagnanelli G, Collina MC, Abeni D, et al. Detection and characterization of IgG, IgE, and IgA autoantibodies in patients with bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors. Journal of the American Academy of Dermatology. 2018;**78**:592-595. DOI: 10.1016/j.jaad.2017.09.051

[36] Horikawa H, Kurihara Y, Funakoshi T, Umegaki-Arao N, Takahashi H, Kubo A, et al. Unique clinical and serological features of bullous pemphigoid associated with dipeptidyl peptidase-4 inhibitors. The British Journal of Dermatology. 2018;**178**:1462-1463. DOI: 10.1111/bjd.16479

[37] Mai Y, Nishie W, Izumi K, Yoshimoto N, Morita Y, Watanabe M, et al. Detection of anti-BP180 NC16A autoantibodies after the onset of dipeptidyl peptidase-IV inhibitor-associated bullous pemphigoid: A report of three patients. The British Journal of

Dermatology. 2018;**179**:790-791. DOI: 10.1111/bjd.16656

[38] Kridin K, Cohen AD. Dipeptidyl-peptidase IV inhibitor-associated bullous pemphigoid: A systematic review and meta-analysis. J Am Acad Dermatol. 2018;**18**:32660-32664. DOI: 10.1016/j.jaad.2018.09.048

[39] Varpuluoma O, Försti AK, Jokelainen J, Turpeinen M, Timonen M, Huilaja L, et al. Vildagliptin significantly increases the risk of bullous pemphigoid: A Finnish Nationwide registry study. The Journal of Investigative Dermatology. 2018;**138**:1659-1661. DOI: 10.1016/j.jid.2018.01.027

[40] Lee SG, Lee HJ, Yoon MS, Kim DH. Association of dipeptidyl peptidase 4 inhibitor use with risk of bullous pemphigoid in patients with diabetes. JAMA Dermatology. 2019;**155**:172-177. DOI: 10.1001/jamadermatol.2018.4556

[41] Oya K, Fujii M, Taguchi S, Nishie W, Izumi K, Shimizu H. Bullous pemphigoid following the replacement of vildagliptin with anagliptin. The Journal of Dermatology. 2017;**44**:e238-e239. DOI: 10.1111/1346-8138.13941

[42] Izumi K, Nishie W, Mai Y, Wada M, Natsuga K, Ujiie H, et al. Autoantibody profile differentiates between inflammatory and noninflammatory bullous Pemphigoid. The Journal of Investigative Dermatology. 2016;**136**:2201-2210. DOI: 10.1016/j.jid.2016.06.622

[43] Nakama K, Koga H, Ishii N, Ohata C, Hashimoto T, Nakama T. Clinical and immunological profiles of 14 patients with bullous Pemphigoid without IgG autoantibodies to the BP180 NC16A domain. JAMA Dermatology. 2018;**154**:347-350. DOI: 10.1001/jamadermatol.2017.5465

[44] Gaudin O, Seta V, Alexandre M, Bohelay G, Aucouturier F, Mignot-Grootenboer S, et al. Gliptin accountability in mucous membrane Pemphigoid induction in 24 out of 313 patients. Frontiers in Immunology. 2018;**9**:1030. DOI: 10.3389/fimmu.2018.01030

[45] Bernard P, Venot J, Constant F, Bonnetblanc JM. Blood eosinophilia as a severity marker for bullous pemphigoid. Journal of the American Academy of Dermatology. 1987;**16**:879-881

[46] Messingham KN, Holahan HM, Frydman AS, Fullenkamp C, Srikantha R, Fairley JA. Human eosinophils express the high affinity IgE receptor, FcεRI, in bullous pemphigoid. PLoS One. 2014;**9**:e107725. DOI: 10.1371/journal.pone.0107725

[47] Kridin K. Peripheral eosinophilia in bullous pemphigoid: Prevalence and influence on the clinical manifestation. The British Journal of Dermatology. 2018;**179**:1141-1147. DOI: 10.1111/bjd.16679

[48] Murrell DF, Daniel BS, Joly P, Borradori L, Amagai M, Hashimoto T, et al. Definitions and outcome measures for bullous pemphigoid: Recommendations by an international panel of experts. Journal of the American Academy of Dermatology 2012;**66**:479-485. DOI: 10.1016/j.jaad.2011.06.032

[49] Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013;**381**(9863):320-332. DOI: 10.1016/S0140-6736(12)61140-4

[50] Sárdy M, Kostaki D, Varga R, Peris K, Ruzicka T. Comparative study of direct and indirect immunofluorescence and of bullous pemphigoid 180 and 230 enzyme-linked immunosorbent assays for diagnosis of bullous pemphigoid. Journal of the American Academy of Dermatology. 2013;**69**:748-753. DOI: 10.1016/j.jaad.2013.07.009

[51] Sakai A, Shimomura Y, Ansai O, et al. Linagliptin-associated bullous pemphigoid that was most likely caused by IgG autoantibodies against the midportion of BP180. The British Journal of Dermatology. 2017;**176**: 541-543. DOI: 10.1111/bjd.15111

[52] García-Díez I, España A, Iranzo P. Epitope spreading phenomena in dipeptidyl peptidase-4 inhibitor-associated bullous pemphigoid. The British Journal of Dermatology. 2019. DOI: 10.1111/bjd.17690. [Epub ahead of print]

[53] Klemann C, Wagner L, Stephan M, von Hörsten S. Cut to the chase: A review of CD26/dipeptidyl peptidase-4's (DPP4) entanglement in the immune system. Clinical and Experimental Immunology. 2016;**185**:1-21. DOI: 10.1111/cei.12781

[54] Röhrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. Frontiers in Immunology. 2015;**6**:386. DOI: 10.3389/fimmu.2015.00386

[55] Gonzalez-Gronow M, Kaczowka S, Gawdi G, Pizzo SV. Dipeptidyl peptidase IV (DPP IV/CD26) is a cell-surface plasminogen receptor. Frontiers in Bioscience. 2008;**13**:1610-1618

[56] Thielitz A, Ansorge S, Bank U, Tager M, Wrenger S, Gollnick H, et al. The ectopeptidases dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN) and their related enzymes as possible targets in the treatment of skin diseases. Frontiers in Bioscience. 2008;**13**:2364-2375

[57] Schmidt E, Wehr B, Tabengwa EM, Reimer S, Bröcker EB, Zillikens D. Elevated expression and release of tissue-type, but not urokinase-type, plasminogen activator after binding of autoantibodies to bullous pemphigoid antigen 180 in cultured human keratinocytes. Clinical and Experimental Immunology. 2004;**135**:497-504

[58] Hofmann SC, Voith U, Schönau V, et al. Plasmin plays a role in the In vitro. Generation of the linear IgA Dermatosis antigen LADB97. Journal of Investigative Dermatology. 2009;**129**:1730-1739. DOI: 10.1038/jid.2008.424

[59] Nishie W, Lamer S, Schlosser A, Licarete E, Franzke CW, Hofmann SC, et al. Ectodomain shedding generates Neoepitopes on collagen XVII, the major autoantigen for bullous pemphigoid. Journal of Immunology. 2010;**185**:4938-4947. DOI: 10.4049/jimmunol.1001524

[60] Forssmann U, Stoetzer C, Stephan M, Kruschinski C, Skripuletz T, Schade J, et al. Inhibition of CD26/dipeptidyl peptidase IV enhances CCL11/eotaxin-mediated recruitment of eosinophils in vivo. Journal of Immunology. 2008;**181**:1120-1127

[61] Filippatos TD, Athyros VG, Elisaf MS. The pharmacokinetic considerations and adverse effects of DPP-4 inhibitors [corrected]. Expert Opinion on Drug Metabolism & Toxicology. 2014;**10**:787-812. DOI: 10.1517/17425255.2014.907274

[62] Ujiie H, Muramatsu K, Mushiroda T, Ozeki T, Miyoshi H, Iwata H, et al. HLA-DQB1*03:01 as a biomarker for genetic susceptibility to bullous pemphigoid induced by DPP-4 inhibitors. The Journal of Investigative Dermatology. 2018;**138**:1201-1204. DOI: 10.1016/j.jid.2017.11.023